QEEG Predictors of Response for Psychotherapy Compared to Pharmacotherapy in Depression

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I. Background and significance

A. Treatment of MDD:

Over two-thirds of patients with MDD treated with first-line medications, such as citalopram, fail to achieve remission during 12 weeks of acute treatment. Patients who fail to achieve remission typically have greater impairment of social and work function and a much higher risk of relapse and recurrence of MDD than those who remit (Paykel et al., 2005). As demonstrated in the STAR*D trial, many patients who go on to achieve remission on pharmacotherapy or CBT do not do so until the second 6 weeks of treatment even with enhanced, measurement-based care (Rush et al., 2006).

Recently, an increasing body of "predictor studies" has emerged which aims to use neuroimaging measures to predict treatment outcomes. These studies are pivotal in advancing treatment options for depression, as validated surrogate markers that predict response at baseline or soon after starting treatment would help clinicians optimize a patient's treatment within the first several weeks of initiation, potentially saving weeks to months of ongoing distress, disability and risk of suicide. In light of the challenges that MDD poses to clinicians and patients alike, identifying biomarkers which are able to predict outcome are urgently needed to help further refine the standard of care for depression. Additionally, to our awareness no studies have used neuroimaging measures to directly compare different psychosocial interventions, such as Cognitive Behavioral Therapy (CBT).

B. Functional Brain Changes Related to Response to CBT:

Functional brain imaging has suggested the possibility that pharmacotherapy and psychotherapy, while both representing effective treatments for MDD, may exert their effects through different mechanisms (Goldapple et al., 2004). CBT is seen as having a "top down" effect, while pharmacotherapy is viewed as generating a "bottom up" neurobiological cascade. Despite the strong evidence base and widespread use of CBT for depression, we still know very little about its biological mechanisms of action, and even less about biological predictors of response to CBT. The identification of early predictors of response using QEEG might further our understanding of the mechanisms underlying the efficacy of CBT in MDD.

C. QEEG:

Quantitative electroencephalography (QEEG) has emerged in recent years as a technology that may help predict eventual response to antidepressants as early as the first week of prescription and may help shed light on the mechanism(s) of action of depression treatments. QEEG has enabled spectral analysis of EEG signals using a digitized signal on magnetic or optical media, providing information that cannot be extracted through visual inspection of the traditional EEG paper tracings. Cordance, a QEEG measure integrating absolute and relative power of the signal, was shown to be decreased in subjects with MDD, compared to normal

subjects (Cook et al, 1998). Researchers have reported differences between responders and non-responders to antidepressant treatment with respect to the absolute or relative power of the EEG signal (Ulrich et al., 1994; Knott et al, 1996). Subsequently, QEEG has been shown to have utility in predicting clinical response to SSRI antidepressants (Cook et al, 1999). Specifically, in a case series, Cook and Leuchter (2001) found that clinical response to antidepressant medications was preceded by decreases in QEEG measurements (theta cordance) in the prefrontal brain regions.

D. Reward Responsiveness Task

This study will also utilize the Signal Detection computer task which measures anhedonia, the loss of pleasure or lack of reactivity to pleasurable stimuli (APA 1994), and has been considered a trait marker related to vulnerability for depression (Loas 1996; Meehl 1975). Depression has been found to be associated with low levels of self-reinforcement (Gotlib 1982); diminished emotional response to pleasant cues (Berenbaum and Oltmanns 1992; Sloan et al 2001); underestimation of the frequency of positive reinforcements received (Buchwald 1977); decreased responsiveness to reward (Hughes et al 1985); and decreased spatial attention to positive but not negative facial expression (Suslow et al 2001). Previous behavioral studies indicate that depressed individuals and subjects with elevated depressive symptoms show altered reward processing as compared with controls, but normal punishment processing (Henriques & Davidson, 2000). The Signal Detection Task has been implemented in a non-depressed sample as well as schizophrenic samples and has shown that increased levels of depressive symptoms are associated with decreased responsiveness to reward cues.

E. Summary and Rationale:

Studies which identify validated surrogate markers at baseline or soon after starting treatment that can predict response to treatment have the potential to refine the standard of care for depression, as these predictor studies will reduce the amount of time that clinicians spend adjusting treatments to find the most optimal treatment option. Additionally, studies which compare predictive biomarkers between treatments, particularly between psychotherapy and pharmacotherapy, will further enable clinicians to choose an optimal treatment.

To our knowledge, QEEG has not been studied in the prediction of response to CBT, an important and widely used non-pharmacologic approach to treating depression. Establishing QEEG technology as a predictor of response to CBT could help to guide treatment selection for individual patients. It is probable that certain patient populations are more likely to respond to either psychotherapeutic or psychopharmacological interventions, while others may benefit from a combination of treatment modalities. The public health significance of a valid technology that provides an objective means of determining likelihood of response to treatment would be enormous. This study will provide preliminary information about the utility of QEEG as a predictor of response in psychotherapy and will furnish the knowledge base of QEEG changes related to clinical variables, providing pilot data for a study in a larger sample.

Additionally, very few studies have assessed changes in reward responsiveness as a function of treatment. It is possible that CBT and pharmacological interventions have different effects on reward responsiveness and anhedonia, and thus the use of this task will allow us to investigate the influence of different treatments on reward processing in this population. We expect that the results of this study will guide future research with the ultimate goal of identifying a behavioral indicator of underlying dysfunction in reward related brain regions. Finally, it is possible that the reward responsiveness will act as a predictor of response to both psychotherapy and pharmacological treatment.

II. Specific Aims:

Primary Aim 1: To determine whether QEEG technology can predict whether a patient with MDD will respond to CBT.
Hypothesis 1: Clinical response (defined as >50% change in HAMD-17 from beginning to endpoint) will correlate with changes in QEEG metrics (ATR, EEG Bispectrum, cordance estimates) from beginning to two weeks after starting treatment.

Primary Aim 2: To determine whether there are unique biological changes in patients undergoing CBT, as measured by the QEEG, that are different than those associated with antidepressants (SSRIs).
Hypothesis 2: QEEG parameters, different from those that predict response to pharmacotherapy, will be associated with response to CBT.

Secondary Aim 1*:* To determine whether there are correlations between QEEG patterns and changes in clinical functioning, assessed by clinical and self-rated instruments (SF-36, Symptom Questionnaire, Beck Depression Inventory), in both arms (CBT vs. escitalopram).

Secondary Aim 2: To determine whether there are any correlations between QEEG metrics and clinical variables (gender, age, comorbid anxiety, chronicity of depression).

Secondary Aim 3: To determine whether the behavioral processes associated with reward responsiveness in a depressed population change as a function of treatment.

III. Subject Selection

A. Inclusion/exclusion criteria:

Inclusion Criteria*:*

1. Subjects will be adults, ages 18 to 75 years.
2. Written informed consent
3. MDD, current according to the fourth version of the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV)
4. 17-item Hamilton Depression Rating Scale (HAM-D-17) score of $\geq$ 14 at screen.
5. Subjects who are not currently taking any antidepressant or other psychotropic medications and who have been free of these medications for 4 weeks prior to screening visit.

Exclusion Criteria:

1. Women who are pregnant, lactating, or planning a pregnancy during the study.
2. Women of child bearing potential who are not using a medically accepted means of contraception (to include oral contraceptive or implant, condom, diaphragm, spermicide, intrauterine device, tubal ligation, or a partner with vasectomy).
3. Any uncontrolled psychiatric disorder.
4. Current use of psychotropic medications: including lithium, benzodiazepine sedatives (such as diazepam, lorazepam, alprazolam, or clonazepam), other sedatives (such as buspirone, zolpidem, and zaleplon), anti-seizure medications (such as valproic acid, or carbamazepine),
5. Current use of other exclusionary medications: beta-blockers (such as metoprolol or propranolol), dehydroepiandrosterone (DHEA), entacapone, hydroxytryptophan (5-HTP), ginkgo, St. John's wort (hypericum), and warfarin (Coumadin).

6. Psychotic features in the current episode or a history of psychotic features.
7. Alcohol or substance abuse or dependence within the past three months.
8. History of head trauma or seizure disorder.
9. History of intolerance of the study medication.
10. Failure to respond to escitalopram up to 20 mg for at least 6 weeks.
11. Failure to respond to 2 or more adequate antidepressant trials (6 weeks or longer on a therapeutic dose, equivalent to fluoxetine 40mg) in the current episode.
12. Currently enrolled in other depression-focused psychotherapy and unwilling to cease treatment.
13. Subjects who, per clinical judgment, are not appropriate candidates for CBT or SSRIs.
14. History or current diagnosis of the following DSM-IV psychiatric illness: organic mental disorder, schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorders not otherwise specified, bipolar disorder, patients with mood congruent or mood incongruent psychotic features, patients with substance dependence disorders, including alcohol, active within the last 3 months.
15. Serious suicide or homicide risk, as assessed by the evaluating clinician or a score of 4 on the third item of the HAM-D.
16. Serious or unstable medical illness, including cardiovascular, hepatic, renal, respiratory, endocrine, neurologic or hematologic disease

B. Source of Subjects and Recruitment Methods:

Patients will be recruited per usual methods, including IRB-approved advertising in newspapers, television and radio, and referrals from other clinicians.

Patients of all ethnic and racial categories will be included.

Children and adolescents under age 18 will not be included. Children under age 18 will not be included. There are limited data available about the efficacy and safety of escitalopram as an antidepressant in children; it would therefore be preferable to obtain more adult data prior to testing this treatment in children. Also, the investigators of the Depression Clinical and Research Program have limited experience in pediatric work, and are not board-certified in the treatment of pediatric populations. We also are not trained in the use of the diagnostic instruments necessary for the appropriate assessment of younger children with depression, which differ from those instruments used in adults and older adolescents. As there are many registered antidepressants available for use in depressed children, exclusion of young children from this study should not prevent them from obtaining appropriate, effective treatment with proven agents.

IV. Subject Enrollment

A. Methods of enrollment/registration/randomization:

Patients are usually screened by telephone to determine tentative eligibility for studies. The subjects then are invited to come to MGH for a full psychiatric diagnostic interview. Patients accepted into the study will be registered through the Depression Clinical and Research Program. Randomization numbers will be provided by the study Biostatistician and will be maintained by the research pharmacists at MGH Research Pharmacy, who will administer the open label escitalopram, 10-20 mg/day, to those subjects who have been randomized to receive medication. The randomization will be 1:1, i.e. half of the patients will be randomized to receive escitalopram (10-20 mg/day, flexible dose) and half will be randomized to receive twelve weekly 50-minute

Cognitive Behavioral Therapy sessions. Both treatment interventions have been strongly validated by the literature, and are considered standard of care for this population.

V. Study Procedures

a) *Study visits and parameters to be measured*:

The study involves the enrollment of 30 outpatients with major depressive disorder.

Patients screened for the study and found to be eligible will return for their baseline visit after one week, at which eligible patients (n = 30) will be randomized to either CBT or to standard pharmacotherapy with an SSRI (escitalopram 10-20mg) for 12 weeks.

The CBT group will receive twelve weekly 50-minute individual sessions over the course of 12 weeks conducted by experienced therapists who are trained in manual based CBT. The medication group will receive open label treatment of escitalopram, 10-20 mg/day, flexible dose, for 12 weeks, and will be seen every two weeks by a study physician. In both arms, study assessors, who are blind to treatment condition, will assess patients monthly (week 0, 4, 8, and 12), and are responsible for the primary outcome measure (HAMD-17).

The QEEG will be administered 5 times during the study (week 0, 1, 2, 8 and endpoint) allowing us to assess whether there are any correlations between QEEG patterns and changes in clinical functioning. We will record EEG from a fronto-parieto-temporal derivation using a 4-channel EEG Monitor (Aspect Medical Systems) connected to the subject via disposable EEG electrodes. The adhesive material of the electrodes is similar to that found in ECG electrodes. All recordings will be analyzed off-line to generate QEEG metrics. Once such QEEG metric, the ATR, is a complex index derived from left-right asymmetry of combined theta+alpha (4-12Hz) power, relative theta powe4r, and percent change from baseline in relative theta power, and ranges from 0 (low probability of response) to 100 (high probability of response). De-identified data will be shared with Aspect Medical Systems for offline calculation of EEG-based metrics.

The Signal Detection Task will be administered at baseline and at endpoint. In the specific Signal Detection Task we will use, called the Face Game (assessing reward sensitivity), we will present simple cartoon faces (diameter: 25 mm; eyes: 7 mm) in the center of the monitor and at the beginning of the trial. The face has no mouth. After a given delay, either a straight mouth of 11.5 mm ("short mouth") or 13 mm ("long mouth") will be presented for 100 ms. Subjects will be instructed to press an appropriate button to decide whether a long or short mouth had been presented. For the present study, the experiment will consist of 300 trials, divided into 3 blocks of 100. Long and short mouths will be presented equally often. A trial will begin with the presentation of an asterisk for 500 ms that will serve as fixation point and warning stimulus that a trial will start. After 500 ms, a mouth-less face will be presented and will stay on the screen until a response is made; after an inter-stimulus interval of 500 ms, one of the two mouths will be presented for 100 ms. Critically, not all correct responses will receive feedback (only positive feedback will be provided). For each block, 40 correct trials will be followed by a reward feedback ("Correct!! You won 5 cents"), presented for 1750 ms immediately after the correct response. For half of the subjects, correct identification of the little mouth will be associated with three times more positive feedback (30/40) than correct identification of the big mouth (10/40). For the other half of the subjects, the contingencies will be reversed. After feedback, an inter-trial interval (ITI) of 250 ms will follow. Subjects will be instructed that the aim of the study is to win as much money as possible, and that they will receive the amount of money won at the end of

experiment (actual money will be shown to the subjects for increasing the credibility of the experiment).

Scales:
Once the patient has agreed to participate in the study by signing the informed consent, the following instruments will be administered by a study assessor who is blind to treatment condition at screen, baseline, and visits 4, 8 and 12:

a. Structured Clinical Interview for DSM-IV (Spitzer et al, 1989). The SCID-I/P, administered by the clinician, proceeds by modules to the different Axis I disorders. Question here are asked exactly as written, and each is based on the individual criteria from DSM-IV. These scales will rely on retrospective reporting from the participant (screen visit only)

b. 28-item Hamilton Rating Scale for Depression (HAM-D 28-item) (Hamilton, 1960; 1967;Williams 1988): This version allows scoring of the HAM-D-17, 21-, 25,and 28-item scales. This instrument is completed by the clinician based on his/her assessment of the patient's depressive symptoms, using a structured interview and defined anchor points. The HAM-D aims to quantify the degree of depression in patients who already have a diagnosis of major depression. These scales will rely on retrospective reporting from the participant.

c. BDI (Beck & Steer, 1987): The Beck Depression Inventory is a widely used 21-item self-report measure that assesses the severity of affective, cognitive, and vegetative symptoms of depression experienced by patients over the past week.

d. CGI-S and I (Guy, 1976): This measure, based on history and scores on other instruments: a) CGI-S (severity): the current condition of the patient on a scale of 1-7 (1 being normal, and 7 being among the most severely ill patients); b) CGI-I (improvement): the degree of improvement, as perceived by the clinician, since the start of treatment on a scale of 1-7.

e. Kellner's Symptoms Questionnaire (SQ) (Kellner, 1987). This instrument is completed by the patient based on his/her assessment of the severity of anxiety, depression, somatic symtpoms, and hostility.

f. Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES) (Endicott, Nee, Harrison, Blumenthal, 1993). This self-report measure is a 16 item sensitive measure of the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning. The summary scores have been found to be realiable and valid measures of these dimensions in a group of depressed outpatients.

g. DAS (Weissman & Beck, 1978): The Dysfunctional Attitude Scale is a 40 item self-report questionnaire that is designed to measure the presence of depressotypic underlying assumptions, or dysfunctional beliefs. It is the most widely used instrument for this purpose.

h. ATQ-R (Kendall, Howard, & Hays, 1989): The Automatic Thoughts Questionnaire-Revised is a self-rated instrument to assess cognitive self-statements related to

depression. It includes 30 negative self-statements and 10 self-statements reflecting positive affect.

i. PSS (Cohen et al., 1983): The Perceived Stress Scale is a self-rated instrument to evaluate a patient's level of perceived stress. Patients are asked to endorse to what degree, over the last month, they felt stressed. Each of the 14 statements presented describes a stressful state.

j. SF36 (Ware, 1993): Medical Outcomes Study (MOS) 36 Item Short-Form Health Survey is a clinician-administered instrument to assess quality of life. It has 36 items and contains subscales that measure physical functioning, physical role functioning, social functioning, emotional role function, general health, energy, mental health, and bodily pain over the past four weeks.

k. Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995). This short 14-item self rated scale assesses self-reported anhedonia.

Adverse events and changes in concommitent medications will be assessed at each visit with the clinician for subjects randomized to the medication arm. The clinician will inquire about any changes in dosages of medications as well as days the medications were not taken. The importance of taking medications as prescribed and refraining from taking a « holiday » from medication on weekends or at any other time during the study will be emphasized from the time the patient enrolls in the study.

For subjects randomized to psychotherapy, adverse events will be assessed by the CBT therapist at baseline and weeks 2, 4, 6, 8, 10 and 12.

Safety Data

The following laboratory tests will be performed at the Screen Visit for only those patients randomized to the medication arm (with the exception of toxicology and pregnancy test, see below):

a. Complete Blood Count with differential (at week 4 as well)
b. Urinalysis
c. Clinical Chemistry (serum concentrations of electrolytes, BUN, creatinine, SGOT, SGPT, alkaline phosphatase, total bilirubin, albumin, total protein, uric acid, glucose, and cholesterol)
d. Electrocardiogram (EKG)
e. Urine pregnancy Test (For patients in both arms, at Screen and Week 12 or endpoint)
f. Toxicology (patients in both arms will be screened for drugs of abuse)

The routine laboratory tests (complete blood count, urinalysis, clinical chemistry tests) will be performed by Massachusetts General Hospital Clinical Laboratories. Significantly abnormal laboratory values will be those falling outside of the normal range for the laboratory and deemed to be clinically significant by the study physicians.

For patients in both groups, weight, oral temperature, and standing and supine pulse and blood pressure (Vital Signs) will be recorded at the screen visit (and at every visit thereafter for patients in the medication arm. For patients in both groups, a physical exam will be performed at screen.

In the case of early termination, patients in both groups will be asked to return for a final study visit within 48 hours of leaving the study. All Week 12 study procedures will be completed at the time of the early termination visit.

b) Drugs to be used:

Patients randomized to receive escitalopram will receive open-label treatment with escitalopram, 10-20 mg/day, flexible dose, for 12 weeks. Dose selections will be determined by the study physician.

c) *Devices to be used:*
None.

d) *Procedures:*
None.

VI. Statistical Analysis

a) *Statistical Plan:* The Mann-Whitney U test will be used to analyze differences in changes of QEEG between responders and non-responders to CBT. We will use logistic regression with the outcome being response/no response on the HAMD-17 and the predictors being other EEG measures. We will test the predictors in a stepwise manner given the limited power with a small N. A power calculation based on a previous QEEG study conducted in our clinic reveals that, to achieve power = 0.80, we would need 34 subjects per group. With N = 30 per group (60 subjects total), our power is 0.76. Power for the current study, with N = 15 per group, is 0.47. While this study is underpowered due to the small N, the goal of this study is to act as a pilot study which can help measure effect sizes, providing a foundation for future, larger projects.

For secondary aims, we will use Pearson r's for pairs of continuous measures, or point-biserial r for pairs of dichotomous and continuous measures.

Data from the Signal Detection Fact Task will be analyzed by Dr. Diego Pizzagalli at Harvard University. Response bias will be the main variable of interest, whereas reaction time, hit rates, and discriminability values will provide control variables. Analyses of variance (ANOVAs) will be used to investigate variables across the three blocks. Discriminability and response biases will be computed using standard formulae (e.g. McCarthy and Davidson 1981).

b) Study Endpoints: Endpoints will be defined as the final study visit at the end of the 12 weeks, or the termination/final visit for patients who choose to (or have to) end participation in the study prematurely.

VII. Risks and Discomforts

a) *Procedures:* None performed

b) Cognitive Behavioral Therapy: Risks and discomforts associated with receiving psychotherapy are generally considered modest, but can include a worsening of depressive and/or anxiety symptoms, and psychological discomfort associated with discussion of one's difficulties. Answering detailed questionnaires may create a mild degree of inconvenience for the subjects and coming in for CBT visits and blind assessor visits may be seen as time consuming and inconvenient. Patients will be given telephone numbers of the doctors involved in the study if they would like to talk about any discomforts. A general risk associated with treatment for depression includes the risk that depression may not respond to treatment. Subjects will be informed of these risks.

c) *Drug:* Escitalopram has been used in over 1 million patients in the US and there is a large well-validated safety database for it. Most common side-effects include nausea, ejaculatory problems, diarrhea and insomnia. The risks posed to the subjects who participate in this study are real but small.

d) *QEEG:* There may be some initial forehead redness after removal of the electrodes. This is temporary and considered normal. There are no known long-term effects of recording brain EEGs. All information associated with study participants that is shared with Aspect Medical Systems will be treated confidentially

e) *Signal Detection Computer Task*: We do not foresee any risks or discomforts presented by this task.

f) *Device*: Not applicable

g) *Radiation*: None

VIII. Potential Benefits

a) Potential benefit to individuals: The study will potentially provide relief of depressive symptoms to participating patients. Subjects will also be compensated $25 per QEEG ($125 total for all 5 QEEGs), and will receive $20 plus earnings per trial of signal detection ($40 plus earnings in total). Subjects will also be offered up to $25 travel reimbursement per visit.

b) Potential benefit to society: This proposal investigates QEEG in the prediction of response to both CBT and escitalopram in patients with major depressive disorder. Establishing QEEG technology as a predictor of response to therapy and/or medications could help guide treatment selection for individual patients. Thus, the study will potentially further our understanding of the neurobiological differences which underly individual differences in responses to certain treatments. The study would be one of the first comparisons of baseline biomarkers between patients who respond to CBT versus those who respond to an SSRI, thus filling an important gap in our knowledge base of predictors of response to different treatments. Establishing QEEG as an accurate predictive tool would have an enormous impact on providing better care to patients suffering from major depressive disorder.

IX. Monitoring and Quality Assurance

a) Independent Monitoring of Source Data: Documentation of the presence of any side-effect or adverse event will be completed at every visit and will be reported in accordance with AE reporting guidelines of the MGH IRB. Patients will be encouraged to contact the investigator or a member of her staff at any time between visits concerning adverse events or worsening of symptoms. An event that is deemed serious will be recorded in the patient's study binder and will be handled in an expeditious manner. A Safety Monitoring Committee, including Drs Fava, Alpert, and Farabaugh, will review SAEs quarterly. Research assistants responsible for data collection and storage will be aware of and comply with all regulatory requirements related to adverse events. In the event that a patient becomes ill or is injured as a direct result of study participation, medical care will be made available. All adverse events will be followed to resolution and reported to the MGH IRB as serious in the event that they are unanticipated, possibly related to the study, and meet any one of the following criteria:

1. Fatal or life threatening
2. Requires prolonged inpatient hospitalization
3. Results in persistent or significant disability or incapacity
4. Congenital anomaly
5. Medical events that require intervention to prevent serious outcome
6. Cancer
7. Overdose
8. Results in substance dependency or abuse

Outcomes Monitoring: Treatment outcomes will be documented so that at study completion appropriate recommendations can be made for further treatment.

b) Safety Monitoring:

Monitoring of Safety Data by the DSMB:

1. Unblinded Reporting – Safety information for this study will be reported to the DSMB in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the investigators unless necessary for safety reasons.

2. Range of Safety Reporting to the DSMB – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but other data that may reflect differences in safety between treatment groups. This includes treatment retention rates, and reasons for drop-out, and laboratory values reflecting potential toxicity.

3. Serious Adverse Events – Expedited review will occur for all events meeting the FDA definition of Serious Adverse Events (SAEs) – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution.

For purposes of this study, all SAEs will be required to be reported to the DSMB, regardless of any judgment of their relatedness to the study drug. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, dosing history of all study drugs, concomitant medications, the subject's medical history and current conditions, and all relevant laboratory data. Notification by e-mail, and FAX transmittal of all related study forms shall be made to the DSMB within 2 days of the occurrence of any SAE. Information will be reviewed and a determination made of whether there was any possible relevance to the study drug. Additional reporting to local IRBs will be done within 24 hours of the SAE.

4. Non-Serious Adverse Events – At periodic intervals (quarterly during the course of the study and then again at its completion), the DSMB will be provided with un-blinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.

5. Other Safety-Related Reports – At three-month intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for dropout, by treatment arm and study phase.

6. Study Stopping Rules – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

X. References:

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