What is the purpose of this form?

This application is to seek initial IRB approval for a research study.

What parts of this application should you submit?

Answer all questions, or mark “not applicable,” when appropriate. Do not alter wording or delete questions from this form.

- For all studies, submit Part A, which consists of these sections:
  - Part A.1. Contact Information, Agreements, and Signatures
  - Part A.2. Summary Checklist
  - Part A.3. Conflict of Interest Questions and Certification
  - Part A.4. Questions Common to All Studies
  - Part A.5. The Consent Process and Consent Documentation (including Waivers)

- For studies that involve direct interaction with human subjects (any contact with subjects including questionnaires, interviews, focus groups, observation, treatment interventions, etc), submit:
  - Part B. Questions for Studies that Involve Direct Interaction with Human Subjects

- For studies that use existing data, records or human biological specimens, including for use in identifying potential subjects, submit:
  - Part C. Questions for Studies using Existing Data, Records or Human Biological Specimens

Note: You should submit Parts B or C only as applicable. If the study involves both direct interaction and use of existing materials, use both Parts B and C in addition to Part A.

Who can serve as principal investigator (PI)?

The PI is the person who will personally conduct or supervise this research study. Under most circumstances, this will be a faculty member. For IRB communication purposes, a trainee/student may be listed as PI. However, a faculty advisor must be identified, who holds ultimate responsibility for ensuring that this project complies with all University, regulatory, and fiscal requirements.

→ See next page for additional instructions

---- Instructions – Do not submit this page with your application ----
Complete submission instructions can be found at http://ohre.unc.edu/submission_instructions.php. All application and consent materials must be copied or printed on one side only. See the checklist on page 1 of the application itself for items to include and number of copies.

Some applications require additional review prior to the IRB submission. Examples include the Clinical and Translational Research Center (formerly the GCRC and CCCT facilities) http://gcrc.med.unc.edu/investigators/admin/gcrcapp.htm or the Oncology Protocol Review Committee (PRC; http://cancer.med.unc.edu/research/prc/default.asp). See their web sites for details.

Many schools, departments, centers and institutes in Academic Affairs have local review committees that review before the IRB. See http://ohre.unc.edu/submission_instructions.php for a list of these units or consult your own unit for details.

**Address for all Applications and Other Correspondence**

IRB  
CB# 7097, Medical Building 52  
105 Mason Farm Road  
Chapel Hill, NC  27599-7097

**Types of Review**

There are three levels of IRB Review (full board, expedited, and exempt), determined by the nature of the project, level of potential risk to human subjects, and the subject population. *The type of review applicable to a particular study is determined by the IRB.* Regardless of the kind of review, all applications use the same submission form.

Exempt and expedited review can be given to studies that constitute no more than minimal risk to the human subjects, i.e., the risk one experiences in daily living. These reviews are done in the IRB office on a continual basis.

Full board review is required for studies that involve greater than minimal risk or vulnerable populations that require special protection by the IRB. These require review by the convened IRB. See http://ohre.unc.edu/guide_to_irb.php for additional guidance.

----- Instructions – Do not submit this page with your application ----
Office of Human Research Ethics
Institutional Review Board

Application for IRB Approval of Human Subjects Research
Version June 25, 2009

Part A.1. Contact Information, Agreements, and Signatures

Date: 10-21-2011

Title of Study: IRB# 09-0939: Sweet Preference and Alcohol Craving Predict Naltrexone Response in Alcoholism

Name and degrees of Principal Investigator: James C. Garbutt, M.D.
Department: Psychiatry  Mailing address/CB #: UNC-Chapel Hill, Neurosciences Hospital, 101 Manning Dr, Chapel Hill, NC 27599 CB#7160
UNC-CH PID: 7042-75407  Pager: 919-216-2842
Phone #: 919-966-4652  Fax #: 919-966-5628  Email Address: jc_garbutt@med.unc.edu

For trainee-led projects:  __ undergraduate  __ graduate  __ postdoc  __ resident  __ other

Name of faculty advisor:  Department: Psychiatry  Mailing address/CB #:
Phone #:  Fax #:  Email Address:

Center, institute, or department in which research is based if other than department(s) listed above:

Name of Project Manager or Study Coordinator (if any): None
Department: Psychiatry  Mailing address/CB #: UNC-Chapel Hill, 101 Manning Dr., 1st Floor Psychiatry, Chapel Hill, NC 27599; CB# 7160
Phone #:  Fax #:  Email Address:

List all other project personnel including co-investigators, and anyone else who has contact with subjects or identifiable data from subjects. Include email address for each person who should receive electronic copies of IRB correspondence to PI:
Alexei B. Kampov-Polevoi, M.D., Ph.D.; Charlotte Boettiger, Ph.D.; Cort Pedersen, M.D.; Vicki West Chanon, Ph.D.; Christopher Smith; Elly Steel; Soleille Everest; Audrey Verde.

Name of funding source or sponsor (please do not abbreviate):
__ not funded  _X_ Federal  __ State  __ industry  __ foundation  __ UNC-CH  __ other (specify):

For external funding, RAMSeS proposal number (from Office of Sponsored Research):

For industry sponsored research (if applicable):

Sponsor’s master protocol version #:  Version date:
Investigator Brochure version #:  Version date:
Any other details you need documented on IRB approval:
Checklist of Items to Include with Your Submission

Include the following items with your submission, where applicable.

- Check the relevant items below and include one copy of all checked items 1-11 in the order listed.
- Also include two additional collated sets of copies (sorted in the order listed) for items 1-7.

Applications must “stand alone” and should provide all information requested, i.e., complete answers must be contained in the application. While you may reference other documents with supporting information, do not respond solely by stating “see attached.”

Applications will be returned if these instructions are not followed.

<table>
<thead>
<tr>
<th>Check</th>
<th>Item</th>
<th>Total No. of Copies</th>
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<tbody>
<tr>
<td>☑</td>
<td>1. This application. One copy must have original PI signatures.</td>
<td>3</td>
</tr>
<tr>
<td>☑</td>
<td>2. Consent and assent forms (include DHHS-approved sample, when one exists), fact or information sheets, phone and verbal consent scripts.</td>
<td>3</td>
</tr>
<tr>
<td>☑</td>
<td>3. HIPAA authorization addendum to consent form.</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>4. All recruitment materials including final copies of printed advertisements, audio/video taped advertisements, scripts, flyers, letters, and emails.</td>
<td>3</td>
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<tr>
<td></td>
<td>5. Questionnaires, focus group guides, scripts used to guide phone or in-person interviews, etc.</td>
<td>3</td>
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<tr>
<td></td>
<td>6. Documentation of reviews from any other committees (e.g., Clinical and Translational Research Center (CTRC), Oncology Protocol Review Committee, or local review committees in Academic Affairs).</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>7. Protocol, grant application or proposal supporting this submission, if any (e.g., extramural grant application to NIH or foundation, industry protocol, student proposal). This must be submitted if an external funding source or sponsor is checked on the previous page.</td>
<td>1</td>
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<td></td>
<td>8. Addendum for Multi-Site Studies where UNC-CH is the Lead Coordinating Center.</td>
<td>1</td>
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<td>9. Data use agreements (may be required for use of existing data from third parties).</td>
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<tr>
<td></td>
<td>10. Only for those study personnel not in the online UNC-CH human research ethics training database (<a href="http://cfx3.research.unc.edu/training_comp/">http://cfx3.research.unc.edu/training_comp/</a>): Documentation of required training in human research ethics.</td>
<td>1</td>
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<tr>
<td></td>
<td>11. For drug studies, Investigator Brochure if one exists. If none, include package insert for previously approved uses.</td>
<td>1</td>
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</table>
Principal Investigator: I will personally conduct or supervise this research study. I will ensure that this study is performed in compliance with all applicable laws, regulations and University policies regarding human subjects research. I will obtain IRB approval before making any changes or additions to the project. I will notify the IRB of any other changes in the information provided in this application. I will provide progress reports to the IRB at least annually, or as requested. I will report promptly to the IRB all unanticipated problems or serious adverse events involving risk to human subjects. I will follow the IRB approved consent process for all subjects. I will ensure that all collaborators, students and employees assisting in this research study are informed about these obligations. All information given in this form is accurate and complete.

_________________________________________________________  __________________________
Signature of Principal Investigator                          Date

Faculty Advisor if PI is a Student or Trainee Investigator: I accept ultimate responsibility for ensuring that this study complies with all the obligations listed above for the PI.

_________________________________________________________  __________________________
Signature of Faculty Advisor                                 Date

Note: The following signature is not required for applications with a student PI.

Department or Division Chair, Center Director (or counterpart) of PI: (or Vice-Chair or Chair’s designee if Chair is investigator or otherwise unable to review): I certify that this research is appropriate for this Principal Investigator, that the investigators are qualified to conduct the research, and that there are adequate resources (including financial, support and facilities) available. If my unit has a local review committee for pre-IRB review, this requirement has been satisfied. I support this application, and hereby submit it for further review.

_________________________________________________________  __________________________
Signature of Department Chair or designee                    Date

_________________________________________________________  __________________________
Print Name of Department Chair or designee                    Department
### Part A.2. Summary Checklist  *Are the following involved?*

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.2.1. Existing data, research records, patient records, and/or human biological specimens?</td>
<td><em>X</em></td>
<td></td>
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<tr>
<td>A.2.2. Surveys, questionnaires, interviews, or focus groups with subjects?</td>
<td><em>X</em></td>
<td></td>
</tr>
<tr>
<td>A.2.3. Videotaping, audiotaping, filming of subjects, or analysis of existing tapes?</td>
<td><em>X</em></td>
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</tbody>
</table>
| A.2.4. Do you have specific plans to enroll subjects from these vulnerable or select populations:  
a. UNC-CH students or UNC-CH employees? | _X_ |  |
| b. Non-English-speaking? | _X_ |  |
| c. Decisionally impaired? | _X_ |  |
| d. Patients? | _X_ |  |
| e. Prisoners, others involuntarily detained or incarcerated, or parolees? | _X_ |  |
| f. Pregnant women? | _X_ |  |
| g. Minors (less than 18 years)? *If yes*, give age range: to years |  |  |
| A.2.5. a. Are sites outside UNC-CH engaged in the research? | _X_ |  |
| b. Is UNC-CH the sponsor or lead coordinating center for a multi-site study?  
  *If yes*, include the *Addendum for Multi-site Studies*.  
  *If yes*, will any of these sites be outside the United States? 
  *If yes*, is there a local ethics review committee agency with jurisdiction? (provide contact information) |  |  |
| A.2.6. Will this study use a data and safety monitoring board or committee?  
  *If yes*:  
  UNC-CH School of Medicine DSMB? (must apply separately)  
  Lineberger Cancer Center DSMC?  
  Other? Specify: | _X_ |  |
| A.2.7. a. Are you collecting sensitive information such as sexual behavior, HIV status, recreational drug use, illegal behaviors, child/physical abuse, immigration status, etc?  
  b. Do you plan to obtain a federal Certificate of Confidentiality for this study?  
  c. Is this research classified (e.g., requires security clearance)? | _X_ |  |
| A.2.8. a. *Investigational* drugs? (provide IND # )  
  b. Approved drugs for “non-FDA-approved” conditions?  
  All studies testing substances in humans must provide a letter of acknowledgement from the *UNC Health Care Investigational Drug Service* (IDS). | _X_ |  |
| A.2.9. Placebo(s)? | _X_ |  |
| A.2.10. *Investigational* devices, instruments, machines, software? (provide IDE # ) | _X_ |  |
| A.2.11. Fetal tissue? | _X_ |  |
| A.2.12. Genetic studies on subjects’ specimens? | _X_ |  |
| A.2.13. Storage of subjects’ specimens for future research?  
  *If yes*, see instructions for Consent for Stored Samples. | _X_ |  |
| A.2.14. Diagnostic or therapeutic ionizing radiation, or radioactive isotopes, which subjects would not receive otherwise?  
  *If yes*, approval by the *UNC-CH Radiation Safety Committee* is required. | _X_ |  |
| A.2.15. Recombinant DNA or gene transfer to human subjects?  
  *If yes*, approval by the *UNC-CH Institutional Biosafety Committee* is required. | _X_ |  |
| A.2.16. Does this study involve UNC-CH cancer patients?  
  *If yes, submit this application directly to the Oncology Protocol Review Committee.* | _X_ |  |
| A.2.17. Will subjects be studied in the Clinical and Translational Research Center (CTRC) or is the CTRC involved in any other way with this study?  
  *If yes*, obtain the *CTRC Addendum* and submit completed application (IRB application and Addendum) directly to the CTRC. The CTRC includes facilities located on the 3rd floor of the Main Hospital (formerly GCRC) and Ground floor Burnett-Womack (formerly CCCT). | _X_ |  |
| A.2.18. Will gadolinium be administered as a contrast agent? | _X_ |  |
| A.2.19. Will subjects’ *Social Security Number* (SSN) be collected for:  
a. processing payments greater than $200 per year, to support IRS reporting (see also B.6)?  
b. processing payments of any amount through UNC-CH Accounts Payable?  
c. use as a unique identifier for study tracking purposes for national registry or database? | _X_ |  |

---

*Application for IRB Approval of Human Subjects Research*  
**Page 4**
## Part A.3. Conflict of Interest Questions and Certification

The following questions apply to **all investigators and study staff** engaged in the design, conduct, or reporting results of this project and/or their immediate family members. For these purposes, “family” includes the individual’s spouse and dependent children. “Spouse” includes a person with whom one lives together in the same residence and with whom one shares responsibility for each other’s welfare and shares financial obligations.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td><strong>A.3.1.</strong> Currently or during the term of this research study, does any member of the research team or his/her family member have or expect to have:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with the sponsor of this study?</td>
<td><em>yes</em></td>
<td><em>X</em> no</td>
</tr>
<tr>
<td>(b) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with an entity that owns or has the right to commercialize a product, process or technology studied in this project?</td>
<td><em>yes</em></td>
<td><em>X</em> no</td>
</tr>
<tr>
<td>(c) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with an entity engaged in the performance of this project as a subcontractor, sub-recipient or vendor?</td>
<td><em>yes</em></td>
<td><em>X</em> no</td>
</tr>
<tr>
<td>(d) A board membership of any kind or an executive position (paid or unpaid) with the sponsor of this study or with an entity that owns or has the right to commercialize a product, process or technology studied in this project?</td>
<td><em>yes</em></td>
<td><em>X</em> no</td>
</tr>
<tr>
<td><strong>A.3.2.</strong> Has the University or has a University-related foundation received a cash or in-kind gift from the sponsor of this study for the use or benefit of any member of the research team?</td>
<td><em>yes</em></td>
<td><em>X</em> no</td>
</tr>
<tr>
<td><strong>A.3.3.</strong> Has the University or has a University-related foundation received a cash or in-kind gift for the use or benefit of any member of the research team from an entity that owns or has the right to commercialize a product, process or technology studied in this project?</td>
<td><em>yes</em></td>
<td><em>X</em> no</td>
</tr>
</tbody>
</table>

*If the answer to ANY of the questions above is **yes**, the affected research team member(s) must complete and submit the form, which is accessible online at [http://coi.unc.edu](http://coi.unc.edu). List name(s) of all research team members for whom any answer to the questions above is **yes**:*

---

**Certification by Principal Investigator:** By submitting this IRB application, I (the PI) certify that the information provided above is true and accurate regarding my own circumstances, that I have inquired of every UNC-Chapel Hill employee or trainee who will be engaged in the design, conduct or reporting of results of this project as to the questions set out above, and that I have instructed any such person who has answered “**yes**” to any of these questions to complete and submit for approval a Conflict of Interest Evaluation Form. I understand that as Principal Investigator I am obligated to ensure that any potential conflicts of interest that exist in relation to my study are reported as required by University policy.

**Signature of Principal Investigator**

**Date**

**Faculty Advisor if PI is a Student or Trainee Investigator:** I accept ultimate responsibility for ensuring that the PI complies with the University’s conflict of interest policies and procedures.

**Signature of Faculty Advisor**

**Date**
Part A.4. Questions Common to All Studies

For all questions, if the study involves only secondary data analysis, focus on your proposed design, methods and procedures, and not those of the original study that produced the data you plan to use.

Complete answers must be provided. While you may reference other documents with supporting information, do not respond solely by stating “see attached.”

A.4.1. Brief Summary. Provide a brief non-technical description of the study, which will be used in IRB documentation as a description of the study. Typical summaries are 50-100 words. Please reply to each item below, retaining the subheading labels already in place, so that reviewers can readily identify the content.

**Purpose:** The proposed 2-year investigation will be the first double-blind, placebo-controlled trial examining the hedonic response to sweet taste (HRST) as a phenotypic predictor of naltrexone (NTX) response in alcohol dependence. HRST yields two primary phenotypes—Sweet Likers (SL) and Sweet Dislikers (SDL). Based on preliminary findings, HRST will be examined in conjunction with craving for alcohol to assess whether the two factors together provide a more robust predictor of NTX response. The identification of methods to predict naltrexone response in alcohol dependence is an important goal for alcohol treatment research. Currently naltrexone is not being used nearly as much as it should be, in part because clinicians do not believe it is very effective. The development of tools that would identify which patients are more likely to have a robust response to naltrexone should lead to increased use of the medication. This could help many patients who are not now having the opportunity of trying naltrexone.

**There are two principal Specific Aims for the study:**

**Specific Aim 1.** To test the hypothesis that a combination of SL/SDL status and initial alcohol craving will predict % abstinent days (%ABST) during treatment with naltrexone.

**Specific Aim 2.** To test whether a combination of SL/SDL status and initial alcohol craving predict % heavy drinking days (%HDD) during treatment with naltrexone.

**Participants:** There will be 130 alcohol-dependent individuals between 18 and 65 years of age recruited to participate in this randomized placebo-controlled clinical trial. Eighty alcohol-dependent individuals will be randomized into the study and we are allowing for 50 screen failures. We will advertise through local newspaper and radio advertisements. In addition, individuals calling for treatment at the UNC outpatient Alcohol and Substance Abuse Program may be offered participation in this study as an alternative to standard treatment. Subjects will be blindly assessed for SL/SDL status to yield 50% representation of each trait.

**Procedures (methods):** Subjects who meet general inclusion/exclusion criteria based on the screening interview will complete a sweet taste assessment. Results, along with craving score, will be given to the Investigational Drug Services for randomization purposes. The study is a double-blind, randomized, placebo-controlled clinical trial in which participants will receive 50 mg oral naltrexone or matching placebo for a 12-week period. In addition participants will meet with a trained therapist for nine 30-minute BRENDA therapy sessions. Medical monitoring will also be conducted by study physicians and will consist of review of vital signs, concomitant medication use, and general inquiries into side effects.

A.4.2. Purpose and Rationale. Provide a summary of the background information, state the research question(s), and tell why the study is needed. If a complete rationale and literature review are in an accompanying grant application or other type of proposal, only provide a brief summary here. If there is no proposal, provide a more extensive rationale and literature review, including references.

The proposed 2-year investigation will be the first double-blind, placebo-controlled trial examining the hedonic response to sweet taste (HRST) as a phenotypic predictor of NTX response in alcohol dependence. Based on preliminary findings, HRST will be examined in conjunction with craving...
for alcohol to assess whether the two factors together provide a more robust predictor of NTX response. The study significantly builds upon our preliminary open label trial by the use of a placebo, balanced randomization on the HRST phenotype and craving and adequate power to test the key hypotheses.

Placebo will allow the separation of overall treatment effects from NTX effects and permit detection of an interaction of HRST phenotype and craving with NTX/placebo—an important aim of the study.

Naltrexone has been approved by the FDA for the treatment of alcohol dependence since 1995. Specifically, it has been shown to reduce relapse to heavy drinking, decrease the number of drinks consumed when relapse does occur and promote abstinence (Anton, et al., 1999; O’Brien, et al., 1996, Volpicelli, et al.; 1992; O’Malley, 1992.) It has also been reported to reduce both the craving and the reinforcing euphoric qualities of alcohol (Volpicelli, et al., 1992.) However, naltrexone is not effective for all patients. Non-compliance has been one reason for ineffectiveness and efforts to address this involve studies of long-acting intramuscularly injectable forms of naltrexone. Nevertheless, even when patients are compliant with their oral naltrexone it is not always effective.

The ability to predict which alcohol dependent individuals are more likely to respond to naltrexone would have clinical value. To date, no clinically useful predictor of naltrexone response has been identified. It is our hypothesis that sweet-liking, a psychophysical trait that may be more prevalent in patients with alcohol dependence, will be predictive of response to naltrexone.

Sweet-liking is defined as a preference for highly concentrated sweet solutions and our group has evidence that sweet-liking is more common in individuals with alcoholism (Kampov-Polevoy et al., 1997, Kampov-Polevoy et al., 1998.) and in individuals at high-risk for alcoholism as determined by family history (Kampov-Polevoy et al., 2003). The perception of the pleasantness of sweets is likely mediated by reward pathways in the brain that also mediate the rewarding properties of alcohol. These pathways are complex and involve a variety of neurotransmitters including dopamine, serotonin, NMDA, norepinephrine, GABA, and opioids. Naltrexone is thought to be effective in alcoholism because it attenuates alcohol-induced opioid activities of the reward pathway. The higher incidence of sweet liking in alcohol dependent individuals may be a function of altered opioid response and thus a marker of opioid dysregulation in the reward pathway and a marker of naltrexone response.

In summary, this study will attempt to determine if response to naltrexone in alcoholics can be predicted using a sweet-preference test along with a measure of craving for alcohol that could be performed in a primary care physician’s or psychiatrist’s office.

A.4.3. **Subjects.** You should describe the subject population even if your study does not involve direct interaction (e.g., existing records). Specify number, gender, ethnicity, race, and age. Specify whether subjects are healthy volunteers or patients. If patients, specify any relevant disease or condition and indicate how potential subjects will be identified. Researchers are reminded that additional approvals may be needed from relevant “gatekeepers” to access subjects (e.g., school principals, facility directors, hospital or healthcare system administrators).

There will be 130 alcohol-dependent individuals between 18 and 65 years of age who will be recruited through local newspaper and radio advertisements and from referrals from UNC Alcohol and Substance Abuse Program. Eighty alcohol-dependent individuals will be randomized into the study and we are allowing for 50 screen failures. Forty participants will be assigned to the naltrexone group and 40 to the placebo group. Every effort will be made to recruit African-American, Hispanic, and other racial/ethnic groups. Women who are pregnant will not be allowed to enter the study, and women who become pregnant will have study medication stopped because the effects of naltrexone on the fetus are unknown (FDA Pregnancy Category C).

A.4.4. **Inclusion/exclusion criteria.** List required characteristics of potential subjects, and those that preclude enrollment or involvement of subjects or their data. Justify exclusion of any group, especially by criteria based on gender, ethnicity, race, or age. If pregnant women are excluded, or if women who become pregnant are withdrawn, specific justification must be provided.
Subjects will be between the ages of 18 and 65 years of age. Subjects must meet the following inclusion/exclusion criteria:

**Inclusion Criteria**
1. Men and women between the ages of 18 and 65 meeting DSM-IV criteria for current alcohol dependence.
2. More than 14 drinks (women) or 21 drinks (men) per week including at least 2 heavy drinking days/week on average (men ≥ 5 drinks/day; women ≥ 4 drinks/day) during a consecutive 30-day period within the 90 days prior to screening.
3. Ability to understand and sign written informed consent.
4. Must have a 0.0 gms/dl breathalyzer reading on the day of screening and 0.0 gms/dl on the day of randomization.
5. Must be willing to refrain from drinking for three days prior to randomization day.
6. Express a desire to achieve abstinence or to greatly reduce alcohol consumption.
7. Must have a stable residence and be able to identify an individual who could locate subject if needed.

**Exclusion Criteria**
1. Clinically significant medical disease that might interfere with the evaluation of the study medication or present a safety concern (e.g., cirrhosis, unstable hypertension, seizure disorder, use of opiate medication). Clinically significant psychiatric illness including: any psychotic disorder, bipolar disorder, severe depression, or suicidal ideation.
2. Other substance abuse or dependence disorder other than nicotine or alcohol.
3. Concurrent use of any psychotropic medication including antidepressants, mood stabilizers, antipsychotics, anxiolytics, stimulants, or hypnotics with the exception of stable doses of antidepressants for one month.
4. History of complicated alcohol withdrawal, i.e. withdrawal seizure or delirium tremens.
5. AST, or ALT > 3 times Upper Limit of Normal (ULN) or bilirubin > ULN.
6. Positive urine toxicology screen with the exception of cannabis. Individuals with positive cannabis screens will be excluded only if they have a history of cannabis dependence.
7. Pregnant women and women of childbearing potential who do not practice a medically acceptable form of birth control (oral or depot contraceptive, or barrier methods such as diaphragm or condom with spermicidal) and women who are breast feeding.
8. Individuals requiring inpatient treatment or more intense outpatient treatment for their alcohol dependence.
9. Participation in any clinical trial within the past 60 days.
10. Court-mandated participation in alcohol treatment or pending incarceration.

A.4.5. **Full description of the study design, methods and procedures.** Describe the research study. Discuss the study design; study procedures; sequential description of what subjects will be asked to do; assignment of subjects to various arms of the study if applicable; doses; frequency and route of administration of medication and other medical treatment if applicable; how data are to be collected (questionnaire, interview, focus group or specific procedure such as physical examination, venipuncture, etc.). Include information on who will collect data, who will conduct procedures or measurements. Indicate the number and duration of contacts with each subject; outcome measurements; and follow-up procedures. If the study involves medical treatment, distinguish standard care procedures from those that are research. If the study is a clinical trial involving patients as subjects and use of placebo control is involved, provide justification for the use of placebo controls.

**Pre Screening & Screening Visit**
Potential participants will be recruited from the Raleigh, Durham, and Chapel Hill areas via advertising and referrals. A preliminary telephone screening will be conducted by the study coordinator (see Appendix). Individuals who appear eligible, as determined by the investigative team, will be scheduled to come to the UNC Hospitals for more comprehensive screening.
We are changing the screening process to have up to two screening visits before the randomization visit. This may be necessary due to our need to randomize participants based on sweet test results. Currently there are four cells: Sweet Likers/High Cravers; Sweet Likers/Low Cravers; Non Sweet Likers/High Cravers and Non Sweet Likers/Low Cravers. At this time, one of the cells is almost completely full. Therefore we need to have each participant complete the Sweet Taste Test and Penn Alcohol Craving Scale and then for us to receive feedback on these test results from Dr. Boettiger who is not involved in care of participants. If they qualify for randomization we would then continue with the next screening visit. It may still be possible to complete this in one screening visit but we need to allow the option for two.

**Screening Visit One:** Prior to full screening, individuals will read and sign the informed consent and be given a copy for their records. A breathalyzer test using an Alco-Sensor III breathalyzer machine (Intoximeters, Inc., St. Louis, MO) will be administered (must be 0.00 gms/dl). Height and weight will be measured and BMI calculated. Medical personnel will conduct a medical history and examination including a neurological examination. Over-the-counter and prescription medication use will be recorded. Laboratory evaluations will include complete blood count (CBC) with differential; chemistries including bilirubin, AST, ALT, Alkaline Phosphatase, GGT, sodium, potassium, chloride, blood urea nitrogen, creatinine, and glucose; and urinalysis and urine toxicology. Women will be given a serum pregnancy test at screening and urine pregnancy tests at weeks 4, 8, and 12. Trained interviewers will conduct the SCID Substance Use Disorders Module to establish DSM-IV criteria for alcohol dependence and to assess for other substance use disorders (First, 2002). The study coordinator will conduct the pretreatment 90-day Timeline Followback interview (TLFB, Sobell et al., 1988). Potential participants will complete The Penn Alcohol Craving Scale (PACS, Flannery et al 1999) to assess craving and the Sweet Taste Questionnaire (Kampov 2006). This visit should take about 2.5 hours.

**Hedonic Response to Sweet Taste Assessment**
Subjects who meet general inclusion/exclusion criteria based on the screening interview will complete a sweet taste assessment after the screening assessment administered by a research assistant not involved in the assessment or management of subjects during the trial. Results, along with craving score, will be given to the Investigational Drug Services for randomization purposes. Test results will not be provided to participants. Participants will be asked not to have eaten or use tobacco for at least two hours prior to the sweet taste test. To estimate each subject’s sensitivity and hedonic response to sweet taste, five concentrations of sucrose solution (0.05, 0.10, 0.21, 0.42, and 0.83 M) will be presented five times in a pseudorandom order as described in our previous work (Kampov-Polevoy et al, 1997). In brief, subjects are asked to rate both intensity and pleasurableness of each tasting on a 200-mm analogue scale. The test takes 5-10 minutes to administer.

To determine the preferred concentration, five scores for each tested solution will be averaged and the solution with the highest average score will be considered the preferred solution. Participants who rate the 0.83 M sucrose solution as their preferred solution will be classified as SL and participants who prefer lower sucrose concentrations (0.05-0.42M) will be classified as SDL.

**Screening Visit Two:** Prior to this second screening, individuals will be given a breathalyzer test using an Alco-Sensor III breathalyzer machine (Intoximeters, Inc., St. Louis, MO) and it must be <0.04 gms/dl. Vital signs will be measured. The Fagerstrom Test for Nicotine Dependence (Heatherton et al, 1991) will be administered to smokers. The study coordinator will conduct the Timeline Followback interview (TLFB, Sobell et al., 1988). Trained interviewers will conduct the psychiatric screening interview using the M.I.N.I. (Sheehan et al., 1999) and potential participants will complete the Alcohol Dependence Scale (ADS, Skinner & Allen, 1982), the Drinker’s Inventory of Consequences (DrInC, Miller et al, 1995), the F-MAST to assess family history of alcohol problems (Levenson et al, 1987), the University of Rhode Island Change Assessment Scale (URICA, McConnaughy et al, 1989) to assess motivation level and the Locus of Control (LOC) (Rotter 1966) questionnaire to measures generalized
expectancies for internal versus external control. Additionally, potential participants will fill out a short evaluation of their treatment goals (see Appendix). This visit should take about 1 hour.

If at any visit the breath alcohol level is >0.08 gms/dl the participant will be considered legally intoxicated and will be asked to have someone drive them home or to wait until the level is below 0.08 gms/dl, the legal limit for intoxication in North Carolina, and they are not impaired. If the participant insists on driving with a breath alcohol level at 0.08gms/dl or greater while impaired, we will notify hospital security.

**Initial Treatment Visit**

Individuals meeting all inclusion/exclusion criteria will be informed and scheduled for the initial treatment visit within 21 days. Eligible individuals will be asked to try and abstain from drinking alcohol for three days prior to their initial treatment visit to reduce potential NTX-related side-effects at randomization (O’Malley et al, 2000) and to establish some degree of motivation. We will decide on a case-by-case basis whether individuals that are unable to abstain for three days can be recruited into the study.

The study coordinator will administer a breathalyzer test (BAC must be <0.04 gms/dl), conduct the TLFB interview, and ask participants to complete the PACS form. The study physician will evaluate withdrawal symptoms using the Clinical Institute Withdrawal Assessment for Alcohol Revised (CIWA-Ar, Sullivan et al., 1989) and note the use of medications.

A 1-week blister pack of NTX/placebo with written instructions will be dispensed from the Investigational Drug Services according to the randomization block along with a 1-week back-up blister pack in case of delayed appointments or lost doses. Participants also will be given a calendar style diary to track pill taking, drinking, and any side effects. **Each participant will receive a NTX Instruction Sheet that lists the medication, dosing instructions, side effects and emergency contact information. In addition participants will be given a NTX wallet card detailing potential problems should the individual require opiates for pain. Explicit instructions will be given to the participant on the use of the wallet card while in the study.** Participants will also meet with a trained therapist to receive the first of 8 BRENDA therapy sessions. The initial treatment visit should be completed in about 1.25–1.5 hours.

The psychosocial treatment for the proposed study will be BRENDA (Volpicelli et al, 2001). Dr. Kampov will be primarily responsible for the counseling. Dr. Kampov is a trained and experienced BRENDA counselor. BRENDA is a low-intensity intervention designed to maintain motivation, encourage change and support compliance with medication. Random BRENDA sessions, a total of 5%, will be audiotaped with participants’ permission. Adherence to the BRENDA model and quality assurance will be conducted by providing audiotapes of BRENDA sessions to an independent reviewer, Ms. Kathy Grace, who is also a trained and experienced BRENDA counselor. She will provide feedback to Dr. Kampov to maintain BRENDA fidelity and be available as backup if needed.

**Subsequent Treatment Visits**

At study week 1, participants will receive a 3-week supply of NTX or placebo. After that, NTX or placebo will be dispensed at study weeks 4 and 8. The pill taking, drinking, and side effects diaries will be collected and new diaries distributed at each visit.

Medical monitoring will be conducted by study physicians and will consist of review of vital signs, concomitant medication use, and general inquiries into side effects.

At each visit, participants will also be given a breathalyzer test (must be < 0.02 gms/dl), TLFB interview, and complete the PACS. Additional 30-minute BRENDA sessions will be conducted at each visit.

At week 4, blood will be drawn for evaluation of liver functioning. At weeks 4, 8, and 12 urine pregnancy testing will be conducted. At week 12 or early termination, a physical will be conducted along with a liver function test (chemistries). Participants will be encouraged to attend Alcoholics Anonymous (AA) during treatment.
With subjects’ permission a saliva sample will be obtained to archive for genetic analyses. Participants will be asked to provide only one sample and it may be collected at any study visit.

Post-Treatment Follow-up

One month following termination or treatment completion, the study coordinator will call each participant, conduct a TLFB interview, and inquire about general health and side effects. Participants who wish to continue treatment at the conclusion of the study will be offered outpatient counseling through the UNC Alcohol and Substance Abuse Program. Participants who wish to try NTX or another medication will be offered these options clinically. The blind will not be broken for any individual subject until the entire study is completed except for an emergency indication. The table of study events is in Protection of Human Subjects.

For research participants who did not provide a saliva sample for genetic purposes, they will be recontacted and asked if they are willing to provide a saliva sample via mail. If interested, they will be mailed a saliva sample kit, a self-addressed envelope and a new consent for storing biological specimens with identifying information.

Adverse Events Monitoring, Medication Adjustments, Medication Interventions and Medication Stopping Rules

Clinical staff will record adverse events based on subject description. Serious adverse events (SAE) are coded based on FDA definitions. SAEs will be reported to the IRB within 24 hours. All individuals experiencing adverse events will be monitored until a return to their baseline state is achieved. The physician may recommend that medication be held for a period of time to deal with an adverse event, e.g. nausea/vomiting and this will be recorded in the Case Report Form. Pepto-Bismol® may be prescribed for nausea/diarrhea. Hydroxyzine may be prescribed for anxiety/insomnia. Medication will be stopped if AST/ALT levels are >5X ULN or bilirubin > 1.5X ULN. If AST/ALT levels are >3X ULN subjects will be monitored and reevaluated in 2 weeks.

Preparation of NTX and Placebo Capsules and Randomization Schedule

UNC Hospital’s Investigational Drug Services (IDS) will purchase NTX tablets and create opaque NTX capsules and matching placebo that will be inserted into blister packs. All used and unused blister cards will be returned to the IDS.

Dr. Robert Gallop, the study biostatistician, will prepare the randomization schedule and include blocking by SL/SDL phenotype and high/low craving, where the high-low designation will be based on the median observed craving of 14 as found in our pilot data. The randomization schedule will be given to IDS personnel; investigators will not have access to this information. If a medical or other emergency necessitates breaking the blind, IDS personnel will provide the identity of the medication to the PI or another medical study team member.

Ancillary Study on Cognitive Behavior Experiment 1

Subjects will be given the opportunity to participate in two testing sessions, one at study intake, prior to receiving medication, and a second, 2-4 weeks after randomization. Participants will be tested in a private testing room in the Boettiger Lab in Davie Hall, in Neurosciences Hospital, or the Biomedical Research Imaging Center (BRIC). Each experimental session will last ~1 hour, which includes participation in both attention tasks. Participants will receive $10/hour for each session up to four sessions.

Dot Probe task: For this task, subjects will view a computer screen and for each trial, visual cues will simultaneously appear on each side of a central fixation cross for 150ms. On each trial, one cue will be an alcohol-related grayscale photo and the other will be a grayscale photo with neutral content. Alcohol and neutral cues will be matched in terms of their basic visual properties. 50ms after cue offset, a target
stimulus (the “dot probe”) will appear in one of the cue locations. Using a keypad, subjects will indicate the target’s location with a right or left button press. Subjects are instructed to respond as quickly as possible. Participants’ reaction times (RT) and accuracy will be recorded for each trial.

**Attentional Blink Task:** Subjects will complete this task in the same session and setting as the Dot Probe task described above. Each trial in this task consists of a rapid visual stream of 15 grayscale photos; each photo is presented for 100ms. Stimuli within each stream consist of neutral images with a superimposed colored letter. Within the stream of images are two target images, T1 and T2. Half of the T1 stimuli will be images with neutral content and the remaining half will contain alcohol-related imagery. Target stimuli have a colored numeral superimposed in the center, and participants are instructed to look for two targets within each stream and to report the numeral appearing in each target via a numeric button pad. T1 occurs at position 4-8 in the stream and the number of stimuli separating T1 and T2 varies from 0 to 4 items. Participants’ accuracy in reporting T1 and T2 will be recorded for each trial.

**Ancillary Study with FMRI – Experiment 2**

Experiment 2: NTX effect on OrbitoFrontalCortex activity during Now/Later decisions vs. NTX therapeutic response

Subjects: As for Experiment 1, but participants will also be screened for contraindications to MRI.

Subjects will be asked to participate in two testing sessions, one at study intake, prior to receiving medication, and a second 2-4 weeks after randomization. Participants will be tested during fMRI sessions at the BRIC. Each session will last 1-1.5 hrs, to acquire structural and functional brain images. Participants will receive $15/hour for taking part in this study as well as a $50 completion bonus after completing the second session.

**Now/Later task:** For this task, subjects will make numerous decisions between hypothetical amounts of money available “Today” versus larger amounts of money available at delays of up to 6 months. The amounts of money, the difference between the two amounts, the delay time, and the right/left position of the delayed reward varies pseudorandomly across trials. Using a keypad, subjects indicate the preferred option for each trial with a right or left button press. Subjects are instructed to respond as quickly as possible. Participants’ reaction time (RT) and choice will be recorded for each trial. Control conditions, in which subjects are instructed to respond based on objective criteria rather than subjective preference, are included.

**Table of Study Events***

<table>
<thead>
<tr>
<th>Study Event</th>
<th>Screen Visit 1</th>
<th>Screen Visit 2</th>
<th>Initial Visit</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 4</th>
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<th>Week 8</th>
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Application for IRB Approval of Human Subjects Research
A.4.6. Benefits to subjects and/or society. Describe any potential for direct benefit to individual subjects, as well as the benefit to society based on scientific knowledge to be gained; these should be clearly distinguished. Consider the nature, magnitude, and likelihood of any direct benefit to subjects. If there is no direct benefit to the individual subject, say so here and in the consent form (if there is a consent form). Do not list monetary payment or other compensation as a benefit.

Subjects can personally benefit from the study from receiving counseling and possibly naltrexone. For individuals with no or limited insurance coverage, this counseling is a significant benefit. Most subjects will have an improvement in their alcohol dependence and some will go on to long-term improvement. The study will provide information on whether HRST and craving for alcohol can enhance the prediction of naltrexone response and, if so, this could have value to the treatment of alcohol dependence in general. The overall risks of the study are minor and the risk/benefit ratio is considered very favorable.

A.4.7. Full description of risks and measures to minimize risks. Include risk of psychosocial harm (e.g., emotional distress, embarrassment, breach of confidentiality), economic harm (e.g., loss of employment or insurability, loss of professional standing or reputation, loss of standing within the community) and legal jeopardy (e.g., disclosure of illegal activity or negligence), as well as known side effects of study medication, if applicable, and risk of pain and physical injury. Describe what will be done to minimize these risks. Describe procedures for follow-up, when necessary, such as when subjects are found to be in need of medical or psychological referral. If there is no direct interaction with subjects, and risk is limited to breach of confidentiality (e.g., for existing data), state this.

The risks to subjects include side-effects from naltrexone, exposure to placebo, and discomfort with discussing problems related to alcohol and mental health and loss of confidentiality.

1) Naltrexone: The risks of naltrexone are well known in the treatment of alcohol dependence because it has been in use as an approved drug for alcohol dependence for nearly 15 years. Risks include nausea (10%) and/or vomiting (3%), sleeplessness (3%), anxiety (2%), nervousness (4%), abdominal cramps, low energy, joint/muscle pain, and headache. Less common side effects include loss of appetite, diarrhea, increased thirst, increased energy, depression, irritability, dizziness, skin rash, delayed ejaculation, and chills. Nausea is the most often encountered side effect. To manage nausea, Pepto-Bismol ® and/or hydroxyzine pamoate (Vistaril) may be used or a reduction of naltrexone dose, or discontinuation of naltrexone until nausea resolves then retitration after premedicating with Vistaril. For anxiety, nervousness, dizziness, and insomnia, dose reduction plus Vistaril if needed, will be used. For headache, over the counter medications such as aspirin, acetaminophen, or ibuprofen will be recommended.

Naltrexone is an opiate antagonist and it can precipitate withdrawal symptoms in individuals using opiates. To prevent the likelihood of this happening, a careful history for opioid use and a urine drug screen will be reviewed upon screening to check for the presence of opiates and methadone. Also subjects who require opioid medication for an emergent injury or surgical procedure will experience less opioid effect if one is prescribed. Non-opioid analgesics such as ketorolac or ibuprofen would be indicated in
these circumstances. Patients in severe pain requiring opioids may be treated with repeated small doses of IV short acting opioids (e.g. hydromorphone). The narcotic dose should be gradually titrated until pain is relieved. The amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged. Patients should be monitored closely by personnel prepared to administer CPR if necessary. In the event of respiratory depression, the narcotic effect may be reversed with Narcan.

Hepatocellular injury has been reported in people receiving large doses of naltrexone (up to 300 mg/day) (Prod. Info ReVia®, 2000). Also, some patients who received high doses (up to 300 mg/day) for treatment of obesity experienced elevations in transaminases that returned to normal once naltrexone was discontinued (Atkinson, et al. 1985; and Mitchell, 1986). However, in the large scale safety study using 50-100 mg/day of naltrexone in alcoholics, hepatotoxicity was not reported (Croop, et al. 1997). However, Anton et al (2006) in the COMBINE trial that utilized 100 mg of naltrexone daily did find higher rates of elevated transaminases in participants in the naltrexone group. But, overall, most clinical trials with naltrexone that have used a 50 mg dose have not reported liver problems. Nevertheless, a baseline liver profile will be reviewed from the screening labs and follow up liver profiles will be drawn at week 4 and at week 12 or early termination. Subjects with AST or ALT elevations ≥ 3X ULN or an elevated bilirubin will not be enrolled in the trial. If these indices arise during the trial medication will be stopped temporarily and the liver profile monitored. If the liver profile does not improve or worsens, a referral will be made to either the subject’s primary care physician or the UNC Urgent Care for further evaluation and treatment. Subjects already enrolled in the study who are asked to discontinue naltrexone will be encouraged to continue to participate in the study to receive counseling.

2) Placebo: Risks associated with placebo would be considered to be low for this trial. The use of medication for alcohol dependence is still not considered a mandatory clinical requirement and, in fact, probably fewer than 10% of alcohol dependent patients in treatment receive medication. Subjects will be receiving monitoring and counseling and this has been shown to be an effective intervention. Therefore, placebo risks are minimal.

3) Hydroxyzine Pamoate (Vistaril): Risks associated with oral hydroxyzine include drowsiness, headache, weakness and dry mouth.

4) Behavioral Intervention: Risks associated with discussing problems related to alcohol and mental health including feelings of shame and embarrassment, increased anxiety and increased depressed feelings. However, in our experience these feelings are generally transient and limited once the subject realizes he or she is in a supportive environment and is not judged. Overall, these risks are minimal.

5) Confidentiality: Risks to confidentiality include the disclosure of sensitive information regarding substance use or mental health to a third party including employers and insurance companies. In nearly 20 years of conducting clinical trials we have not had an incident of a breach of confidentiality. We make certain that all paper and electronic records do not contain unique identifying information. Staff is instructed not to use subjects’ names when talking to anyone outside of the immediate research team. The linkage file containing the ID codes with subjects’ names is kept in a locked file cabinet in a locked office. Confidentiality is taken seriously.

6) Other Risks: Other Risks include the risk of venipuncture including the possibility of bruising, pain, vein thrombosis, or infection. We have extensive experience with venipuncture and use trained staff to draw blood. We have never had a serious complication from venipuncture.

7) Ancillary Studies on Cognitive Test/fMRI:
The Cognitive Function Tests: There are no known risks for injury involved in the cognitive testing of this study. However, some individuals may experience boredom or fatigue. Subjects will be given brief rests or breaks as needed.

Functional Magnetic Resonance Imaging: Only a subset of participants – those who are interested and eligible for MRI – will participate in an fMRI study. After being screened for contra-indicators on the day of scanning, participants will read and sign an informed consent document detailing the general purposes and procedures of the experiment. Any questions that they may have will be answered by study staff. The informed consent form clearly states that subjects may end participation at any time without prejudice. Subjects are verbally read the experimental instructions just prior to scanning. After testing is complete, the purposes and predictions of the research will be clearly explained to the subjects and their questions will be answered. Throughout the duration of the fMRI session, it is ensured that the participants are well and comfortable. Participant status is assessed after each scan and adjustments are made to ensure participant comfort as necessary.

Participants will be excluded from fMRI studies if they have electrically, magnetically or mechanically activated implants (such as cardiac pacemakers), intracerebral vascular clips (surgically implanted metal clips in any blood vessels within the brain), other non-removable body metal, tattoos, or if they are pregnant or claustrophobic. Participants will also be excluded from fMRI testing if they are left-handed, as previous research has shown that handedness may impact the localization of brain activity.

Functional data will be acquired using a gradient-echo EPI pulse sequence (TR = 2 sec., TE = 40 msec., 31 axial slices oriented for best whole head coverage, acquisition voxel size = 3.125 X 3.125 X 3 mm with a .3 mm inter-slice gap). The first four EPI volumes will be discarded to minimize any startle-induced motion effects and to allow tissue magnetization to reach equilibrium. Run acquisitions will be approximately 6 minutes. Anatomical high-resolution MPRAGE T1 scans will be obtained for each subject during the same scan session. Head movement will be comfortably restricted with cushioning. Stimuli will be presented with a computer controlled LCD projector onto a back projection screen placed in the back of the scanner bore, which is viewed by participants through a mirror mounted above the head coil. When necessary, vision will be corrected to normal using MRI compatible plastic lenses and frames.

The MRI scanning will be conducted by the trained scanning technicians of the UNC Biomedical Research Imaging Center (BRIC). Study personnel will also be present in the scanner control room during scanning to interact with the subject (via intercom) and to monitor the behavioral response collection equipment and computer.

Potential minor risks and discomforts are associated with MRI acquisition. Although it is hoped that subjects will complete the study, subjects may stop participation at any time during scanning. No known health risks are associated with this type of MRI, and detailed routine screening will exclude individuals with contra-indications to MRI, such as metal in the body or pregnancy. The only significant risk with MRI is the presence of ferromagnetic materials, so all subjects will be carefully checked for metal prior to entering the magnet room. As the risks of MRI to a fetus are unknown (Pregnancy Risk Category C), participants will be provided with a urine early-pregnancy test on the day of scanning. People with claustrophobia may feel uncomfortable in the scanner, therefore people with a history of claustrophobia will be excluded and all subjects will be warned of this possibility. A temperature and pressure sensitive foam pillow is used to comfortably restrict head motion during scanning, thereby reducing fatigue and motion artifact. The MRI makes loud noises as it acquires data, so subjects are provided with ear plugs and fitted with MR compatible headphones, which protect subjects’ hearing but still permit communication between the investigator and subject. Subjects must lie still in the MRI scanner for approximately 50-60 minutes. Efforts will be made to make the subjects as comfortable as possible, and procedures will be explained thoroughly prior to scanning. The testing and MRI session can be
stopped at any time at the subject’s request or due to investigator concerns about subject safety or comfort.

A.4.8. **Data monitoring and analysis.** Tell how the qualitative and/or quantitative data will be analyzed. Explain how the sample size is sufficient to achieve the study aims. This might include a formal power calculation or explanation of why a small sample is sufficient (e.g., qualitative research, pilot studies). Describe the provisions for monitoring the data to ensure the safety of participants. These plans could range from the investigator monitoring subject data for any safety concerns to a sponsor-based DSMB, depending on the study.

**Baseline Variables**
Study participants will be characterized on baseline demographic variables (age, gender, education, etc.), alcohol dependence severity (ADS; DrInC; SCID-IV severity and presence of physiological dependence), drinking history variables (e.g., years of alcohol use, prior treatments), pretreatment drinking frequency and quantity (TLFB), and craving (PACS). These variables will be summarized by calculating means, standard deviations and percentile ranges for all continuous variables and by calculating proportions for all categorical variables.

An independent sample t-test will be used to assess group differences for continuous variables. Nominal variables will be analyzed via chi-square tests of independence. Ordinal variables will be analyzed via proportional odds tests. For categories with low prevalence, Fisher’s exact tests will be used to determine if the proportions across categories are independent of treatment.

**Primary Outcome Analyses:**

**Specific Aim 1. To test the hypothesis that a combination of SL/SDL status and initial alcohol craving will predict % ABST during treatment with naltrexone.**

Summary measures of the proportion of abstinence days will be derived from the TLFB for the entire medication period. In addition, we will derive weekly drinking measures from TLFB which will provide a linkage between periodic craving assessments and usage during the corresponding period. Descriptive statistics and exploratory graphing will be used to assess the normality of the data in terms of the presence of skew and/or outliers. The continuous outcome data will be transformed if necessary by using an appropriate transformation. Potential covariates will also be inspected as well to determine the most appropriate way to treat these variables. The analytical approach should adequately address the nature of the outcome, as well as accommodate the within individual variability. In addition, the results from the given approach will be inspected for bias due to drop out and/or missing data.

**Primary Efficacy Analysis:** For the Summary measure, we will fit a general linear model on the outcome variable, which will be transformed if necessary, consisting of main effect for HRST status, main effect for treatment status, main effect for craving, and all two-way and three-way interactions. To assess goodness-of-fit, residuals will be analyzed for assessment of outliers and influential observations. For the weekly measures, we will fit a mixed effects model consisting of main effect for HRST status, main effect for craving, and the interaction of craving and HRST. This approach provides more information and therefore, more power compared to cross-sectional analyses which focus on the analysis of one summary index or time-until event methods. This Mixed effects modeling will allow us the flexibility to categorize the on-average behavior or growth curves describing the change over time in average behavior. In addition, the mixed effects framework offers flexibility for the outcomes. For binary or count outcome data, a special class of a Mixed models will be implemented, Generalized Linear Mixed Models (GLMM) (Wolfinger and O’Connell, 1993; Breslow and Clayton, 1993). Appropriate covariance structure will be determined based on the AIC (Akakie Information Criteria). To assess goodness-of-fit, Mixed effects models yield residuals for assessment of outliers and distribution of error terms.

**Treatment of Missing Data:** With repeated assessments, missing data/attrition is inevitable, but the key thing is that the specified contrasts are not affected due to the presence/absence of data. The mixed effects framework is robust with respect to drop-out and missing data, unless the drop-out mechanism or cause of
missing is informative. We will use pattern-mixture models to assess if there is bias due to drop out or missing data. As described by Hedeker and Gibbons (1997), these mixed models allow us to assess whether important estimates (e.g., Group differences in abstinence) are dependent on missing data patterns, and provide overall estimates of effects by averaging over the various missing-data patterns. To apply the pattern mixture approach the number of patterns examined must be manageable. Typically, various patterns are combined and often reduced to two clinically meaningful patterns: e.g., completers and dropouts. We will determine the best definition of pattern based on the available data. In addition, we will consider the extension of the Pattern-Mixture models as described by Guo et al (2004) which includes the incorporation of random effects in the Pattern mixture model, which allow subject-to-subject heterogeneity.

Adjustment for Covariates: Both modeling approaches allow for the inclusion of covariates such as ADS and Family History. An additional benefit of the weekly measures is it allows for the inclusion of time-varying and time-invariant covariates. Therefore, in our inspection of the effect of craving, we can consider baseline craving, previous week’s craving, or concurrent craving, as well as controlling for ADS and Family History.

Specific Aim 2. To test whether a combination of SL/SDL status and initial alcohol craving predict % HDD during treatment with naltrexone.

For this specific aim, the analytical approach described above will be replicated.

Statistical Power and Sample Size

In the pilot study, power derivations for assessing the highest order effect, namely a significant interaction of sweet liking status and craving score was implemented through SAS PROCLMPOWER, using the estimated mean abstinence during the medication period for various combinations of HRST and craving, coded as High versus Low. Estimates means are 0.692 for SDL-Low craving, 0.285 for SDL-High craving, 0.086 for SL-Low craving, and 0.425 for SL-High craving with a pooled standard deviation of 0.294. Based on these means, a two-sided test with alpha=0.05, and 2:3 ratio for SL compared to SDL, a total sample size of 30 medicated subjects provides 90.6% power to assess a significant two-way interaction and a sample size of 40 medicated subjects provides 96.9% power. With an additional 40 subjects receiving placebo, and assuming similar means for the 4 combinations of SDL-SL status and craving, we have 78.3% power to detect a significant three-way interaction. We are aware of the recently published article by Kraemer et al. (2006), which emphasizes extreme caution in the use of pilot data to estimate sample size and calculation of power for randomized clinical trials (RCT). But unlike the issues raised by Kraemer et al. (2006) where there are distinguishable differences between pilot study and the later randomized, placebo-controlled trial, such as procedure, training of study personnel, entry criteria of subjects, this proposal is exactly the same with the exception of an additional sample of 40 placebo patients. Thus, we are comfortable that the 40 NTX subjects provide sufficient power to assess a significant two-way interaction. The proposed study will provide this information, which could be used to justify power in a larger follow-up study if indicated.

Statistical Analysis for Ancillary Studies

Dot Probe: To assess the effect of NTX on performance in this task, RT and accuracy data will be analyzed by mixed model repeated measures ANOVA, testing for effects of pill (NTX vs. placebo), session (1 vs, 2), and cue (alcohol vs. neutral), as well as interactions between these factors. A priori power analysis shows that testing n=20 in each group (total n = 40) will obtain 80% power to detect a small effect size (0.23), and 95% power to detect an effect size of 0.29.

Attentional Blink: Target detection will be quantified as % of accurately detected T2s, given an accurately detected T1, and will be analyzed by mixed model repeated measures ANOVA, testing for effects of pill (NTX vs. placebo), target (alcohol vs. neutral), and target spacing (close vs. far), as well as interactions between these factors. As for the other task, a sample size of 40 should be
adequately powered to detect a modest effect of NTX on attention.

**Overall.** We will use a strategy like that proposed in the main funded study. In brief, we will fit a general linear model on the drinking outcome variable, which will be transformed if necessary, consisting of main effect for attentional capture change, main effect for attentional hold change, main effect for treatment status, and all two-way and three-way interactions between factors.
A.4.9. **Will you collect or receive any of the following identifiers?** Does not apply to consent forms.

___ No  ___ X ___ Yes  If yes, check all that apply:

a. ___ X ___ Names
b. ___ X ___ Telephone numbers
c. ___ X ___ Any elements of dates (other than year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death. For ages over 89: all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 and older
d. ___ X ___ Any geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code
e. ___ Fax numbers
f. ___ X ___ Electronic mail addresses
g. ___ Social security numbers
h. ___ X ___ Medical record numbers
i. ___ Health plan beneficiary numbers
j. ___ Account numbers
k. ___ Certificate/license numbers
l. ___ Vehicle identifiers and serial numbers (VIN), including license plate numbers
m. ___ Device identifiers and serial numbers (e.g., implanted medical device)
n. ___ Web universal resource locators (URLs)
o. ___ Internet protocol (IP) address numbers
p. ___ Biometric identifiers, including finger and voice prints
q. ___ Full face photographic images and any comparable images
r. ___ Any other unique identifying number, code, or characteristic, other than dummy identifiers that are not derived from actual identifiers and for which the re-identification key is maintained by the health care provider and not disclosed to the researcher

A.4.10. **Identifiers in research data.** Are the identifiers in A.4.9 above linked or maintained with the research data?

___ X ___ yes ___ no

A.4.11. **Confidentiality of the data.** Describe procedures for maintaining confidentiality of the data you will collect or will receive. Describe how you will protect the data from access by those not authorized. How will data be transmitted among research personnel? Where relevant, discuss the potential for deductive disclosure (i.e., directly identifying subjects from a combination of indirect IDs).

Every effort will be taken to protect the identity of the subjects in the study. However, there is no guarantee that the information cannot be obtained by legal process or court order. The FDA may be allowed to examine the records for safety reasons. No subjects will be identified in any report or publication of this study or its results. If a health condition is detected during this trial the subject will be told about it and if necessary they will be advised to seek medical attention. Only the research staff at UNC will have access to the study number, name, and personal information for the purpose of mailings, as well as maintaining and updating study records. This information will be kept separate from their research data in locked filing cabinets where access is limited to the PI and Coordinator. Study records will be kept indefinitely for analysis and follow-up.

We received a Certificate of Confidentiality.
A.4.12. **Data sharing.** With whom will identifiable (contains any of the 18 identifiers listed in question A.4.9 above) data be shared outside the immediate research team? For each, explain confidentiality measures. Include data use agreements, if any.

- **X** No one
- [ ] Coordinating Center:
- [ ] Statisticians:
- [ ] Consultants:
- [ ] Other researchers:
- [ ] Registries:
- [ ] Sponsors:
- [ ] External labs for additional testing:
- [ ] Journals:
- [ ] Publicly available dataset:
- [ ] Other:

A.4.13. **Data security for storage and transmission.** Please check all that apply.

*For electronic data stored on a desk top computer:*

- **X** Secure network
- **X** Password access
- [ ] Data encryption
- [ ] Password protected file(s)
- [ ] Other comparable safeguard (describe):

*For portable computing devices/external storage devices (e.g. laptop computer, PDA, CDs, memory sticks):*

- **X** Power-on password
- **X** Automatic log-off
- [ ] Data encryption
- [ ] Password protected file(s)
- [ ] Other comparable safeguard (describe):

*For hardcopy data (including human biological specimens, CDs, tapes, etc.):*

- **X** Data de-identified by research team (stripped of the 18 identifiers listed in question A.4.9 above)
- [ ] Locked suite or office
- [ ] Locked cabinet
- **X** Data coded by research team with a master list secured and kept separately
- [ ] Other (describe):

A.4.14. **Post-study disposition of identifiable data or human biological materials.** Describe your plans for disposition of data or human biological specimens that are identifiable in any way (directly or via indirect codes) once the study has ended. Describe your plan to destroy identifiers, if you will do so.

Samples collected for specified laboratory tests will be destroyed after the test is run and results confirmed. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid.

**Genetic Testing:** Genetic testing may be a part of this study in that samples will be archived for future genetic studies. If the Subject consents, genetic material derived from samples may be tested for polymorphisms of opioid receptor genes, possibly other genes related to alcoholism and for common genetic variation that may affect attentional performance. Saliva samples for genotyping will be collected...
only once and may be collected at any study visit. These samples will be destroyed once the genetic testing is completed.

Part A.5. The Consent Process and Consent Documentation (including Waivers)

The standard consent process is for all subjects to sign a document containing all the elements of informed consent, as specified in the federal regulations. Some or all of the elements of consent, including signatures, may be altered or waived under certain circumstances.

- If you will obtain consent in any manner, complete section A.5.1.
- If you are obtaining consent, but requesting a waiver of the requirement for a signed consent document, complete section A.5.2.
- If you are requesting a waiver of any or all of the elements of consent, complete section A.5.3.
- If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a limited waiver of HIPAA authorization. This is addressed in section B.2.

You may need to complete more than one section. For example, if you are conducting a phone survey with verbal consent, complete sections A.5.1, A.5.2, and possibly A.5.3.

A.5.1. Describe the process of obtaining informed consent from subjects.
Describe who will be obtaining consent (or permission) and from whom. Include discussion, as relevant, any waiting period between the initial consent discussion and obtaining consent, and steps that will be taken to minimize coercion or undue influence. If children will be enrolled as subjects, describe the provisions for obtaining parental permission and assent of the child. If decisionally impaired adults are to be enrolled, describe the provision for obtaining surrogate consent from a legally authorized representative (LAR). If non-English speaking people will be enrolled, explain how consent in the native language will be obtained. Address both written translation of the consent and the availability of oral interpretation. It is expected that the information in the consent document(s) will be communicated to participants or their LAR. After you have completed this part A.5.1, if you are not requesting a waiver of any type, you are done with Part A.5.; proceed to Part B.

Prior to full screening, individuals will read and sign the informed consent document and be given a copy for their records. The nature of the study and its risks and benefits will be explained to the subject by the Investigator (or designated staff). Informed consent will be obtained by the research coordinator and study physicians at the initial visit. Each subject will receive an informed consent document with subject information and will be given ample time to read the information. If the subject chooses to participate, the subject must sign the informed consent document. A breathalyzer test using an AlcoHawk Pro will be administered, and breath alcohol concentration (BAC) must be 0.00 gms/dl in order for the consent process to be considered valid. The study physician will discuss the protocol with the subject to insure that all questions have been addressed.

A.5.2. Justification for a waiver of written (i.e., signed) consent. The default is for subjects to sign a written document that contains all the elements of informed consent. Under limited circumstances, the requirement for a signed consent form may be waived by the IRB if either of the following is true. Choose only one:

We request oral consent for a telephone screen to be conducted by the study coordinator. Individuals who call in response to advertising would first be screened by telephone after obtaining oral consent. If
individuals appear eligible as determined by the investigative team, they will be scheduled to come to the UNC Hospital for more comprehensive screening.

a. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., study topic is sensitive so that public knowledge of participation could be damaging). Participants should be asked whether they want documentation linking them with the research and the participants’ wishes will govern whether they sign the form. Note: This justification cannot be used in FDA-regulated research. __ yes __ no

Explain.

b. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (e.g., phone survey). __ yes __ no

Explain.

If you checked “yes” to either (and you are not requesting a waiver in section A.5.3) consent must be obtained orally, by delivering a fact sheet, through an online consent form, or be incorporated into the survey itself. Include a copy of the consent script, fact sheet, online consent form, or incorporated document.

If you have justified a waiver of written (signed) consent (A.5.2), you should complete A.5.3 only if your consent process will not include all the other elements of consent.

A.5.3. Justification for a full or partial waiver of consent. The default is for subjects to give informed consent. A waiver might be requested for research involving only existing data or human biological specimens (see also Part C). More rarely, it might be requested when the research design requires withholding some study details at the outset (e.g., behavioral research involving deception). In limited circumstances, parental permission may be waived. This section should also be completed for a waiver of HIPAA authorization if research involves Protected Health Information (PHI) subject to HIPAA regulation, such as patient records.

__ Requesting waiver of some elements (specify; see SOP 28 on the IRB web site):
__ Requesting waiver of consent entirely
If you check either of the boxes above, answer items a-f. To justify a full waiver of the requirement for informed consent, you must be able to answer “yes” (or “not applicable” for question c) to items a-f. Insert brief explanations that support your answers.

a. Will the research involve no greater than minimal risk to subjects or to their privacy? __ yes __ no

Explain.

b. Is it true that the waiver will not adversely affect the rights and welfare of subjects? (Consider the right of privacy and possible risk of breach of confidentiality in light of the information you wish to gather.) __ yes __ no

Explain.
c. When applicable to your study, do you have plans to provide subjects with pertinent information after their participation is over? (e.g., Will you provide details withheld during consent, or tell subjects if you found information with direct clinical relevance? This may be an uncommon scenario.)
Explain.

__ yes __ not applicable

 d. Would the research be impracticable without the waiver? (If you checked “yes,” explain how the requirement to obtain consent would make the research impracticable, e.g., are most of the subjects lost to follow-up or deceased?).
Explain.

__ yes __ no

 e. Is the risk to privacy reasonable in relation to benefits to be gained or the importance of the knowledge to be gained?
Explain.

__ yes __ no

If you are accessing patient records for this research, you must also be able to answer “yes” to item f to justify a waiver of HIPAA authorization from the subjects.

f. Would the research be impracticable if you could not record (or use) Protected Health Information (PHI)? (If you checked “yes,” explain how not recording or using PHI would make the research impracticable).
Explain.

__ yes __ no

Part B. Questions for Studies that Involve Direct Interaction with Human Subjects

→ If this does not apply to your study, do not submit this section.

B.1. Methods of recruiting. Describe how and where subjects will be identified and recruited. Indicate who will do the recruiting, and tell how subjects will be contacted. Describe efforts to ensure equal access to participation among women and minorities. Describe how you will protect the privacy of potential subjects during recruitment. For prospective subjects whose status (e.g., as patient or client), condition, or contact information is not publicly available (e.g., from a phone book or public web site), the initial contact should be made with legitimate knowledge of the subjects’ circumstances. Ideally, the individual with such knowledge should seek prospective subjects’ permission to release names to the PI for recruitment. Alternatively, the knowledgeable individual could provide information about the study, including contact information for the investigator, so that interested prospective subjects can contact the investigator. Provide the IRB with a copy of any document or script that will be used to obtain the patients’ permission for release of names or to introduce the study. Check with the IRB for further guidance.

Prospective participants will call in response to advertising in local newspapers, web sites, mass-email or radio spots. Healthcare professionals within the UNC Healthcare system will be informed about the study and may also refer prospective participants. A telephone screening will be conducted by the study coordinator after obtaining oral consent. If individuals appear eligible as determined by the investigative team, they will be scheduled to come to the UNC Hospital for more comprehensive screening. If they are deemed ineligible during the phone screen, that phone screen record will be placed in the confidential shredder.
B.2. **Protected Health Information (PHI).** If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a *limited waiver of HIPAA authorization*. If this applies to your study, please provide the following information and complete Section C.

a. Under this limited waiver, you are allowed to access and use only the minimum amount of PHI necessary to review eligibility criteria and contact potential subjects. What information are you planning to collect for this purpose? *Once subject is enrolled into the study and has signed the HIPAA authorization and consent document, we will only be collecting or viewing information in their PHI that enables us to contact the subject or verify contact information.*

b. How will confidentiality/privacy be protected prior to ascertaining desire to participate? *For subjects who contact us from the general population, the information will be taken on a screening form and then stored in a locked filing cabinet.*

c. When and how will you destroy the contact information if an individual declines participation? *If the subject declines participation, the forms will be placed in a confidential shredding bin.*

B.3. **Duration of entire study and duration of an individual subject’s participation, including follow-up evaluation if applicable.** Include the number of required contacts and approximate duration of each contact.

The duration of the study is two years. Each participant will be involved for about 12-16 weeks. Prospective subjects will contact us in response to our advertisement and be scheduled for a screening visit. During the screening visit that will last for approximately 3-4 hours, patient will be consented and screened. They will have 3-21 days from screening visit date to decide if they want to participate in the study. The randomization visit will occur between 4-21 days from the Screening Visit. This visit will last approximately one-two hours. At the randomization visit the patient will begin naltrexone or placebo as well as the first BRENDA session.

The follow-up visits should take place according to the following schedule: Visit 1-4 should be schedule 4-10 days from the randomization visit. Visits 5-12 should occur every 11-17 days. Follow-up Call 16 should occur between 27-33 days. All visits will last for approximately one hour each and will have a window of ± 3 days.

B.4. **Where will the subjects be studied?** Describe locations where subjects will be studied, both on and off the UNC-CH campus.

The screening visit will take place at offices within the Neurosciences Hospital. All follow-up subject visits will occur at the Alcohol and Substance Abuse Program at Timberlyne or at offices within the Neurosciences Hospital.
B.5. **Privacy.** Describe procedures that will ensure privacy of the subjects in this study. Examples include the setting for interviews, phone conversations, or physical examinations; communication methods or mailed materials (e.g., mailings should not indicate disease status or focus of study on the envelope).

Sensitive information will be gathered during the study. Only individuals directly associated with the study will have access to this information. A link will be maintained to the subjects name to facilitate contact and communication, and this link will be destroyed once the study is completed. Records will be maintained in locked cabinets in locked offices with only the investigators having access to these records. Interviews, phone conversations, and physical examinations will be conducted in a private office space. All correspondence that is sent to the subject will list only the UNC Medical School and Department.

B.6. **Inducements for participation.** Describe all inducements to participate, monetary or non-monetary. If monetary, specify the amount and schedule for payments and if/how this will be prorated if the subject withdraws (or is withdrawn) from the study prior to completing it. For compensation in foreign currency, provide a US$ equivalent. Provide evidence that the amount is not coercive (e.g., describe purchasing power for foreign countries). Be aware that payment over a certain amount may require the collection of the subjects’ Social Security Numbers. If a subject is paid more than $200.00 per year, collection of subjects’ Social Security Number is required (University policy—see [SSN Guidance](#)) using the Social Security Number collection consent addendum found under [forms on the IRB website](#) (look for Study Subject Reimbursement Form).

Individuals will not receive monetary compensation for participating in the main study. The primary inducement for participation is the provision of free counseling sessions. We will provide parking vouchers.

Past participants who provide saliva samples for genotyping purposes via mail will be paid $10.

**Ancillary Studies:** Ancillary Study 1) Participants will receive $10/hour for each session for up to four sessions. Ancillary Study 2) FMRI Participants will receive $15/hour plus a $50 completion bonus after completing the second session.

B.7. **Costs to be borne by subjects.** Include child care, travel, parking, clinic fees, diagnostic and laboratory studies, drugs, devices, all professional fees, etc. If there are no costs to subjects other than their time to participate, indicate this.

Participants will be responsible for their transportation to UNC.

**Literature Cited:**


Kampov-Polevoy AB, Tzoi MV, Zvartau EE, Neznanov NG, Khalitov E. Sweet liking and family history of alcoholism in hospitalized alcoholic and non-alcoholic patients. Alcohol and Alcoholism. 2001; 36:165-170.


Statistical Analysis Plan

D.8.1 Baseline Variables

Study participants will be characterized on baseline demographic variables (age, gender, education, etc.), alcohol dependence severity (ADS; SCID-IV severity and presence of physiological dependence), drinking history variables (e.g., years of alcohol use, prior treatments), pretreatment drinking frequency and quantity (TLFB), and craving (PACS). These variables will be summarized by calculating means, standard deviations and percentile ranges for all continuous variables and by calculating proportions for all categorical variables.

An independent sample t-test will be used to assess group differences for continuous variables. Nominal variables will be analyzed via chi-square tests of independence. Ordinal variables will be analyzed via proportional odds tests. For categories with low prevalence, Fisher’s exact tests will be used to determine if the proportions across categories are independent of treatment.

D.8.2 Outcome Variables

Specific Aim 1. To test the hypothesis that a combination of SL/SDL status and initial alcohol craving will predict %ABST during treatment with naltrexone.

Summary measures of the proportion of abstinence days will be derived from the TLFB for the entire medication period. In addition, we will derive weekly drinking measures from TLFB which will provide a linkage between periodic craving assessments and usage during the corresponding period. Descriptive statistics and exploratory graphing will be used to assess the normality of the data in terms of the presence of skew and/or outliers. The continuous outcome data will be transformed if necessary by using an appropriate transformation. Potential covariates will also be inspected as well to determine the most appropriate way to treat these variables. The analytical approach should adequately address the nature of the outcome, as well as accommodate the within individual variability. In addition, the results from the given approach will be inspected for bias due to drop out and/or missing data.

Primary Efficacy Analysis: For the Summary measure, we will fit a general linear model on the outcome variable, which will be transformed if necessary, consisting of main effect for HRST status, main effect for treatment status, main effect for craving, and all two-way and three-way interactions. To assess goodness-of-fit, residuals will be analyzed for assessment of outliers and influential observations.

For the weekly measures, we will fit a mixed effects model consisting of main effect for HRST status, main effect for craving, and the interaction of craving and HRST. This approach provides more information and therefore, more power compared to cross-sectional analyses which focus on the analysis of one summary index or time-until event methods. This Mixed effects modeling will allow us the flexibility to categorize the on-average behavior or growth curves describing the change over time in average behavior. In addition, the mixed effects framework offers flexibility for the outcomes. For binary or count outcome data, a special class of a Mixed models will be implemented, Generalized Linear Mixed Models (GLMM) (Wolfinger and O’Connell, 1993; Breslow and Clayton, 1993). Appropriate covariance structure will be determined based on the AIC (Akakie Information Criteria). To assess goodness-of-fit, Mixed effects models yield residuals for assessment of outliers and distribution of error terms.
Treatment of Missing Data: With repeated assessments, missing data/attrition is inevitable, but the key thing is that the specified contrasts are not affected due to the presence/absence of data. The mixed effects framework is robust with respect to drop-out and missing data, unless the drop-out mechanism or cause of missing is informative. We will use pattern-mixture models to assess if there is bias due to drop out or missing data. As described by Hedeker and Gibbons (1997), these mixed models allow us to assess whether important estimates (e.g., Group differences in abstinence) are dependent on missing data patterns, and provide overall estimates of effects by averaging over the various missing-data patterns. To apply the pattern mixture approach the number of patterns examined must be manageable. Typically, various patterns are combined and often reduced to two clinically meaningful patterns: e.g., completers and dropouts. We will determine the best definition of pattern based on the available data. In addition, we will consider the extension of the Pattern-Mixture models as described by Guo et al (2004) which includes the incorporation of random effects in the Pattern mixture model, which allow subject-to-subject heterogeneity.

NOTE: We did not include the results of the pattern-mixture analysis in the published paper for space reasons. However, in our sample, 70% of the patients (56/80) provided weekly results through the 12th week of the medication period. Implemented pattern-mixture models used to determine if our results were dependent on missing data yielded non-significant associations. For the heavy-usage analysis, pattern-mixture models yielded non-significant relationship of pattern to our previously reported significant results (p>0.23). Similar results were found for the abstinence analysis (p>0.28).

Adjustment for Covariates: Both modeling approaches allow for the inclusion of covariates such as ADS and Family History. An additional benefit of the weekly measures is it allows for the inclusion of time-varying and time-invariant covariates. Therefore, in our inspection of the effect of craving, we can consider baseline craving, previous week’s craving, or concurrent craving, as well as controlling for ADS and Family History.

Specific Aim 2. To test whether a combination of SL/SDL status and initial alcohol craving predict %HDD during treatment with naltrexone.

For this specific aim, the analytical approach described above will be replicated.

D.9 Statistical Power and Sample Size

In the pilot study, power derivations for assessing the highest order effect, namely a significant interaction of sweet liking status and craving score was implemented through SAS PROCGLMPower, using the estimated mean abstinence during the medication period for various combinations of HRST and craving, coded as High versus Low. Estimates means are 0.692 for SDL-Low craving, 0.285 for SDL-High craving, 0.086 for SL-Low craving, and 0.425 for SL-High craving with a pooled standard deviation of 0.294. Based on these means, a two-sided test with alpha=0.05, and 2:3 ratio for SL compared to SDL, a total sample size of 30 medicated subjects provides 90.6% power to assess a significant two-way interaction and a sample size of 40 medicated subjects provides 96.9% power. With an additional 40 subjects receiving placebo, and assuming similar means for the 4 combinations of SDL-SL status and craving, we have 78.3%
power to detect a significant three-way interaction. We are aware of the recently published article by Kraemer et al. (2006), which emphasizes extreme caution in the use of pilot data to estimate sample size and calculation of power for randomized clinical trials (RCT). But unlike the issues raised by Kraemer et al. (2006) where there are distinguishable differences between pilot study and the later randomized, placebo-controlled trial, such as procedure, training of study personnel, entry criteria of subjects, this proposal is exactly the same with the exception of an additional sample of 40 placebo patients. Thus, we are comfortable that the 40 NTX subjects provide sufficient power to assess a significant two-way interaction. The proposed study will provide this information, which could be used to justify power in a larger follow-up study if indicated.