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14. ABSTRACT
The protocol, sponsored by the Department of Defense, is a 6-week study examining whether Methylphenidate-induced euphoria can be attenuated by co-administration with Naltrexone in medication naïve young adults (age 18-30) with a euphoric response to MPH administered on the 'Drug Feeling Visit.' In this double-blind study, subjects will receive MPH and Naltrexone or a placebo to treat their ADHD symptoms over the course of the 6-week trial. Results have not been analyzed so as to not prematurely break the medication blind. A total of 31 subjects completed the Week 3 Drug Feeling Visit, which is the midpoint of the study and the point at which subjects' data is useful for analysis. The findings from this study provide support for the concept of combining opioid receptor antagonists with stimulants to provide an effective stimulant formulation with less abuse potential. This study has, to date, resulted in one accepted manuscript, two accepted abstracts, and one additional manuscript currently in preparation.

15. SUBJECT TERMS
Clinical Trial, Methylphenidate, Naltrexone, ADHD, stimulant-induced euphoria

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Section I: Introduction

The protocol, sponsored by the Department of Defense, is a 6-week study examining whether methylphenidate-induced euphoria can be attenuated by co-administration with naltrexone in medication naïve young adults (age 18-30) who exhibit a euphoric response to methylphenidate. In this double-blind study, subjects will receive methylphenidate and naltrexone or a placebo to treat their ADHD symptoms over the course of the 6-week trial.

Section II: Keywords

Clinical Trial, Methylphenidate, Naltrexone, ADHD, stimulant-induced euphoria

Section III: Overall Project Summary

As requested, the following section is organized in accordance with the aims outlined in the approved Statement of Work:

Specific Aims of the Trial

Primary Aim 1:

The hypothesis that "MPH-induced euphoria in adults with ADHD can be attenuated by co-administration of naltrexone" was tested through examination of euphoria and other subjective responses in a placebo controlled trial of naltrexone in MPH-treated adults with ADHD who are sensitive to the euphoric effects of MPH. 64 subjects were consented to complete screening procedures, with 38 subjects experiencing the stimulant-induced euphoria needed to move on to the main arm of the trial. A total of 31 subjects completed the Week 3 Drug Feeling Visit, which is the midpoint of the study and the point at which their data is useful for analysis. As this trial aimed to collect data from 30 subjects, we exceeded this goal. 25 subjects completed the study through Week 6. Naltrexone significantly diminished the euphoric

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effect of an acute bolus of a supra therapeutic dose of immediate release (IR)-MPH during the titration phase (first three weeks) but not the stabilization phase (weeks 4 to 6) of Spheroidal Oral Drug Absorption System (SODAS)-MPH treatment. The titration phase of open label treatment with SODAS-MPH appears to be a period of heightened vulnerability for such effects. These findings are consistent with prior work by us and Volkow et al. that emphasized the importance of the rate of delivery of stimulants to the brain for abuse liability [14-16]. Also consistent with this notion is the finding that naltrexone had little effect on euphoria during the last 3 weeks of the trial in which subjects remained on a stable optimized therapeutic dose of SODAS-MPH.

Also noteworthy is the finding that the euphoric response to the acute bolus supra therapeutic dose of IR-MPH was significantly decreased at week 3 regardless of naltrexone. This finding is consistent with the hypothesis that chronic treatment with MPH is associated with some desensitization to IR-MPH associated euphoria. Yet, it is noteworthy that despite the lower euphoric response to IR-MPH at week three, naltrexone was associated with a further decrease in euphoric response. These findings extend to human preclinical findings showing that naltrexone may mitigate stimulant-associated euphoria. Our findings provide support for the concept of combining opioid receptor antagonists with stimulants to provide an effective stimulant formulation with less abuse potential.

Specific Aim 2:

The hypothesis that "the co-administration of naltrexone with MPH would not interfere with the clinical effectiveness of MPH for ADHD symptoms was also tested." The observed response to MPH on ADHD symptoms was equally robust in subjects receiving MPH with and without the co-administration of naltrexone. AISRS scores decreased from a highly symptomatic score of 38.4±9.1 at baseline to a score of 10.5±5.7 at endpoint, which corresponds to scores associated with remission of ADHD symptoms. While the high degree of effectiveness of MPH in reducing ADHD symptoms has been documented in the literature [13], it has never before

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been documented with the concomitant administration of naltrexone with MPH. These results show that the co-administration of naltrexone does not diminish the benefits expected with MPH treatment.

Specific Aim 3:

The hypothesis that "serum concentrations of MPH will not be affected by the co-administration of naltrexone with MPH" was unable to be completed due to freezer malfunction. However, this aim was not central to the main study objectives.

Specific Aim 4:

The hypothesis that "the MPH-associated reduction of serum prolactin concentrations will be similar in subjects with and without co-administration of naltrexone" was also unable to be completed due to freezer malfunction. However, this aim was not central to the main study objectives.

Project Tasks

1. To prepare to initiate the clinical trial (Months 1-6) *and*
2. Conduct clinical trial (Months 6-30)

The first subject was enrolled on January 24th, 2013, followed by a 2-month (no cost) break from the project to allow for Dr. Spencer's full recovery from his emergency coronary bypass surgery. A total of 64 subjects were been initially screened and signed informed consent. For each subject, clinicians performed a psychiatric evaluation and physical exam, as well as reviewed inclusion and exclusion criteria. The enrollment report can be found at the end of this report in Table A.

Following informed consent and an initial interview with a study physician, research assistants conducted structured interviews (SCID) and assisted the research coordinator in

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obtaining vital signs, a urine pregnancy and drug test, and administration of an electrocardiogram. A total of 56 subjects completed these further screening procedures.

After these screening and evaluation procedures, subjects completed the baseline Drug Feeling Visit to determine if they experienced stimulant-induced euphoria. While we initially expected only 38% of participants to experience the desired likeability response (≥5 on the Drug Rating Questionnaire DRQ-S), 38 out of 44 subjects that participated in this visit, or 86.44%, fulfilled this portion of the inclusion criteria.

Upon completing the baseline Drug Feeling Visit, participants moved on to the randomized clinical trail for treatment with long acting methylphenidate (Ritalin LA) and double blind naltrexone. For this part of the study, participants came in for weekly visits with a study physician to monitor their response to the medication, changes in their ADHD symptoms, and any adverse events that arise. Medication was adjusted per the physicians' discretion and, depending on the response of the subject, may be titrated up to a maximum daily dose of 1.3mg/Kg/day. At the weekly visits, clinicians completed the AISRS and the CGI-ADHD to assess the subjects' ADHD symptoms and improvement.

On the week 3 and week 6 visits, subjects repeat the protocol from the Drug Feeling Visit with single day, double-blind doses of instant release methylphenidate (IR MPH). Whereas the rating scales used following single blind IR MPH determine subject eligibility at the baseline Drug Feeling Visit, the same rating scales during the Week 3 and Week 6 Drug Feeling Visits are used as outcome measures. A total of 31 subjects completed the Week 3 Drug Feeling Visit, which is the midpoint of the study and the point at which their data is useful for analysis. As this trial aims to collect data from 30 subjects, we have exceeded this data collection goal. Finally, 25 subjects have completed the entire study (6 weeks), compared to 18 subjects in the previous annual performance period.

The remaining subjects did not complete the study for various reasons. A total of 12 subjects were found ineligible after they consented, which were either due to cardiovascular concerns about using stimulant treatment, a positive urine drug screen, comorbidity, or failure to

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experience stimulant-induced euphoria on the baseline Drug Feeling Visit. A total of 23 subjects have withdrawn or were later dropped due to being lost to follow-up, the demanding time commitment of participating in the study, or plans of moving out of the area. Finally, a total of 4 subjects have been terminated from the study due to adverse events. Of these subjects, one developed negative mood side effects, most likely attributed to the study medication, and was subsequently terminated from the study and transitioned to clinical care for her ADHD treatment and to monitor her mood. Another subject was terminated after he developed enlarged lymph nodes throughout his abdominal cavity, which was later identified as cancer. Study staff notified the Partners Healthcare IRB of this event, which confirmed the clinical assessment that this event was unrelated to study medication. The third subject experienced a reoccurrence of her peptic stress ulcers, and was thus terminated from the study and triaged to clinical care for her ADHD treatment. Lastly, one subject experienced substantial nausea and vomiting after taking the medication, and was therefore transitioned to clinical care for continued treatment of her ADHD symptoms.

3. Conduct Statistical Analysis (Months 30-36)

We compared demographics, clinical features, and adverse events among placebo and naltrexone groups using Student's t-tests and Pearson's χ^2 tests for parametric data and Wilcoxon rank-sum and Fisher's exact tests for non-parametric data. Analyses of outcomes of the six-week clinical trial were performed using mixed-effects Poisson regression, linear regression, Wilcoxon signed-rank tests, and Fisher's exact tests. Regression models used robust standard errors to account for the repeated measures on each subject.

We performed a non-inferiority test to evaluate whether naltrexone + MPH was significantly non-inferior to placebo + MPH in the treatment of ADHD. As described by Walker at al., (2011) we used a non inferiority analysis vs. a simple t-test comparison of difference since we were not testing whether the two therapies were different but whether methylphenidate with naltrexone was inferior to methylphenidate without naltrexone. First we defined our non-inferiority margin as a difference of five points between naltrexone + MPH and placebo + MPH in total score on

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the Adult ADHD Investigator Symptom Report Scale (AISRS[4]). We chose a five-point difference because we estimated that this would represent a small clinical difference. We then used a t-test to compare the difference score with the non-inferiority margin to show that the difference between the two groups was greater than the margin. To further show this, we compared the lower bound of the 95% confidence interval with the non-inferiority margin.

All tests were two-tailed and performed at the 0.05 alpha level. We did not control for any demographic or clinical characteristics since none reached statistical significance. Analyses were performed using Stata® (version 14).

4. Present Results to Professional Meetings and Write Primary and Secondary Manuscripts (Months 30-36)

Please refer to Section VI: Publications, Abstracts, and Presentations

IV: Key Research Accomplishments

- In total, 64 subjects were consented to complete screening procedures, and 38 subjects experienced the stimulant-induced euphoria needed to move on to the main arm of the trial. A total of 31 subjects completed the Week 3 Drug Feeling Visit, which is the midpoint of the study and the point at which subjects' data is useful for analysis. As this trial aimed to collect data from 30 subjects, we exceeded this goal.
- Clinical Point: The addition of naltrexone to methylphenidate significantly diminished the euphoric effect of an acute bolus of a supra therapeutic dose of immediate release (IR)-MPH during the titration phase (first three weeks) but not the stabilization phase (weeks 4-6) of Spheroidal Oral Drug Absorption System (SODAS)-MPH treatment.
- Clinical Point: The euphoric response to the acute bolus supra therapeutic dose of immediate release (IR)-MPH was significantly decreased at week 3 regardless of naltrexone. This finding is consistent with the hypothesis that chronic treatment with MPH is associated with some desensitization to IR-MPH associated euphoria. Yet, it is noteworthy that despite the lower euphoric response to IR-MPH at week three, naltrexone was associated with a further decrease in euphoric response.
- Clinical Point: The addition of naltrexone to methylphenidate did not interfere with the clinical effectiveness of methylphenidate for ADHD symptoms

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- The findings from this study provide support for the concept of combining opioid receptor antagonists with stimulants to provide an effective stimulant formulation with less abuse potential.
- This study has to date resulted in one accepted manuscript, two accepted abstracts, and one additional manuscript currently in preparation

Section V: Conclusion

While stimulant medicines are documented effective treatments of ADHD across the lifecycle, persistent concerns remain about their abuse potential that greatly inhibit their therapeutic use in clinical practice. Unfortunately, untreated ADHD is associated with high levels of impairment and disability that can profoundly adversely impact the lives of those affected during and after their military service. These include difficulties performing complex and demanding cognitive tasks under time constraints as required in the military, deficits in impulsivity, distractibility and emotional regulation that could endanger the life of the affected soldier and his or her peers, deficits in the interactions with peers and superiors, emotional impulsivity that could lead to low self esteem, substance abuse, criminality and accidents [1].

ADHD also affects veterans. Upon returning to civilian life, military personnel face many hurdles in redefining their role in society and securing employment. ADHD can certainly affect the ability to negotiate this transition. One stark example of this very issue is a study of homeless veterans that found that the majority (50/80) had ADHD [2]. Thus, the safe and effective treatment of ADHD is of great importance for military personnel after active service.

In addition to causing serious problems for enlisted personnel and veterans, ADHD is also a serious problem for military families. Since ADHD is estimated to afflict up to 10% of children, a sizable number of servicemen's children may be afflicted with ADHD and suffer from its adverse impacts on the family and school. Such concerns may distract the enlisted man and interfere with the soldier's ability to perform his or her duties effectively during their absence from home. Thus, safe and effective treatment for ADHD can have a substantial, direct

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benefit to the families of servicemen and the piece of mind of the enlisted soldier.

Stimulants have long been used by the military for non-ADHD indications in the context of sleep loss and stress to diminish fatigue and motion sickness [3] as well as enhance alertness of pilots during lengthy flight [4, 5] as well as to enhance the abilities, marksmanship, cognitive performance and mood of soldiers [6-8].

Yet, despite their clear and unequivocal benefits, stimulants can also be abused. For example, in a study of almost 20,000 army inductees, 12 % (2,369) reported that they had used amphetamines prior to enlistment. This number represented 38% of all cases of drug use [9]. Further surveys indicate that 10 % of military personnel abuse stimulants during active duty [10] and there is increasing concern that stimulant misuse is often from diverted prescriptions. The concern about abuse potential of stimulants is compounded by the fact that ADHD is a known risk factor for drug and alcohol abuse and dependence [11]. Hence a safe stimulant formulation free of abuse potential would allow for effective treatment of ADHD for active military personnel, their children as well as veterans without concerns about misuse, abuse and diversion.

In addition to other researchers, we have documented that stimulants mediate abuse through their effects on brain opioid receptors [12]. This insight allowed us to posit a novel pharmacological approach to help mitigate the emergence of stimulant-associated abuse through blocking opiate receptors with Naltrexone, an opiate receptor antagonist.

This double-blind, randomized clinical trial showed that naltrexone significantly diminished the euphoric effect of immediate release (IR) MPH during the titration phase (first three weeks) but not the stabilization phase, (weeks 4 to 6) of Spheroidal Oral Drug Absorption System (SODAS)–MPH treatment. The titration phase of open label treatment with SODAS-MPH appears to be a period of heightened vulnerability for such effects. These findings are consistent with prior work by us and Volkow et al. that emphasized the importance of the rate of delivery of stimulants to the brain for abuse liability [14-16]. Also consistent with this notion is the finding that naltrexone had little effect on euphoria during the last 3 weeks of the trial in which subjects remained on a stable optimized therapeutic dose of SODAS-MPH. Also

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noteworthy is the finding that the euphoric response to the acute bolus supra therapeutic dose of IR-MPH was significantly decreased at week 3 regardless of naltrexone. This finding is consistent with the hypothesis that chronic treatment with MPH is associated with some desensitization to IR-MPH associated euphoria. Yet, it is noteworthy that despite the lower euphoric response to IR-MPH at week three, naltrexone was associated with a further decrease in euphoric response. These findings extend to humans preclinical findings showing that naltrexone may mitigate stimulant-associated euphoria.

In addition, this double-blind, randomized clinical trial showed that the combination of naltrexone with methylphenidate (MPH) was highly effective in the treatment of ADHD and was well tolerated. The observed benefits were indistinguishable in subjects receiving MPH with and without naltrexone: AISRS scores decreased from a highly symptomatic score of 38.4±9.1 at baseline to a score of 10.5±5.7 at endpoint, which corresponds to scores associated with remission of ADHD symptoms. While the high degree of effectiveness of MPH in reducing ADHD symptoms has been documented in the literature [13], it has never before been documented with the concomitant administration of naltrexone with MPH. Thus, these results show that the co-administration of naltrexone does not diminish the benefits expected with MPH treatment.

If confirmed, these results could pave the way for the development of a non-abusable, highly effective novel formulation of a non-addictive stimulant treatment for ADHD. Such a treatment could have profound benefits to enlisted soldiers, veterans and their families, their treating physicians, and the military at large.

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Section VI: Publications, Abstracts, and Presentations

Accepted Manuscripts

Spencer TJ, Bhide P, Zhu J, Faraone SV, Fitzgerald M, Yule A, Uchida M, Spencer A, Hall A, Koster A, Biederman J. Do Opiate Antagonists Interfere with the Clinical Benefits of Stimulants in ADHD? A Double Blind, Placebo Controlled Trial of the Mixed Opioid Receptor Antagonist Naltrexone. Journal of Clinical Psychiatry. In Press, 2017.

Manuscript in Submission:

Spencer TJ, Bhide P, Zhu J, Faraone SV, Fitzgerald M, Yule A, Uchida M, Spencer A, Hall A, Koster A, Feinberg L, Kassabian S, Storch B, Biederman J. Does the Mixed Opioid Receptor Antagonist Naltrexone Mitigate Stimulant- Induced Euphoria: A Double Blind, Placebo Controlled Trial of Naltrexone.

Abstracts accepted:

Spencer TJ, Bhide P, Zhu J, Faraone SV, Fitzgerald M, Yule A, Uchida M, Spencer A, Hall A, Koster A, Biederman J. Do Opiate Antagonists Interfere with the Clinical Benefits of Stimulants in ADHD? A Double Blind, Placebo Controlled Trial of the Mixed Opioid Receptor Antagonist Naltrexone. Scientific proceedings of the 8th Annual Mass General Hospital for Children, Research Day, Boston, March 29th, 2016.

Spencer TJ, Bhide P, Zhu J, Faraone SV, Fitzgerald M, Yule A, Uchida M, Spencer A, Hall A, Koster A, Biederman J. Effect of an Opioid Receptor Antagonist on Stimulant treatment of Adults with ADHD. Scientific proceedings of the 60th Congress of Asociación Española de

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Psiquiatría del Niño y el Adolescente and American Academy of Child and Adolescent Psychiatry, San Sebastian, Spain, June 2016

Section VII: Inventions, Patents, and Licenses

No new patent was developed from this grant. However much of the work was based on a pre-existing US Patent Application. Dr. Spencer and colleagues have a prior US Patent Application pending (Provisional Number 61/233,686), through MGH corporate licensing, on a method to prevent stimulant abuse entitled: Effects of Co-administration of Central Nervous System Stimulants and Opioid Receptor Antagonists.

Section VIII: Reportable Outcomes

- 31 subjects completed the Week 3 Drug Feeling Visit (the point at which their subject data was useful for analysis), exceeding the original goal of 30 subjects.
- The data from these subjects were subsequently analyzed, and resulted in one accepted manuscript, one manuscript in submission, and two accepted abstracts to date.
- The findings offer important information about the co-administration of naltrexone and MPH, in this case that co-administration of naltrexone significantly diminished the euphoric effect of immediate release (IR) MPH during the titration phase (first three weeks) but not the stabilization phase (weeks 4 to 6) of Spheroidal Oral Drug Absorption System (SODAS)-MPH treatment. In addition, co-administration of naltrexone does not significantly reduce the clinical effectiveness of MPH. Thus, the findings from this study could aid in the development of an abuse-free stimulant, a non-addictive ADHD treatment that could have benefits to many populations, including but not limited to enlisted soldiers, veterans and their families, their treating physicians, and the military at large.

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Section IX: Other Achievements

Nothing to report

Section X: References

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16. Volkow ND. Stimulant medications: how to minimize their reinforcing effects? Am J Psychiatry. 2006 Mar;163(3):359-61. PubMed PMID: 16513852

Section XI: Appendices

Documentation of all Study Amendments through February 2017

AME 1	IRB Approval: 8/29/12
Approves revised Consent Form (1): 1. Changing study coordinator contact information; 2. Correcting minor formatting inconsistencies; 3. Clarifying that subjects will be taking Naltrexone (or placebo) once daily for the entire study, but will be taking SODAS-MPH twice daily for the entire study; 4. Removing reference to "study diaries" as subjects will not complete diaries as part of this trial.	
AME 2	IRB Approval: 9/28/12
Added: Ariana Koster as a Research Coordinator/Mgr	
AME 3	IRB Approval: 11/2/12
Approves revised Protocol Summary and Detailed Protocol decreasing the dose of naltrexone to 25 mg daily if the 50 mg dose is not well tolerated.	
AME 4	IRB Approval: 11/15/13
Added: Jefferson Prince MD as a Co-Investigator. Removed: Anela Bolfek MD	
AME 5	IRB Approval: 11/28/12
Approves revised Detailed Protocol (dated 06/15/2012) and Consent Form (1): 1. Changing the IR-MPH dosing to single-blind on the first likability assessment day (pre-baseline) only. The IR-MPH dosing will remain double-blind at the week 3 and week 6 likability assessments; 2. Adding handout "Likability Assessment Day Instructions;" 3. Executing the clinical blood labs on the first likability assessment day instead of at the initial visit.	
AME 6	IRB Approval: 12/7/12
Notification that the Certificate of Confidentiality CC-MH-12-184 (dated 10/23/2012) has been approved by the NIMH.	

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AME 7	IRB Approval: 12/29/12
1. Increase of age range for eligible participants from 18-24 to 18-30. 2. Subjects will be seen at a Massachusetts General Hospital outpatient site located at 55 Fruit St. WRN 705. Boston, MA 02114, instead of at 185 Alewife Brook Pkwy, Suite 2000. Cambridge, MA 02139. -A revised Detailed Protocol, Protocol Summary (Version Date: 12/04/2012), and one Informed Consent (Version Date: 12/04/2012) reflect the changes made.	
AME 8	IRB Approval: 1/2/13
Added: Andrea Spencer MD & Mai Uchida MD as Co-Investigators.	
AME 9	IRB Approval: 2/5/13
Approves use of "Addiction Research Center Inventory -- Subject" form to be completed by the participant after completing the DQRS.	
AME 10	IRB Approval: 2/4/13
Added: Emma Issenberg as a Reg. Coordinator/mgr. Removed: Paul Hammerness MD	
AME 11	IRB Approval: 3/20/13
Added: Christopher Keary as a Co-Investigator	
AME 12	IRB Approval: 3/14/13
Updated the Consent Form with the Principal Investigator's current contact phone number and reworks the description of the office location to improve clarity (p.2).	
AME 13	IRB Approval: 7/16/13
Added: Rebecca Grossman as a Research Assistant.	
AME 14	IRB Approval: 8/13/13
Approves posting for the MGH Clinical Trials Website and Broadcast emails, images and text for Facebook advertising, and a Facebook Ad Landing Page (the internet webpage that will open if potential subject clicks on the Facebook advertisement).	
AME 15	IRB Approval: 9/19/13
Added: Olivia Bogucki, Stephannie Furtak, Brittany Hughes, Tara Kenworthy, Amanda Pope, and Courtney Zulauf as research assistants. Removed: Emma Issenberg and Katie McDermott from study staff.	

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AME 16 IRB Approval: 10/15/13

1. Approves the option of breaking up the first screening visit so that it can be completed over the course of several days
2. Updates protocol documents to accurately reflect that Joseph Gonzalez-Heydrich, M.D. is the DSMB chair, not Marlene Freeman, M.D.
3. Corrects an error on the Consent Form that states that subjects will know whether they are receiving IR-methylphenidate or placebo on the Drug Feeling Visit. Subjects will not know whether they receive the active drug or placebo
4. Updates the length of the Drug Feeling Visit indicated on the Consent Form from 8 hours to 10-11 hours
5. Removes the text on the Consent Form stating that the Drug Feeling Day will take place within a month of the first Screening Visit
6. Updates study documents to include contact information for Dr. Andrea Spencer, an additional study clinician.

AME 17 IRB Approval: 12/2/13

Approves the addition of urine drug screens based on clinician assessment of the subject's drug use history and concerns of the subject using drugs after the initial screen. These additional urine drug screens may be conducted as frequently as each study visit and, like the baseline urine drug screen, will be confidential, labeled only with coded identifiers, and will be kept separate from the subject's medical record.

AME 18 IRB Approval: 1/17/14

Approves revised Protocol Summary and Detailed Protocol allowing subjects to complete visits 4, 5, 7, and 8 by phone and subjects may not complete two consecutive visits by phone. Consistent with office visits, all rating scales and assessments will be complete by a licensed psychiatrist during study phone visits, with the exception of collecting vital signs.

AME 19 IRB Approval: 2/3/14

Approves revised Protocol Summary (dated 02/03/2014), Detailed Protocol (dated 02/03/2014), and Consent Form (dated 02/03/2014) updating the Demographic Interview to be collected using a new form.

AME 20 IRB Approval: 3/12/14

Removes Jefferson Prince, M.D. from study staff.

AME 21 IRB Approval: 5/6/14

Adds Leah Feinberg to study staff as the Regulatory Coordinator/Manager.

AME 22 IRB Approval: 5/29/14

Adds Brittany Albright, M.D. to study staff as a Co-Investigator.

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AME 23	IRB Approval: 6/22/14
Added Lauren Rhodewalt to study staff as a Research Assistant.	
AME 24	IRB Approval: 7/14/14
Added Anna Hall to study staff as Clinical Research Coordinator.	
AME 25	IRB Approval: 7/24/14
Updated funding information in EPIC, the new healthcare software.	
AME 26	IRB Approval: 7/28/14
Added Jessica Abrams to study staff as a Research Assistant and removes Rebecca Grossman.	
AME 27	IRB Approval: 7/31/14
Added Nicholas Carrellas, Kristina Conroy, Jacqueline Davis, Emily Grimsley, and Natalie Plascencia to study staff as Research Assistants. Also added Amy Yule MD to study staff as Co-Investigator.	
AME 28	IRB Approval: 9/8/14
Added James Chan to study staff as a Statistician.	
AME 29	IRB Approval: 12/8/14
1. Correct inaccuracies in the descriptions and citations for the cognitive assessments in the detailed protocol. 2. Update consent form and protocol: Use data from a subject's previous structured clinical interview or cognitive-neuropsychological exam if the assessment has been completed in the past year as part of another study 3. Update the Consent Form and recruitment material to reflect the contact information for the study's new coordinator. 4. Update the Consent Form, detailed protocol, and protocol summary to reflect that participation in the study and information related to general medical care may be added to the subject's electronic medical record. 5. Update the Consent Form, detailed protocol, and protocol summary to allow subjects the option to receive text message appointment reminders. 6. Update the study population in the description of the study in the online IRB platform to reflect the age range in the inclusion criteria, which were already updated in all other study documents in Amendment 7 (12/29/12).	
AME 30	IRB Approval: 12/17/14
Removed Daniel Grossman and Arrielle Bressler Lopez. Added to study staff Sarah Kassabian and Jennifer Wicks as Research Assistants, as well as Atilla Ceranoglu MD and Jane Viner MD as Co-Investigators.	

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AME 31	IRB Approval: 3/6/15
Removed Christopher Keary MD from study staff.	
AME 32	IRB Approval: 4/14/15
Removed Stephanie Furtak from study staff.	
AME 33	IRB Approval: 6/17/15
1. Correcting inaccuracies in the descriptions and citations for the cognitive assessments; 2. Explicitly stating that subjects may request to receive the results of their cognitive testing; 3. Approves Cognitive Results Letter (Regular) Cognitive Results Letter (poor); 4. Changing the protocol status to Closed to Enrollment: All research activities complete, long term follow-up only.	
AME 34	IRB Approval: 6/26/15
Removed Emily Grimsley, Brittany Hughes, Tara Kenwtorthy, Amanda Pope	
AME 35	IRB Approval: 2/9/16
Removed Brittany Albright and James Chan	
AME 36	IRB Approval: 8/8/16
Added Barbara Storch to study staff as Research Coordinator/Manager	
AME 37	IRB Approval: 8/25/16
Added Alexa Pulli to study staff as Regulatory Coordinator/Manager Removed Leah Feinberg and Anna Hall	
AME 38	IRB Approval: 10/26/16
Removed Kristina Conroy, Jacqueline Davis, Natalie Plasencia, Lauren Rhodewalt, Dr. Andrea Spencer	

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Table A: Enrollment Report

Self-Reported Ethnicity and Gender of All Enrolled Subjects				
Ethnic Category	**Males**	**Females**	**Unknown**	**Total**
Hispanic or Latino	5	4	0	9**
Not Hispanic or Latino	22	33	0	55
Unknown (individuals not reporting ethnicity)	0	0	0	0
Totals of All Enrolled Subjects*	27	37	0	64*
***Ethnic and Racial Categories: These totals must agree.**				

Self-Reported Race and Gender of All Enrolled Subjects				
Racial Categories	**Males**	**Females**	**Unknown**	**Total**
American Indian/Alaska Native	0	0	0	0
Asian	2	2	0	4
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	3	4	0	7
White	19	29	0	48
More than one race	1	2	0	3
Unknown or not reported	2	0	0	2
Totals of All Enrolled Subjects*	27	37	0	64*
***Ethnic and Racial Categories: These totals must agree.**				

Self-Reported Race and Gender of All Enrolled Hispanic or Latino Subjects				
Racial Categories	**Males**	**Females**	**Unknown**	**Total**
American Indian or Alaska Native	0	0	0	0
Asian	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	1	0	0	1
White	2	3	0	5
More than one race	0	1	0	1
Unknown or not reported	2	0	0	2
Totals of Enrolled Hispanic or Latino Subjects**	5	4	0	9**
****Hispanic or Latino Ethnic and Hispanic or Latino Race Enrollment Reports: These totals must agree.**				

Ethnic and Racial Definitions for the Minimum Standard Categories Above	
Hispanic or Latino:	A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.
American Indian or Alaska Native:	A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
Asian:	A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent.
Native Hawaiian or Other Pacific Islander:	A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
Black or African American:	A person having origins in any of the black racial groups of Africa.
White:	A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Table B: Adverse Events Log

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Adverse Event Tracking Log

Adverse events are "any untoward or unfavorable medical occurrence in a human subject including any abnormal sign, symptom or disease,...whether or not associated with the subject's participation in the research". **Internal** adverse events that are **unexpected** and **related/possibly related** to the research and **external** adverse events that are **serious, unexpected and related/possibly related** must be reported to the IRB within 5 working days/7 calendar days of the date the investigator first become aware of them. Adverse events that are **expected** i.e., documented in the protocol are not reported to the IRB. For investigator-monitored studies a cumulative report of all adverse events must be submitted at continuing review.

Instructions: This log facilitates tracking and timely reporting of all applicable adverse events according to **PHRC Reporting Unanticipated Problems including Adverse Events policy**: http://healthcare.partners.org/phsirb/Guidance/Reporting_Unanticipated_Problems_including_Adverse_Events.1.11.pdf. A key for recording adverse event data is attached to this log. **NOTE: Entries in the log must be typed.**

Investigator:	Thomas Spencer, M.D.
Study Title:	Prevention of Stimulant Induced Euphoria with an Opioid Receptor Antagonist
Protocol #:	2012-P-000918

Subject ID	Date of Adverse Event	Description of Event	Location	Severity	Expectedness	Relatedness	Requires Changes /Corrective Action	Date Reported To PHRC, If Applicable
1770701	7/16/13	Stomache discomfort due to food	Internal	Mild	Expected	Unrelated	None	N/A
1770401	7/29/13	Seasonal Allergies	Internal	Mild	Expected	Unrelated	Pharmacologic	N/A
1770901	7/29/13	Headache	Internal	Mild	Expected	Unrelated	Pharmacologic	N/A
1770401	8/3/13	Increased Energy	Internal	Mild	Expected	Probable	None	N/A
1770401	8/3/13	Agitated/Irritable	Internal	Mild	Expected	Probable	None	N/A
1770701	8/3/13	Mild Headache in afternoon	Internal	Mild	Expected	Possible	None	N/A
1770401	8/13/13	Mild Abdominal Discomfort	Internal	Mild	Expected	Probable	None	N/A
1770701	8/15/13	Trouble falling asleep	Internal	Mild	Expected	Possible	None	N/A
1770701	8/15/13	Cough-Bronchitis	Internal	Moderate	Unexpected	Unrelated	None	N/A
1770401	8/19/13	Headache	Internal	Moderate	Expected	Unrelated	None	N/A
1770501	8/19/13	Headache	Internal	Mild	Expected	Unrelated	Pharmacologic	N/A
1770701	8/23/13	Difficulty Falling Asleep	Internal	Mild	Expected	Probable	None	N/A
1770701	8/24/13	Delayed Sleep	Internal	Mild	Expected	Possible	None	N/A
1770401	8/29/13	Headache Pain 5/10	Internal	Moderate	Expected	Possible	None	N/A
1770701	8/29/13	Cheek Biting	Internal	Mild	Expected	Possible	Pharmacologic	N/A
1770701	9/5/13	Cheek Biting	Internal	Mild	Expected	Possible	None	N/A
1770401	9/6/13	Headache When sstopped coffee	Internal	Moderate	Expected	Possible	None	N/A
1770401	9/14/13	Decreased Energy. Hard to get up in AM	Internal	Moderate	Expected	Possible	None	N/A
1770601	9/17/13	Insomnia- Difficulty Falling Asleep	Internal	Severe	Expected	Definitely	Pharmacologic + Altered Dose/Changed schedule	N/A
1770601	9/17/13	Early Waking	Internal	Mild	Expected	Possible	None	N/A
1770601	9/17/13	Less hungry than usual	Internal	Mild	Expected	Probable	None	N/A
1770601	9/17/13	Shakey Feeling	Internal	Moderate	Expected	Probable	Altered Dose/Changed Schedule	N/A
1770601	9/17/13	"Pressure"	Internal	Severe	Expected	Probable	Altered Dose/Changed Schedule	N/A
1770601	9/17/13	Just Nausea	Internal	Mild	Expected	Probable	None	N/A
1770601	9/17/13	Back Pain	Internal	Mild	Unexpected	Unrelated	None	N/A
1771001	9/17/13	More irritated than normal	Internal	Moderate	Expected	Possible	None	N/A
1771001	9/17/13	Decreased Appetite	Internal	Mild	Expected	Probable	None	N/A
1771001	9/17/13	Headache	Internal	Mild	Expected	Possible	Pharmacologic	N/A
1770601	9/23/13	Decreased Appetite	Internal	Mild	Expected	Possible	None	N/A
1770601	9/23/13	Middle Insomnia (waking up before alarm	Internal	Mild	Expected	Possible	None	N/A
1770801	9/23/13	hospitalized for enlarged lymph nodes throughout the abdominal cavity	Internal	Severe	Unexpected	Unrelated	Terminated From Trial	9/23/13

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Subject ID	Date of Adverse Event	Description of Event	Location	Severity	Expectedness	Relatedness	Requires Changes /Corrective Action	Date Reported To PHRC, If Applicable
1771001	9/24/13	anxious/worried	Internal	Mild	Expected	Possible	Altered Dose/Changed Schedule	N/A
1771001	9/24/13	Headache	Internal	Mild	Expected	Possible	Altered Dose/Changed Schedule	N/A
1770601	10/5/13	Increased Energy	Internal	Mild	Expected	Possible	None	N/A
1771001	10/11/13	Tense/Jittery	Internal	Moderate	Expected	Probable	Non-Pharmacological	N/A
1771001	10/11/13	Insomnia- Restless Sleep	Internal	Mild	Expected	Probable	None	N/A
1771001	10/18/13	Sad/Down	Internal	Moderate	Expected	Possible	None	N/A
1771001	10/18/13	Insomnia- Restless Sleep	Internal	Mild	Expected	Probable	None	N/A
1771001	10/18/13	Tense/Jittery	Internal	Moderate	Expected	Probable	None	N/A
1771001	10/18/13	Headache	Internal	Mild	Expected	Unrelated	Pharmacologic	N/A
1771001	10/18/13	Nausea	Internal	Mild	Expected	Unrelated	Pharmacologic	N/A
1771001	10/26/13	Insomnia- Restless Sleep	Internal	Moderate	Expected	Possible	Terminated From Trial	N/A
1771001	10/26/13	Sad/Down	Internal	Severe	Expected	Probable	Terminated From Trial	N/A
1771001	10/26/13	Nausea	Internal	Moderate	Expected	Probable	Terminated From Trial	N/A
1770601	10/27/13	Nausea	Internal	Moderate	Expected	Probable	None	N/A
1771401	10/27/13	Increased GI Activity	Internal	Mild	Expected	Probable	None	N/A
1771701	11/12/13	Takes 15 min to fall asleep	Internal	Mild	Expected	Probable	None	N/A
1771701	11/25/13	Nausea following sleep deprivation	Internal	Moderate	Expected	Probable	None	N/A
1771401	11/26/13	Heart beating fast on first day of meds. Tookd meds w/out food	Internal	Mild	Expected	Probable	None	N/A
1772701	12/7/13	Tingliness in extremities and pressure in head	Internal	Mild	Expected	Probable	None	N/A
1771401	12/13/13	Insomnia	Internal	Mild	Expected	Probable	None	N/A
1772401	12/19/13	Mild nausea when took medication without food	Internal	Mild	Expected	Probable	None	N/A
1772201	12/20/13	Felt anxious several hours following Ritalin IR administration although improved within a few hours	Internal	Mild	Expected	Probable	None	N/A
1772501	12/20/13	Tense/Jittery feeling in chest	Internal	Moderate	Expected	Probable	None	N/A
1772501	12/20/13	Dry mouth	Internal	Mild	Expected	Probable	None	N/A
1772201	12/23/13	1 hr nausea (resolve on own)	Internal	Mild	Expected	Possible	None	N/A
1772701	12/23/13	Mild Nausea after taking PM dose	Internal	Mild	Expected	Probable	None	N/A
1772201	1/2/14	Anxious/Worried at night	Internal	Moderate	Expected	Probable	None	N/A
1772201	1/2/14	Nausea between doses	Internal	Mild	Expected	Probable	None	N/A
1772701	1/3/14	Nausea	Internal	Mild	Expected	Probable	None	N/A
1772701	1/3/14	Sad/Down	Internal	Moderate	Expected	Probable	None	N/A
1772501	1/21/14	Emotional Dreams	Internal	Mild	Expected	Unlikely	None	N/A
1772501	1/21/14	anxious/worried	Internal	Mild	Expected	Probable	None	N/A
1772101	1/25/14	Stomach Cramp/Upset stomache	Internal	Mild	Expected	Possible	None	N/A
1772201	1/25/14	anxious/worried in AM	Internal	Moderate	Expected	Probable	None	N/A
1772201	1/25/14	Insomnia	Internal	Moderate	Expected	Probable	None	N/A
1772501	1/25/14	Tense/Jittery when took meds without food	Internal	Moderate	Expected	Probable	None	N/A
1772701	1/25/14	Nausea	Internal	Moderate	Expected	Probable	None	N/A
1772701	1/25/14	Decreased Energy at end of day	Internal	Moderate	Expected	Probable	None	N/A
1773401	1/25/14	Tense/Jittery for a few hours	Internal	Mild	Expected	Probable	None	N/A

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Subject ID	Date of Adverse Event	Description of Event	Location	Severity	Expectedness	Relatedness	Requires Changes /Corrective Action	Date Reported To PHRC, If Applicable
1772001	2/11/14	Going to bed a bit later	Internal	Mild	Expected	Definitely	None	N/A
1773101	2/11/14	Nausea	Internal	Mild	Expected	Probable	None	N/A
1773101	2/11/14	Decreased Energy	Internal	Mild	Expected	Probable	None	N/A
1773101	2/11/14	Agitated/Irritable	Internal	Mild	Expected	Probable	None	N/A
1773401	2/11/14	Slight indigestion feeling	Internal	Mild	Expected	Probable	None	N/A
1772001	2/18/14	Palpitations	Internal	Mild	Expected	Probable	Non-Pharmacological	N/A
1773401	2/19/14	Insomnia	Internal	Mild	Expected	Probable	None	N/A
1773101	2/25/14	"feeling warm"	Internal	Mild	Expected	Possible	None	N/A
1772001	3/8/14	pulse increase	Internal	Mild	Expected	Possible	Altered Dose/Changed Schedule	N/A
1772001	3/8/14	Insomnia	Internal	Mild	Expected	Possible	None	N/A
1773101	3/8/14	"feels hot"	Internal	Mild	Expected	Possible	None	N/A
1773501	3/10/14	jitteriness x36hours	Internal	Moderate	Expected	Probable	None	N/A
1773501	3/10/14	Sweating at night	Internal	Moderate	Expected	Probable	None	N/A
1773501	3/10/14	Decreased Appetite	Internal	Mild	Expected	Probable	None	N/A
1773301	3/13/14	Dry mouth	Internal	Mild	Expected	Probable	None	N/A
1773501	3/18/14	Poor Appetite	Internal	Mild	Expected	Probable	Altered Dose/Changed Schedule	N/A
1773501	3/18/14	Pain from injured toe	Internal	Mild	Unexpected	Unrelated	None	N/A
1773501	3/18/14	Tense/Jittery	Internal	Mild	Expected	Probable	None	N/A
1773101	3/20/14	flushed at times	Internal	Mild	Expected	Probable	None	N/A
1773301	3/21/14	Nausea	Internal	Mild	Expected	Probable	None	N/A
1773301	3/21/14	Headache	Internal	Mild	Expected	Possible	None	N/A
1773301	3/29/14	dry mouth	Internal	Mild	Expected	Probable	Altered Dose/Changed Schedule	N/A
1773301	3/29/14	Headache	Internal	Moderate	Expected	Possible	Pharmacologic + Altered Dose/Changed schedule	N/A
1773301	3/29/14	Insomnia	Internal	Mild	Expected	Possible	None	N/A
1773301	4/4/14	Headache	Internal	Mild	Expected	Probable	Pharmacologic	N/A
1773501	4/10/14	"Crash" at end of day	Internal	Mild	Expected	Possible	Altered Dose/Changed Schedule	N/A
1773301	4/14/14	Palpitations	Internal	Mild	Expected	Probable	None	N/A
1774201	6/10/14	Nausea	Internal	Mild	Expected	Possible	None	N/A
1774701	6/10/14	eye twitch	Internal	Mild	Expected	Possible	None	N/A
1774701	6/10/14	insomnia	Internal	Mild	Expected	Probable	None	N/A
1774701	6/10/14	Headache	Internal	Mild	Expected	Possible	None	N/A
1774501	6/12/14	nausea/ vomiting	Internal	Moderate	Expected	Probable	Terminated From Trial	N/A
1774201	6/17/14	Tense/Jittery	Internal	Moderate	Expected	Possible	None	N/A
1774201	6/17/14	sedation	Internal	Moderate	Unexpected	Possible	None	N/A
1774201	6/17/14	Mentral Cramps	Internal	Moderate	Unexpected	Unrelated	Pharmacologic	N/A
1774701	7/3/14	Increased sweating	Internal	Moderate	Expected	Possible	None	N/A
1774701	7/3/14	Insomnia	Internal	Mild	Expected	Probable	None	N/A
1774701	7/17/14	Increased sweating	Internal	Mild	Expected	Possible	Altered Dose/Changed Schedule	N/A
1774801	7/29/14	Headache	Internal	Mild	Expected	Probable	Pharmacologic	N/A
1774801	7/29/14	Mucosal Dryness- dry mouth	Internal	Mild	Expected	Probable	None	N/A
1774801	8/7/14	Headache	Internal	Mild	Expected	Probable	None	N/A
1774801	8/7/14	Mucosal Dryness- dry mouth	Internal	Mild	Expected	Probable	None	N/A
1775201	8/19/14	Neurological- Numbness of right index finger	Internal	Mild	Unexpected	Unlikely	None	N/A
1774801	8/22/14	Mucosal Dryness- dry mouth	Internal	Mild	Expected	Probable	None	N/A

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Subject ID	Date of Adverse Event	Description of Event	Location	Severity	Expectedness	Relatedness	Requires Changes /Corrective Action	Date Reported To PHRC, If Applicable
1775101	8/28/14	Nausea/Vomit/Diarrhea (Gastrointestinal)- acute episode, likely food related, went to ER and received hydration	Internal	Moderate	Unexpected	Unlikely	Non-Pharmacological	N/A
1775201	9/5/14	Decreased Appetite	Internal	Mild	Expected	Possible	None	N/A
1775201	9/5/14	Nausea	Internal	Mild	Expected	Possible	None	N/A
1775201	9/5/14	Headache	Internal	Mild	Expected	Possible	Pharmacologic	N/A
1774301	9/9/14	Depressed mood	Internal	Mild	Expected	Probable	None	N/A
1775201	9/12/14	Nausea	Internal	Mild	Expected	Possible	None	N/A
1775201	9/12/14	Decreased Appetite	Internal	Mild	Expected	Possible	None	N/A
1775401	9/19/14	Mucosal Dryness- dry mouth	Internal	Mild	Expected	Probable	None	N/A
1774301	9/23/14	Headache- discomfort in temporal part of head	Internal	Moderate	Expected	Probable	Pharmacologic + Altered Dose/Changed schedule	N/A
1775201	9/27/14	Decreased Appetite	Internal	Moderate	Expected	Probable	Altered Dose/Changed Schedule	N/A
1775201	10/1/14	Headache	Internal	Mild	Expected	Possible	Pharmacologic	N/A
1775201	10/1/14	Decreased Appetite	Internal	Moderate	Expected	Probably	None	N/A
1774301	10/7/14	Muscoloskeletal- knee soreness from hiking	Internal	Moderate	Unexpected	Unrelated	Pharmacologic	N/A
1774301	10/7/14	Headache	Internal	Moderate	Expected	Probable	Altered Dose/Changed Schedule	N/A
1775301	10/15/14	Gastrointestinal- upper abdominal pain related to indigestion	Internal	Serious	Unexpected	Unrelated	Pharmacologic	N/A
1774301	10/17/14	Headache	Internal	Mild	Expected	Probable	None	N/A
1774301	10/31/14	Headache	Internal	Mild	Expected	Unlikely	Pharmacologic	N/A
1775001	11/7/14	Headache	Internal	Mild	Expected	Possible	None	N/A
1775001	11/14/14	Agitated/Irritable - irritability with boyfriend in late afternoon, 2 to 3 times per week, lasting 30 min	Internal	Mild	Unexpected	Possible	None	N/A
1776001	1/20/15	Cold/Infection/Allergy- Concern for upper respiratory infection	Internal	Mild	Unexpected	Unrelated	Pharmacologic	N/A
1775701	1/30/15	Headache	Internal	Moderate	Unexpected	Unlikely	Pharmacologic	N/A
1775701	2/4/15	Headache	Internal	Mild	Expected	Possible	Pharmacologic + Altered Dose/Changed schedule	N/A
1775701	2/4/15	Muscoloskeletal- Muscle tension	Internal	Mild	Expected	Possible	Pharmacologic + Altered Dose/Changed schedule	N/A
1775801	2/5/15	Headache	Internal	Mild	Expected	Unlikely	None	N/A
1775801	2/5/15	Anxious/worried	Internal	Mild	Expected	Probable	None	N/A
1775801	2/5/15	Other- "tingly" feeling in head and chest	Internal	Mild	Expected	Probable	None	N/A
1775801	2/5/15	Extra Pyramidal Sxs- Hands shaking	Internal	Mild	Expected	Probable	None	N/A
1776001	2/11/15	Insomnia- falling asleep	Internal	Mild	Expected	Possible	None	N/A
1775801	2/13/15	Headache	Internal	Mild	Expected	Unrelated	Pharmacologic	N/A
1775701	2/13/15	Decreased Appetite	Internal	Mild	Expected	Possible	None	N/A
1775701	2/13/15	Headache	Internal	Mild	Expected	Possible	Pharmacologic	N/A
1775801	2/19/15	Headache	Internal	Mild	Expected	Unlikely	Pharmacologic	N/A
1775801	2/19/15	Cold/Infection/Allergy- allergies	Internal	Mild	Unexpected	Unrelated	Pharmacologic	N/A
1775701	2/19/15	Decreased Appetite	Internal	Mild	Expected	Probable	None	N/A
1775701	2/19/15	Mucosal Dryness- thirst increased	Internal	Mild	Expected	Probable	None	N/A

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Subject ID	Date of Adverse Event	Description of Event	Location	Severity	Expectedness	Relatedness	Requires Changes /Corrective Action	Date Reported To PHRC, If Applicable
1775701	2/19/15	Nausea/Vomit/Diarrhea (Gastrointestinal)- stomach cramps today	Internal	Mild	Expected	Possible	None	N/A
1775701	2/19/15	Muscoloskeletal- Back pain	Internal	Mild	Unexpected	Unrelated	Pharmacologic	N/A
1775701	2/19/15	Dermatological- Cold sores	Internal	Mild	Unexpected	Unrelated	Pharmacologic	N/A
1775701	2/19/15	Muscoloskeletal- Muscle tension	Internal	Mild	Expected	Possible	None	N/A
1775701	2/25/15	Decreased Appetite	Internal	Mild	Expected	Probable	None	N/A
1775701	2/25/15	Nausea/Vomit/Diarrhea (Gastrointestinal)- gas related pain	Internal	Mild	Expected	Possible	None	N/A
1775801	2/26/15	Nausea/Vomit/Diarrhea (Gastrointestinal)- stomach growling	Internal	Mild	Expected	Possible	None	N/A
1775801	2/26/15	Cardiovascular- heart racing after increased dose	Internal	Mild	Expected	Probable	None	N/A
1775701	3/3/15	Headache	Internal	Mild	Expected	Probable	Altered Dose/Changed Schedule	N/A
1776201	3/3/15	Insomnia- took 1 to 2 hours to fall asleep	Internal	Mild	Expected	Unlikely	None	N/A
1776401	3/4/15	Insomnia- initially	Internal	Mild	Expected	Unrelated	Pharmacologic	N/A
1775801	3/6/15	Cold/Infection/Allergy- congestion headache	Internal	Mild	Expected	Unlikely	Altered Dose/Changed Schedule	N/A
1775701	3/10/15	Headache	Internal	Mild	Expected	Possible	None	N/A
1775701	3/10/15	Decreased Appetite	Internal	Mild	Expected	Probable	None	N/A
1775801	3/12/15	Headache	Internal	Moderate	Expected	Possible	Pharmacologic	N/A
1775801	3/12/15	Dizzy/Lightheaded- lightheaded	Internal	Moderate	Expected	Probable	Altered Dose/Changed Schedule	N/A
1776301	3/13/15	Insomnia	Internal	Mild	Expected	Possible	None	N/A
1776301	3/13/15	Nausea/Vomit/Diarrhea (Gastrointestinal)- nausea	Internal	Mild	Expected	Possible	None	N/A
1776301	3/13/15	Sad/Down- flat mood	Internal	Mild	Expected	Possible	None	N/A
1776101	3/17/15	Cold/Infection/Allergy- common cold	Internal	Mild	Expected	Unrelated	Pharmacologic	N/A
1775801	3/17/15	Headache	Internal	Moderate	Expected	Probable	Pharmacologic	N/A
1776401	3/20/15	Other- Menstrual cramps	Internal	Moderate	Unexpected	Unlikely	Pharmacologic	N/A
1776201	3/27/15	Insomnia- falling asleep once a week	Internal	Mild	Expected	Possible	None	N/A
1776401	3/28/15	Insomnia	Internal	Moderate	Expected	Probable	Altered Dose/Changed Schedule	N/A
1776401	4/3/15	Insomnia- difficulty falling asleep	Internal	Mild	Expected	Probable	None	N/A
1776301	4/10/15	Headache	Internal	Mild	Expected	Probable	None	N/A
1776401	4/10/15	Cold/Infection/Allergy- cough, nasal congestions	Internal	Mild	Unexpected	Unlikely	Pharmacologic	N/A
1776301	4/18/15	Headache	Internal	Mild	Expected	Probable	None	N/A

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Table C: Minor Deviations

Minor Deviations Tracking Log

Protocol deviations are any deviation from the IRB-approved protocol that are not approved prospectively by the IRB. **Major protocol deviations** are deviations from the IRB approved protocol that "has the potential to negatively impact subject safety, the integrity of study data or subject's willingness to participate in the study". **Minor protocol deviations** are deviations that do not have the potential to negatively impact subjects, their willingness to participate or data integrity. **Minor deviations include,** but are not limited to, protocol deviations such as out of window visits, missing tests/labs, missing original/signed consent form (copy exists), missing PI signature on consent form(s), use of expired/outdated consent form that includes all relevant information, over-enrollment, failure to submit continuing review prior to expiration of IRB approval.

Instructions: This log is to be used for tracking and reporting minor deviations according to Reporting Unapproved Deviations in PHRC-Approved Research policy: http://healthcare.partners.org/phsirb/Guidance/Reporting_Unapproved_Deviations_in_PHRC-Approved_Research.1.11.pdf. Minor deviations are to be reported **ONLY** at continuing review. **NOTE: Entries in the log must be typed**.

PI:	Thomas Spencer, M.D.
Protocol #	2012-P-000918
Title:	Prevention of stimulant Induced Euphoria with an Opioid Receptor Antagonist
Sponsor:	Department of Defense

Date Deviation Discovered	Date Deviation Occurred	Subject Study ID	Description of Deviation	Description of Corrective Action	Date Sponsor Notified	Date Sponsor Approved	Recorded by / Date
6/14/13	6/14/13	1770201	The blood draw was not completed on Drug Feeling visit after 2 different phlebotomy-trained RAs attempted to locate the subject's veins but were unable to.	Under instruction of the PI, we will continue without 1770201's blood sample. A note to file was prepared to explain this. While safety labs are usually completed at this visit, 1770201 did not meet criteria at the Drug Feeling Visit and therefore 1770201 will not be able to move to the randomized trial. Thus the safetly labs were not completed.	N/A	N/A	Ariana Koster 6/20/13
8/5/13	8/5/13	1770401	At the Drug Feeling Visit, subject 1770401 informed study staff last minute that he had to leave early and did not complete the final DRQS and ARCI.	Under direction of the PI, we will proceed without having the subject complete these rating scales. A note to file was prepared to explain the situation. The subject was reminded of the time commitment necessary to participate in the study.	N/A	N/A	Ariana Koster 8/5/14
8/24/13	8/24/13	1770401	The Blood draw was not completed on Drug Feeling visit after 2 different phlebotomy-trained RAs attempted to locate the subject's veins but were unable to	Under instruction of the PI, we will continue without 1770401's blood sample from this visit. A note to file was prepared to explain this. The missed blood draw did not include safety labs,	N/A	N/A	Ariana Koster 8/27/14
9/16/13	9/16/13	1770401	Subject 1770401refused to have his blood drawn for his week 6 visit as he did not want to have bruises on his arm.	Under instruction of the PI, will continue without 1770401 blood sample from this visit. The missed blood draw did not include safety labs.	N/A	N/A	Ariana Koster 9/17/13
9/17/13	7/16/13	1770701	Subject 1770701's screening procedures were completed over several visits.	This policy is consistent with other studies within the department and we have submitted an amendment to allow the screening procedures to be broken up over several days, going forward.	N/A	N/A	Ariana Koster 9/17/13
8/3/13	8/3/13	1770701	The Blood draw was not completed on Drug Feeling visit after 2 different phlebotomy-trained RAs attempted to locate the subject's veins but were unable to.	Under instruction of the PI, we will continue without 1770701's blood sample from this visit. 1770701 went to the MGH official lab to complete her safety labs for the visit after she was done with her study visit.A note to file was prepared to explain this.	N/A	N/A	Ariana Koster 9/17/13
9/17/13	8/2/13	1770601	Subject 1770601's screening procedures were completed over several visits.	This policy is consistent with other studies within the department and we have submitted an amendment to allow the screening procedures to be broken up over several days, going forward	N/A	N/A	Ariana Koster 9/17/13

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Date Deviation Discovered	Date Deviation Occurred	Subject Study ID	Description of Deviation	Description of Corrective Action	Date Sponsor Notified	Date Sponsor Approved	Recorded by / Date
8/24/13	8/24/13	1770401	Subject 1770401 informed study staff that he needed to leave his week 3/ Drug Feeling Visit early and therefore did not have a break between the morning and afternoon dosing, as approved by the PI	Study staff re-emphasized the importance of being present for the full study visits and asked 1770401 to confirm that he will be able to stay for the full study visits for the rest of the study.	N/A	N/A	Ariana Koster 9/17/13
10/2/01	10/2/13	1770501	Subject 1770501completed her 4th morning DQRS rating scale 37min late on her baseline Drug Feeling visit. 1770501did not notice the DQRS after completing the ARCI and study staff did not notice this oversight for 37 min.	The subject completed the rating scale as soon as the problem was noticed. Study staff were reminded to check to make sure all rating scales are completed at the appropriate times during the visit. A note to file was prepared to explain this.	N/A	N/A	Ariana Koster 10/5/13
10/3/13	10/3/13	1770501	Subject 1770501ate prior to arriving for her baseline Drug Feeling Visit	Study staff emphasized the importance of following the instructions for study visits. A note to file was prepared to document this	N/A	N/A	Ariana Koster 10/5/13
10/3/13	10/3/13	1770501	The Blood draw was not completed on Drug Feeling visit after 2 different phlebotomy-trained RAs attempted to locate the subject's veins but were unable to.	Under instruction of the PI, we will continue without 1770501 blood sample from this visit. 1770501 was instructed to go to the MGH official laboratory to complete her safety labs but was lost to follow up as study staff could not contact her after this visit. A note to file was prepared to document this.	N/A	N/A	Ariana Koster 10/5/13
10/5/13	10/5/13	1770601	Subject 1770601's week 3 visit was 12 days after her week 2 visit, outside of the 9-day visit window.	Study staff were reminded of the importance of scheduling study visits within 9 days of the last study visit. The subject was reminded to contact study staff with any study related problems between visits.	N/A	N/A	Ariana Koster 10/5/13
10/5/13	10/5/13	1770601	On Subject 1770601week 3 Drug Feeling Visit, the 2nd morning DQRS rating scale was not completed. 1770601 did not notice the DQRS after completing the first rating scale, and study staff did not realize that the rating scale was incomplete until it was time for the next rating scale.	Study staff were reminded to check to make sure all rating scales are completed at the appropriate times during the visit. A note to file was prepared to document this missing data.	N/A	N/A	Ariana Koster 10/5/13
10/25/13	10/25/13	1771001	Study clinician's CITI certification had expired when she completed a study visit.	The study clinician completed CITI re-certification on 10/27/2013. A note to file was prepared, and study staff were reminded of the importance of ensuring that all certifications are current.	N/A	N/A	Ariana Koster 10/25/13
10/25/13	10/25/13	1772001	Study clinician's CITI certification had expired when she completed a study visit.	The study clinician completed CITI re-certification on 10/27/2013. A note to file was prepared, and study staff were reminded of the importance of ensuring that all certifications are current.	N/A	N/A	Ariana Koster 10/25/13
10/25/13	6/14/13	1770201	The first and second screening visit were completed over a month apart	This policy is consistent with other studies within the department and we have submitted an amendment to allow this going forward.	N/A	N/A	Ariana Koster 10/25/13
10/25/13	10/2/13	1770301	The first and second screening visit were completed over a month apart	This policy is consistent with other studies within the department and we have submitted an amendment to allow this going forward.	N/A	N/A	Ariana Koster 10/25/13

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Date Deviation Discovered	Date Deviation Occurred	Subject Study ID	Description of Deviation	Description of Corrective Action	Date Sponsor Notified	Date Sponsor Approved	Recorded by / Date
10/25/13	10/2/13	1770501	The first and second screening visit were completed over a month apart	This policy is consistent with other studies within the department and we have submitted an amendment to allow this going forward.	N/A	N/A	Ariana Koster 10/25/13
10/27/13	10/27/13	1770601	Subject 1770601 did not complete a blood draw on her week 6 Drug Feeling Visit. Subject 1770601 became sick to her stomach the second hour after her morning dose. While subject 1770601 wanted to finish the study visit, she felt as though a blood draw would exacerbate her nausea and requested that we not draw her blood.	Since this blood draw is not essential for subject safety or the integrity of the study data, under the direction of the PI we will forgo the blood samples from this visit. A note to file was prepared to document this.	N/A	N/A	Ariana Koster 10/28/13
11/19/13	11/19/13	1770301	Subject 1770301's week 3 visit was 13 days after his week 2 visit, outside of the 9 day visit window.	Study staff were reminded of the importance of scheduling study visits within 9 days of the last study visit. The subject was reminded to contact study staff with any study related problems between visits.	N/A	N/A	Ariana koster 11/22/13
12/7/13	12/7/13	1772501	After subject Subject 1772501's screening visit, study staff 1772501 that her EKG had been incorrectly administered. We therefore readministered the EKG at the beginning of her Drug Feeling Visit, prior to administering the study drug.	The EKG was completed and signed off by a study physician prior to completing any Drug Feeling Visit tasks. Study staff was reminded to confirm that the EKG was properly administered before the end of the Screening visit visit. A note to file was prepared to document this.	N/A	N/A	Ariana Koster 12/11/13
12/12/13	12/12/13	1771201	At his first Drug Feeling Visit, subject 1771201 informed study staff last minute that he had to leave early and did not complete the final DRQS and ARCI.	As compliance during study visits has been a consistent problem for subject 1771201, study staff decided to terminate Subject 1771201 from the trial.	N/A	N/A	Ariana Koster 12/12/13
12/13/13	12/13/13	1771701	Subject 1771701's week 6 visit was 10 days after her week 5 visit, outside of the 9 day study window.	Study staff were reminded of the importance of scheduling study visits within 9 days of the last study visit. The subject was reminded to contact study staff with any study related problems between visits.	N/A	N/A	Ariana Koster 12/13/13
12/20/13	12/20/13	1772501	Subject 1772501was only able to complete part of her Cognitive Battery assessment during her week 0 visit as her visit with the clinician ran late and she had to leave for a previous engagement.	Subject 1772501 completed the rest of her Cognitive Battery assessment at her wk1 visit. Subject 1772501was reminded to budget sufficient time to complete all study tasks and to leave extra time in her schedule in case her visit runs late. A note to file was completed.	N/A	N/A	Ariana Koster 12/27/13
1/3/14	1/3/14	1772701	Subject 1772701's wk 2 visit occurred 11 days after his week 1 visit, outside the 9 day visit window.	Study staff were reminded of the importance of scheduling study visits within 9 days of the last study visit. The subject was reminded to contact study staff with any study related problems between visits.	N/A	N/A	Ariana Koster 1/3/14

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1/25/14	1/25/14	1772501	While subjects are asked to fast until the 3rd hour of the Drug Feeling Visit, on subject 1772501's wk6 visit/Drug Feeling Visit she expressed concerns that she would experience the same discomfort due to dry mouth that she had experienced on the previous Drug Feeling Visit. In an effort to cause as little discomfort to the subject as possible, study staff provided her with a sucking candy to consume if she experienced dry mouth.	Under direction of the doctor on site, study staff continued with the Drug Feeling Visit as usual and a note to file was completed explaining the situation.	N/A	N/A	Ariana Koster 2/5/14
1/25/14	1/25/14	1773101	The Blood draw was not completed on Drug Feeling visit after 2 different phlebotomy-trained RAs attempted to locate the subject's veins but were unable to.	Under instruction of the PI, we will continue without Subject 1773101's blood sample from this visit. A note to file was prepared. Study staff accompanied Subject 1773101's to the central MGH phlebotomy lab to complete her safety labs.	N/A	N/A	Ariana Koster 2/5/14
2/20/14	2/14/14	1773501	During his Cognitive Battery assessment, subject 1773501did not complete the 1st page of WRAT math as his scrap paper was covering the missed page.	Under direction of the PI we will proceed without this portion of the assessment as all necessary information for inclusion in the study was already obtained. A note to file was completed to document this.	N/A	N/A	Ariana Koster 2/20/14
3/31/14	2/1/13	170201	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	7/12/13	1770301	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	7/15/13	1770401	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	8/7/13	1770501	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	7/24/13	1770601	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	7/29/13	1770701	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14

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3/31/14	7/30/13	1770801	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	8/8/13	1770901	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	8/13/13	1771001	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	8/22/13	1771101	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	10/3/13	1771201	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	10/18/13	1771401	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	9/30/13	1771601	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	9/26/13	1771701	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	10/15/13	1771801	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	10/18/13	1772001	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	10/24/13	1772101	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	11/11/13	1772201	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14

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3/31/14	11/14/13	1772301	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	11/15/13	1772401	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	12/12/13	1772501	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	11/20/13	1772601	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	12/2/13	1772701	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	1/10/14	1773101	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	1/9/14	1773201	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	1/31/14	1773301	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	1/23/14	1773401	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	2/14/14	1773501	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	2/4/14	1773601	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	3/12/14	1773701	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14

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4/2/14	4/2/14	1773901	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
3/31/14	3/13/14	1774001	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
4/16/14	4/16/14	1774101	A Neuropsychological Battery was administered without prior IRB approval to assess participant I.Q. to determine eligibility for the trial.	The script for the Neuropsychological Battery was submitted for IRB approval with the 2014 Continuing Review Submission.	N/A	N/A	Ariana Koster 4/22/14
4/24/14	4/24/14	N/A	On 4/24/14, this study expired because the Continuing Review was not submitting on time. The IRB immediately approved the Continuing Review on the same day. No patients were seen in the brief time the study was expired.	All study staff have been reminded of the importance of completing all reports to the IRB in a timely fashion.	4/24/14	N/A	Anna Hall 2/25/15
7/24/14	7/22/14	1774801	On 7/14/14, Olivia Bogucki was removed from study staff. On 7/22/14, the new coordinator was unable to complete vitals because she was not trained. Olivia Bogucki completed vitals without being on study staff.	All study staff have been reminded of the importance of following the approved protocol.	N/A	N/A	Anna Hall 07/24/14
7/24/14	7/23/14	1775001	On 7/14/14, Olivia Bogucki was removed from study staff. On 7/23/14, the new coordinator was unable to complete vitals because she was not trained. Olivia Bogucki completed vitals without being on study staff.	All study staff have been reminded of the importance of following the approved protocol.	N/A	N/A	Anna Hall 07/24/14
7/25/14	7/15/14	1775101	A physical exam was not conducted during Subject 1775101's Week 99 visit on 07/15/14. A physician will conduct the physical exam before administering any medication on the subject's baseline Liking Day visit. There is no impact on subject safety	All study staff have been reminded of the importance of being mindful that all planned assessments be conducted at the appropriate visit.	N/A	N/A	Anna Hall 07/29/14
9/9/14	9/9/14	1774301	On the Drug Feeling visit, the protocol states that the subject will have blood drawn 2 hours after the dose and eat 3 hours after the dose. The subject expressed concerns of passing out if not given food before a blood draw, so the PI directed study staff to give the subject food after the first hour (rather than the third), to reduce unnecessary subject burden. All following Drug Feeling Visits for this subject will give food at the first hour.	All study staff have been reminded of the importance of following the approved protocol, while also acknolweding subject's particular needs.	N/A	N/A	Anna Hall 9/10/14

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9/27/14	10/24/14	1775201	Morning and afternoon doses on Drug Feeling Visits are randomized (and double-blinded). The subject was accidentally given the afternoon designated dose in the morning and vice versa for the afternoon. No blood was drawn on this visit, so this data is not threatened. There is no impact on subject safety.	Study staff searched all records for similar errors to ensure data integrity. All study staff have been reminded of the importance of double checking the labels on medication bottles. A check was added to the Task Sheet to ensure that this double-checking occured.	N/A	N/A	Anna Hall 10/24/14
9/9/14	10/17/14	1774301	On the Drug Feeling visit, the protocol states that the subject will have blood drawn 2 hours after the dose and eat 3 hours after the dose. On 9/19/14, the subject expressed concerns of passing out if not given food before a blood draw, so the PI directed study staff to give the subject food after the first hour (rather than the third), to reduce unnecessary subject burden. All following Drug Feeling Visits for this subject will give food at the first hour.	All study staff have been reminded of the importance of following the approved protocol, while also acknolweding subject's particular needs.	N/A	N/A	Anna Hall 10/17/14
10/18/14	10/24/14	1775301	Morning and afternoon doses on Drug Feeling Visits are randomized (and double-blinded). The subject was accidentally given the afternoon designated dose in the morning and vice versa for the afternoon. Blood was only drawn in the afternoon, which was labelled to reflect the correct corresponding morning dose. There is no impact on subject safety.	Study staff searched all records for similar errors to ensure data integrity. All study staff have been reminded of the importance of double checking the labels on medication bottles. A check was added to the Task Sheet to ensure that this double-checking occured.	N/A	N/A	Anna Hall 10/17/14
9/9/14	11/4/14	1774301	On the Drug Feeling visit, the protocol states that the subject will have blood drawn 2 hours after the dose and eat 3 hours after the dose. On 9/19/14, the subject expressed concerns of passing out if not given food before a blood draw, so the PI directed study staff to give the subject food after the first hour (rather than the third), to reduce unnecessary subject burden. All following Drug Feeling Visits for this subject will give food at the first hour.	All study staff have been reminded of the importance of following the approved protocol, while also acknolweding subject's particular needs.	N/A	N/A	Anna Hall 11/04/14
12/30/14	4/29/14	1774701	Due to coordinator error, the screening procedures for this subject did not include a structured clinical interview (as stated in the protocol). However, a study clinician recorded the subject's medical and psychiatric history, and also met with the subject on a weekly basis. There is no impact on subject safety.	All study staff have been reminded of the importance of following the approved protocol in its entirety	N/A	N/A	Anna Hall 12/31/14

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4/17/15	10/15/13	1770601	This subject signed consent on 7/16/13, with a consent form that was approved on 5/7/13. However, on 10/15/13, Amendment 16 updated the consent form and the IRB instructed site staff to reconsent active subjects. The site thoroughly reviewed all consent forms and found that this subject was not reconsented after a new consent form was approved.	Per email discussion with Rosalyn Gray, IRB director of compliance, on 4/24/15, this can be considered a minor deviation. Study staff have been reminded to reconsent when applicable.	N/A	N/A	Anna Hall 06/24/15
4/17/15	10/15/13	1771001	This subject signed consent on 8/6/13, with a consent form that was approved on 5/7/13. However, on 10/15/13, Amendment 16 updated the consent form and the IRB instructed site staff to reconsent active subjects. The site thoroughly reviewed all consent forms and found that this subject was not reconsented after a new consent form was approved.	Per email discussion with Rosalyn Gray, IRB director of compliance, on 4/24/15, this can be considered a minor deviation. Study staff have been reminded to reconsent when applicable.	N/A	N/A	Anna Hall 06/24/15
4/17/15	10/15/13	1771601	This subject signed consent on 9/17/13, with a consent form that was approved on 5/7/13. However, on 10/15/13, Amendment 16 updated the consent form and the IRB instructed site staff to reconsent active subjects. The site thoroughly reviewed all consent forms and found that this subject was not reconsented after a new consent form was approved.	Per email discussion with Rosalyn Gray, IRB director of compliance, on 4/24/15, this can be considered a minor deviation. Study staff have been reminded to reconsent when applicable.	N/A	N/A	Anna Hall 06/24/15
4/17/15	10/15/13	1771801	This subject signed consent on 9/30/13, with a consent form that was approved on 5/7/13. However, on 10/15/13, Amendment 16 updated the consent form and the IRB instructed site staff to reconsent active subjects. The site thoroughly reviewed all consent forms and found that this subject was not reconsented after a new consent form was approved.	Per email discussion with Rosalyn Gray, IRB director of compliance, on 4/24/15, this can be considered a minor deviation. Study staff have been reminded to reconsent when applicable.	N/A	N/A	Anna Hall 06/24/15
4/17/15	12/8/14	1775001	This subject signed consent on 7/8/14, with a consent form that was approved on 4/24/14. However, on 12/8/14, Amendment 29 updated the consent form and the IRB instructed site staff to reconsent active subjects. The site thoroughly reviewed all consent forms and found that this subject was not reconsented after a new consent form was approved.	Per email discussion with Rosalyn Gray, IRB director of compliance, on 4/24/15, this can be considered a minor deviation. Study staff have been reminded to reconsent when applicable.	N/A	N/A	Anna Hall 06/24/15

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4/17/15	12/8/14	1775701	This subject signed consent on 12/8/14, with a consent form that was approved on 4/24/14. However, on 12/8/14, Amendment 29 updated the consent form and the IRB instructed site staff to reconsent active subjects. The site thoroughly reviewed all consent forms and found that this subject was not reconsented after a new consent form was approved.	Per email discussion with Rosalyn Gray, IRB director of compliance, on 4/24/15, this can be considered a minor deviation. Study staff have been reminded to reconsent when applicable.	N/A	N/A	Anna Hall 06/24/15
4/17/15	1/25/13	1770201	On 1/25/13, this subject signed consent. The consent form is missing the time of signature for both the subject and study doctor However, the Document of Consent form was signed by the study doctor stating that the subject signed "prior to the start of any procedures." The consent form is also missing the subject's initials to allow collection of social security number and contacting the subject for future studies. However, the subject signed the "Study Completion Form," in which they produced their social security number and allowed remuneration.	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15
4/17/15	9/9/13	1771301	On 9/9/13, this subject signed consent. The consent form is missing the study doctor's signature, time of signature, and date of signature. However, the Document of Consent form was signed by the study doctor, stating that the subject signed "prior to the start of any procedures."	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15
4/17/15	9/16/13	1771501	On 9/16/13, this subject signed consent. The consent form is missing the study doctor's signature, time of signature, and date of signature. However, the Document of Consent form was signed by the study doctor, stating that the subject signed "prior to the start of any procedures."	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15
4/17/15	10/29/13	1772301	On 10/29/13, this subject signed consent. The consent form is missing the subject's time of signature. However, the Document of Consent form was signed by the study doctor, stating that the subject signed "prior to the start of any procedures."	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15

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4/17/15	12/3/13	1772801	On 12/3/13, this subject signed consent. The consent form is missing the subject's time of signature. However, the Document of Consent form was signed by the study doctor, stating that the subject signed "prior to the start of any procedures."	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15
4/17/15	12/13/13	1773001	On 12/13/13, this subject signed consent. The consent form is missing the subject's time of signature. However, the Document of Consent form was signed by the study doctor, stating that the subject signed "prior to the start of any procedures."	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15
4/17/15	12/18/13	1773101	On 12/18/13, this subject signed consent. The consent form is missing the subject's time of signature. However, the Document of Consent form was signed by the study doctor, stating that the subject signed "prior to the start of any procedures."	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15
4/17/15	12/27/13	1773301	On 12/27/13, this subject signed consent. The consent form is missing the study doctor's time of signature. However, the Document of Consent form was signed by the study doctor, stating that the subject signed "prior to the start of any procedures."	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15
4/17/15	1/15/14	1773401	On 1/15/14, this subject signed consent. The consent form is missing the subject's time of signature. However, the Document of Consent form was signed by the study doctor, stating that the subject signed "prior to the start of any procedures."	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15
4/17/15	1/24/14	1773501	On 1/24/14, this subject signed consent. The consent form is missing the study doctor's signature, time of signature, and date of signature. However, the Document of Consent form was signed by the study doctor, stating that the subject signed "prior to the start of any procedures."	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15
4/17/15	1/28/14	1773601	On 1/28/14, this subject signed consent. The consent form is missing the study doctor's time of signature. However, the Document of Consent form was signed by the study doctor, stating that the subject signed "prior to the start of any procedures."	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15

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4/17/15	3/25/14	1774101	On 3/25/14, this subject signed consent. The consent form is missing the study doctor's time of signature. However, the Document of Consent form was signed by the study doctor, stating that the subject signed "prior to the start of any procedures." The consent form is also missing the subject's initials to allow collection of social security number. However, the subject signed the "Study Completion Form," in which they produced their social security number and allowed remuneration.	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15
4/17/15	3/31/14	1774201	On 3/31/14, this subject signed consent. The consent form is missing the subject's time of signature. However, the Document of Consent form was signed by the study doctor, stating that the subject signed "prior to the start of any procedures." The consent form is also missing the subject's initials to allow collection of social security number. However, the subject signed the "Study Completion Form," in which they produced their social security number and allowed remuneration.	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15
4/17/15	4/1/14	1774301	On 4/1/14, this subject signed consent. The consent form is missing the subject's time of signature. However, the Document of Consent form was signed by the study doctor, stating that the subject signed "prior to the start of any procedures." The consent form is also missing the subject's initials to allow collection of social security number. However, the subject signed the "Study Completion Form," in which they produced their social security number and allowed remuneration.	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15
4/17/15	4/3/14	1774401	On 4/3/14, this subject signed consent. The consent form is missing the subject's initials to allow collection of social security number. However, the subject signed the "Study Completion Form," in which they produced their social security number and allowed remuneration.	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15

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4/17/15	4/10/14	1774501	On 4/10/14, this subject signed consent. The consent form is missing the subject's initials to allow collection of social security number. However, the subject signed the "Study Completion Form," in which they produced their social security number and allowed remuneration.	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15
4/17/15	6/23/14	1774901	On 6/23/14, this subject signed consent. The consent form is missing the time of signature for both the subject and study doctor However, the Document of Consent form was signed by the study doctor stating that the subject signed "prior to the start of any procedures."	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15
4/17/15	12/8/14	1775701	On 12/8/14, this subject signed consent. The consent form is missing the time of signature for both the subject and study doctor However, the Document of Consent form was signed by the study doctor stating that the subject signed "prior to the start of any procedures."	Study staff were reminded to check that all details of the Consent Form are recorded.	N/A	N/A	Anna Hall 06/24/15