Reversal of General Anesthesia With Intravenous Methylphenidate

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BACKGROUND AND SIGNIFICANCE

The aim of this study is to investigate whether methylphenidate can actively induce emergence from general anesthesia in patients having surgery.

General Anesthesia

General anesthesia (GA) is a reversible, drug-induced state consisting of unconsciousness, amnesia, analgesia, and immobility with maintenance of physiological stability. Every day, approximately 60,000 people in the United States undergo GA for surgery alone, and many more people receive general anesthetics for non-surgical interventions in critical care, emergency medicine, radiology, gastroenterology, pediatrics, obstetrics, and dentistry. At some point in life, most of us will undergo GA.

Emergence from General Anesthesia

In clinical practice, GA is rapidly induced and maintained by the active administration of intravenous or inhalational drugs. In contrast, emergence from GA is a slow and passive process dictated by the pharmacokinetics of drug clearance. That is, the general anesthetic agents are merely discontinued at the end of surgery and the effects of the drug are allowed to wear off. This leaves the anesthesiologist, surgeon and other members of the operating room to wait for the patient to recover consciousness. We use the term “passive emergence” to define this current clinical paradigm. Newer inhaled anesthetic drugs with faster pharmacokinetics, such as desflurane and sevoflurane, and intravenous drugs such as remifentanil, have been developed to promote rapid emergence. However, these agents are expensive and they do not prevent the problems associated with passive emergence.

Passive emergence is hazardous because at low doses, general anesthetics can cause paradoxical excitation of the central nervous system (CNS) [1, 2] leading to complications such as laryngospasm, hemodynamic instability, and delirium. Because passive emergence relies on the relatively slow clearance of general anesthetic drugs, all patients undergo some period of paradoxical CNS excitation during emergence from GA. In a five-year review of more than 80,000 anesthetics, difficult emergence was found to be the second most common anesthesia-related problem after difficult intubation [3]. Of the cases in which problems with emergence were noted, more than half of the cases were related to misjudgment of residual drug effect leading to severe airway or oxygenation problems.

Methylphenidate and General Anesthesia

During the 1950s and 1960s, the clinical utility of methylphenidate (MPH, Ritalin) was explored by psychiatrists and anesthesiologists. MPH belonged to the class of drugs known as analeptics, i.e. CNS stimulants [4], but its mechanism of action was unknown at the time. Psychiatrists reported using the drug to promote arousal in somnolent patients [5], to treat barbiturate overdose [6] and to facilitate psychiatric interviewing [7]. Some studies conducted in the perioperative period found that MPH promotes faster recovery after GA [8-10], but one placebo-controlled, double-blinded study [11] reported no difference in recovery time when intramuscular MPH was compared with IM normal

saline. MPH patients did have an appreciable respiratory stimulant effect in the treated group compared with the controls.

It was later discovered that MPH acts by blocking the dopamine transporter protein thereby enhancing dopaminergic neurotransmission at synapses throughout the brain [12, 13]. There is also evidence to suggest that MPH may block reuptake of norepinephrine and histamine as well [14]. Today, oral MPH is widely prescribed to treat attention deficit hyperactivity disorder (ADHD, which has an incidence of 6-9% in children) [15], and there have been reports of increased anesthetic requirements in patients taking MPH [16, 17]. Swanson and Volkow [18] reported that MPH levels in the striatum are at approximately 70% of the peak concentration one hour after intravenous (IV) administration in humans, indicating that MPH clearance is slow. This suggests that if it does enhance arousal after general anesthesia, this effect should be sustained for a period after administration.

Our FDA IND application (attached in Insight) provides a literature review on previous experience with IV MPH in human subjects. In it we cite numerous papers that reported an MPH dose of 0.5 mg/kg IV or greater in healthy human subjects, with no major adverse effects. We also cited several papers that detail the use of IV MPH in humans under general anesthesia. In a study by Gale, the dose of IV MPH used during general anesthesia was 0.8 mg/kg or higher and no major adverse effects were reported [8]. After carefully reviewing the literature, we concluded that MPH 0.5 mg/kg IV is safe in the perioperative setting. As in previous studies, MPH will be administered as an IV bolus. All of the previous human studies cited in our IND application administered MPH as an IV bolus, indicating that this is safe.

MPH-Induced Emergence from General Anesthesia

Propofol is by far the most widely used intravenous general anesthetic. It is almost always the drug of choice for the induction of general anesthesia in adults. In addition, continuous propofol infusions are often used as part of total intravenous anesthesia (TIVA) that is, general anesthesia maintained by use of only intravenous drug. This is becoming an increasingly common practice, particularly in cases in which inhaled anesthetics are contraindicated. Examples include patients at risk of malignant hyperthermia, undergoing complex spine surgery requiring neurologic monitoring, and those with a history of post-operative nausea and vomiting.

After a prolonged propofol TIVA, it is not uncommon to wait 30 minutes or more for a patient to regain consciousness.

Sevoflurane is currently the most widely used inhaled anesthetic. It is often the drug of choice for maintenance of general anesthesia, as it is well tolerated by most patients and the pharmacokinetics of elimination are more favorable than older inhaled anesthetics such as isoflurane and halothane. After several hours of general anesthesia, however, the clearance of sevoflurane can be quite slow, and anesthesia providers often discontinue the delivery of sevoflurane well before the end of surgery, in the hopes of waking up the patient soon after surgery is over.

A drug that hastens the restoration of consciousness would likely improve patient care as well as operating room efficiency by allowing patients to recover more quickly from the effects of the anesthetics when they are no longer required.

In a rat model, we have demonstrated that MPH actively induces emergence from isoflurane general anesthesia [19] and from propofol general anesthesia [20]. Because isoflurane and sevoflurane are both halogenated ether anesthetics with similar chemical and clinical properties, it is very likely that MPH will induce active emergence from sevoflurane anesthesia. In support of this hypothesis, we recently found that dextroamphetamine, which has a mechanism of action very similar to MPH, induces active emergence from sevoflurane general anesthesia in rats [21]. We found that in addition to promoting emergence from general anesthesia, MPH increased the respiratory rate. Our observation regarding the effect of MPH on respiration has been previously reported in human subjects [16]. We further demonstrated that the arousal and respiratory effects could be blocked by pre-treatment with droperidol—a known dopamine antagonist—prior to administration of MPH.

Summary

Presently, emergence from GA is a passive process. Basic science and clinical data suggest that activation of one or more of the brain's arousal pathways is a highly plausible way to actively induce emergence from GA. These data also suggest that IV MPH would be safe to administer to patients and that in addition to inducing arousal, it would increase respiratory rate. Furthermore, we have compelling experimental data demonstrating that MPH is highly effective in actively inducing emergence from isoflurane and propofol GA in rodents.

SPECIFIC AIMS

The specific aims of this study are to test the hypothesis that:

Specific Aim 1: The administration of IV MPH to patients at the end of GA is safe. The Phase I trial will test this hypothesis.

Specific Aim 2: Patients receiving IV MPH at the end of GA maintained by combined epidural regional anesthesia and an IV propofol infusion will have a shorter emergence time than control patients receiving a placebo treatment of IV normal saline at the end of the same type of general anesthesia. Arm 1 of the Phase II trial with Dr. Fernandez's patients will test this hypothesis.

Specific Aim 3: Patients receiving IV MPH at the end of GA maintained by sevoflurane will have a shorter emergence time than control patients receiving a placebo treatment of IV normal saline at the end of the same type of general anesthesia. Arm 2 of the Phase II trial with Dr. McGovern's patients will test this hypothesis.

Specific Aim 4: Patients treated with MPH will have improved cognitive function at ½ hour, 1 hour and 2 hours after emergence relative to placebo treated controls. Both Arms of the Phase II trial will test this hypothesis.

SUBJECT RECRUITMENT, SELECTION AND ENROLLMENT

Subject Recruitment

This study will take place at Massachusetts General Hospital. We will aim to enroll 95 patients aged 18 to 75, scheduled to undergo surgery with Dr. Carlos Fernandez Del Castillo or Dr. Francis McGovern. If the patient is interested in participating he/she will give Dr. Fernandez Del Castillo or Dr. McGovern permission for our study staff to contact him/her. An anesthesiologist on the study team will contact the patient by telephone to determine if they are interested in enrolling, and to answer any questions. If the patient in interested, the anesthesiologist will conduct a telephone screening to rule out any medical conditions that may disqualify the patient from participating. The

anesthesiologist will also provide their contact information, so that patients will have the ability to call and ask questions about the study at any time before the day of surgery. A voided copy of the consent form will be mailed or emailed to the patient. E-mails will be sent in accordance with Partners Information Security policies.

Subject Selection
Only those patients capable of giving their own consent will be considered for this study.

All study subjects will be American Society of Anesthesiologists (ASA) physical status classification 1 or 2 [21]. The ASA physical status classification of the patient will be determined by a PATA anesthesiologist who is not a member of our study group. That is, all study subjects will have at most mild systemic disease that is well controlled. For example, patients with uncontrolled hypertension, uncontrolled diabetes, or unstable angina would not be eligible for the study. The subject's complete medical history and results of the subject's complete preoperative evaluation including physical examination, laboratory testing, and any relevant imaging studies will be evaluated by one of our study anesthesiologists with the subject's written permission to determine eligibility.

Inclusion Criteria:
1. Age 18-75 years
2. ASA classification 1 or 2

Exclusion Criteria
In general, patients will be excluded from the study if the state of their chronic health problems gives them an ASA physical status classification of 3 or beyond. Chronic health conditions that will be considered in deciding to exclude a patient include but are not limited to:

Cardiovascular:	poorly controlled hypertension, myocardial infarction, coronary artery disease, peripheral vascular disease, dysrhythmias, congestive heart failure, valvular disease, cardiomypathy, other structural cardiac abnormalities.
Neurologic:	seizure, stroke, positive neurological findings on neurological examination, multiple sclerosis, Meniere's disease, Parkinson's disease.
Endocrine:	hyperthyroidism or thyrotoxicosis
Psychiatric:	bipolar disorder, patients with history of traumatic brain injury, stroke, seizures, epilepsy, insomnia.
Reproductive:	pregnancy, breast-feeding.
Ophthalmologic:	glaucoma
Allergies:	methylphenidate, bisulfite, eggs or egg products, propofol, soybeans, soybean oil, or phenylephrine.
Drugs/Medications:	MAO inhibitors, ketamine during surgery

Subject Enrollment
If a patient is deemed eligible for the study, the consent form will be sent to the patient by email or postal mail. Potential subjects will therefore be given the time from the day they receive the consent form until the day of surgery to review the consent form. This will allow adequate time for the potential subject to review the consent form in detail, have any questions answered and consider enrollment.

On the day of surgery, each subject will sign informed consent to participate in the study. The study consent form will be a separate document from the surgical and anesthesia consent forms. We will make clear to the subject that he/she may withdraw from the study at any time prior to the start of the study or once the study has begun.

Remuneration
There will be no remuneration for this protocol. All study related activities will take place during the patients hospital stay; no additional visits will be required.

STUDY PROCEDURE
Patient Preparation
The subject will be instructed to arrive at the MGH preoperative evaluation clinic on the day of his/her surgery two hours prior to the scheduled time of surgery. Two hours is the standard amount of time patients are requested to arrive prior to their surgery to complete standard, immediate pre-operative preparations. At this time, a study anesthesiologist will obtain written consent from the subject after reviewing the form in detail and answering any remaining questions.

After consent is obtained, the subject will be asked to take a Mini Mental Status Exam (MMSE) to assess the subject's cognitive ability prior to surgery. The examinations will be administered by our study coordinator. We will administer the test after the subject gives informed consent for the study, but prior to pre-anesthesia preparation by the patient's anesthesiology care team.

An EEG montage with a maximum of 256 channels will be placed on the subject. The baseline EEG measurements will be taken as the subject rests quietly for 5 minutes. The EEG will be recorded for the entire duration of the surgery and for up to 2 hours afterwards. The raw (unprocessed) EEG data will be recorded to analyze the relationship between EEG patterns and anesthetic drug levels, clinical events, and methylphenidate administration.

Randomization Protocol
The literature indicates that the administration of MPH at a dose of 0.5 mg/kg IV is safe in human subjects. This information is summarized in our FDA IND application. Nevertheless, we will first perform a Phase I study to evaluate the safety of administering IV MPH at the end of surgery. We will request the DSMB to review our results before proceeding with the Phase II trial.

Phase I: The first 5 patients enrolled in this study will receive a lower dose of MPH (0.25 mg/kg IV) in an unblinded fashion, and will be closely monitored for hemodynamic and behavioral changes. IV MPH is known to increase blood pressure and heart rate, but these predictable changes should be easily manageable by an anesthesiologist, who is always prepared for large hemodynamic changes. The operating room is the ideal

setting to test for the safety of IV MPH because patients will be appropriately monitored and a full armamentarium of vasoactive drugs will be immediately available.

Assuming that 0.25 mg/kg of IV MPH does not cause any adverse events, the next 5 patients enrolled in the study will receive the full dose of 0.5 mg/kg IV (unblinded) to confirm that this dose is safe in the setting of recovery from GA. If no adverse events occur during the Phase I trial, we will then request the DSMB to review our results before proceeding with the Phase II trial.

Because the sole purpose of the Phase I trial is to ensure the safety of IV MPH in the setting of general anesthesia, we will recruit both Dr. Fernandez's patients as well as Dr. McGovern's patients to complete the Phase I trial.

Phase II: Based on a randomization performed prior to the study, each subject will be assigned in a double-blind manner to receive at the end of surgery either a placebo treatment of normal saline or MPH at a dose of 0.5 mg/kg. The MGH Research Pharmacy will consult the randomization assignment and will prepare the appropriate treatment for the subject.

Pre-Anesthetic Preparations

Each subject in Arm 1 of this study will undergo a Whipple surgical procedure which is comprised of a pancreaticoduodenectomy, antrectomy, pancreaticojejunostomy, hepatojejunostomy, and gastrojejunostomy; or they will undergo a distal pancreatectomy for pancreatic cancer. These surgeries will be performed by Dr. Fernandez under propofol TIVA.

Each subject in Arm 2 of this study will undergo a prostatectomy by Dr. McGovern under sevoflurane anesthesia.

The anesthetic management of the subject will be directed by the attending anesthesiologist assigned to the patient on the day of surgery, not the study anesthesiologist. Participating in this research study will in no way change the standard surgical and anesthetic preparations for surgery. The pre-operative preparations will take place in a pre-operative holding area outside of the operating room. After informed consent for surgery and for anesthesia has been verified and an assessment has been made that there are no new active problems that need attention, standard pre-operative preparations will begin. For patients in Arm 1 of this study, if the attending anesthesiologist decides to forgo placement of the epidural catheter, the subject will be excluded from the study.

If the attending anesthesiologist caring for the patient decides to place an arterial line for the operation, it will allow for continuous BP monitoring and will be used instead of the noninvasive cuff. If an arterial line is needed for an otherwise uncomplicated surgery because the patient has cardiac disease, the patient would be excluded from the study.

The American Society of Anesthesiologists (ASA) has established minimum monitoring standards for all patients undergoing general anesthesia. These are: (1) ECG, (2) non-invasive blood pressure (at least every 5 minutes), (3) pulse oximetry, (4) end-tidal carbon dioxide, and (5) temperature. Therefore, all of our study subjects (in both the Phase I and II studies) will have these monitors in place, and hemodynamic data will be continuously monitored and recorded as part of their anesthetic care.

Additionally, on the day of surgery the primary anesthesia team will receive a card from the study anesthesiologist to inform them that their patient has enrolled in the study and to detail the study protocol.

Surgical Procedure
The surgical procedure will be directed by the subject's physician, and will adhere to the approved standard surgical practices at MGH. Participation in our study will not increase the subject's risks from surgery.

Emergence from General Anesthesia
The end of the surgery is defined by the final closure of the skin incision. For Dr. McGovern's patients, a transverse abdominis plane (TAP) block is often performed for post-operative analgesia after the prostatectomy is completed, so the end of surgery will be defined by the end of the TAP block procedure if it is performed. (For Dr. Fernandez's patients, the TAP block is unnecessary because there is an epidural catheter in place for post-operative analgesia. If the patient experiences a serious adverse event during surgery, methylphenidate will be withheld. At this point video and audio recording may begin and proceed until the patient leaves the operating room. The automatic blood pressure cuff will be set to cycle every three minutes and the IV MPH bolus will be administered by the study anesthesiologist.

Changes in heart rate and blood pressure are common during emergence from general anesthesia and increases in both are more likely in the patients who receive MPH. Therefore MPH will not be administered if the patient's systolic blood pressure is greater than 140, diastolic blood pressure is greater than 90, or heart rate is greater than 100. A study protocol checklist will be used by the study team to ensure that the patient's blood pressure is not greater than 140, diastolic blood pressure is not greater than 90, or heart rate is not greater than 100 before administering the study drug. Hypertension and/or tachycardia will be appropriately managed by standard use of vasoactive medications at the discretion of the anesthesiology care team assigned to the patient, not the study anesthesiologist. The only exception is that ephedrine and clonidine will not be used because there is evidence that, in addition to increasing blood pressure and heart rate, they can also alter arousal states [6]. Although they will be asked to consider other therapeutic options first, if they are the best choice of medication to manage the patient's clinical problem, the anesthesiology care team will use it.

The subject will be extubated when he/she meets the criteria set forth by the DACCPM. Once the patient is extubated and vital signs are stable, the patient will be transferred from the operating table to the transport stretcher and transported to the PACU.

Important time points we will record are: 1) emergence time, defined as the time from administration of the MPH or placebo until extubation; and 2) the time from administration of the MPH or placebo until the patient is either ready to leave the operation room or leaves the operating room. The emergence time is the primary endpoint of the study. Documenting the time at which the patient is ready to leave the operating room will allow us to correct for prolonged end of surgery stays in the operating room due to PACU delays. The first assessment of the patient's cognitive status will include whether the patient met vegetative state criteria or minimally conscious state criteria for extubation [22]. The former is that there was only evidence of spontaneous respirations and ability to protect the airway. The latter includes the former

in addition to some evidence of appropriate responses to commands such as squeezing a hand, opening the mouth for suctioning or lifting the head upon request.

Post Anesthesia Care Unit (PACU)
Upon arrival in the PACU the standard monitors will be reattached. Standard baseline assessments for arrival in the PACU will be carried out as is standard procedure.

The first post-operative Mini-MSE will be performed by the research assistant 30 minutes after extubation. If the patient does not respond or does not wish to undergo the Mini-MSE, this will be noted. At all times the needs of the patient and the caregivers will be respected and given top priority, and every effort will be made to ensure that patient care is not compromised in any way. The time and result of the first post-operative Mini-MSE will be recorded, and the exam will be conducted again at 1 hour and 2 hours after extubation. If the patient achieves the same score as their preoperative baseline score during any of the post-operative assessments, the Mini-MSE will not be repeated.

If a patient experiences a significant neurologic or cardiovascular adverse event, the patient will be monitored continuously and treated immediately. Any patient with a life-threatening myocardial infarction or cardiac dysrhythmia will be treated according to ACLS protocols, and a cardiologist will be promptly consulted for management recommendations. Acute hemodynamic changes that are not life-threatening will be managed at the discretion of the anesthesia care team assigned to the patient, not the study anesthesiologist. Should a neurologic adverse event occur a neurologist will be promptly consulted to guide further management. We will perform an ECG prior to patients being discharged from the PACU **only** when clinically indicated.

Post-operative Follow Up
The patient will be visited on the first and second post-operative days. The Quality of Recovery-40 (QoR-40) Questionnaire (a widely used and psychometrically validated measure of quality of recovery from anesthesia) will be administered. [23, 24] This useful tool will allow us to assess quality of recovery from the patients' perspective. We predict that patients who received MPH will report a higher quality of recovery from general anesthesia.

BIOSTATISTICAL ANALYSIS
Sample Size Calculation
Because we hypothesize that MPH will shorten the average time to emergence from general anesthesia, the primary outcome will be the emergence time measured as the difference between the time at which the patient is extubated and the time at which the placebo or MPH is administered. An average decrease in the emergence time of 10 minutes for the MPH relative to the placebo group could suggest a substantial impact on the recovery of cognitive function in patients and on operating room utilization. Therefore, we assume a probability of type I error of 0.05 and a minimal power of 0.80 for detecting a difference of 10 minutes or greater in extubation time. We further assume that the standard deviations in the placebo and the MPH groups equal 10 minutes. This leads to a minimum sample of 16 patients per group for testing a two-sided alternative hypothesis. As a consequence, this sample size will also provide adequate power against the one-sided alternative that the emergence in the MPH group will be shorter than emergence in the placebo group. We will ask to empanel a total of 40 patients for each Arm of the Phase II trial to allow for a possible 25% (4 patients per group) rate of

failure to complete the study per group. This will be in addition to the 15 patients empaneled in the Phase I trial, bringing the total to 95 patients.

Emergence Time Analysis
We hypothesize that the MPH group will have a shorter emergence time. The analyses of the emergence time recordings will be conducted using a two-sample t-test. We will also repeat each two-sample t-test analysis with a rank sum test to provide a conservative comparison of the emergence time between the placebo and MPH groups.

Mini-MSE and Psychomotor Vigilance Test Analysis
We hypothesize that the patients in the MPH group will show a more rapid recovery of cognitive function as evaluated by the Mini-MSE. The Mini-MSE results will be analyzed using repeated measures analysis of variance with a between group comparison to evaluate the difference between the placebo and MPH group.

EEG Acquisition Preprocessing: Continuous EEG will be recorded with up to 256 channels. All data will be stored for subsequent off-line analysis.

RISK AND DISCOMFORT
Methylphenidate
The risks of MPH are fall in two categories: cardiovascular risks and non-cardiovascular risks.

Cardiovascular Risks: The predictable side-effects of IV MPH are increases in heart rate, systolic and diastolic blood pressure [25]. Because the cardiovascular side-effects occur within 4 to 10 minutes of the drug's administration, and because these cardiovascular parameters will be continuously monitored in our study subjects, the anesthesiology care team can readily treat these side-effects with standard agents as soon as they appear. Medications to treat these side-effects will be prepared in advance and will be ready to administer prior to administering the MPH or the placebo. Because of general concerns that the FDA has recently expressed regarding the effects of CNS stimulants on the cardiovascular system and possible increased risk of sudden death and stroke, we will exclude any potential subjects with known structural cardiac abnormalities, cardiomyopathies, serious dysrhythmias, coronary artery disease, or other serious cardiac problems [25].

Non-Cardiovascular Risks: In a subset of patients nausea, anxiety, euphoria and insomnia may occur [25]. Nausea was more prevalent at IV MPH doses greater than 0.5mg/kg. As is our standard practice, we will treat nausea preemptively by administering an anti-nausea/anti-emetic agent. In our study, to avoid the potential confounding effects of antidopaminergic anti-nausea agents such as haloperidol, droperidol and metaclopramide and the soporific effects of anticholinergic drugs such as scopolamine and promethazine we will administer the serotonin receptor subtype 3 antagonist, ondansetron.

General Anesthesia Risk
Except for the possible increase in heart rate and blood pressure that may follow administration of MPH, participation in our study will not increase the subject's risk of general anesthesia.

EEG Risk

EEG is a well-established and safe clinical diagnostic tool. Using standard EEG equipment poses no significant risks to subjects and this component of the study will not interfere with the other procedures. Minor discomfort such as irritation of the scalp may occur.

POTENTIAL BENEFITS

One potential benefit of this study is the amount of time it takes to emerge from general anesthesia for subjects who receive MPH. If our hypotheses (shorter emergence time and faster return of cognitive function) are correct, these subjects could have a shorter recovery time due to the effects of MPH. Subjects may also benefit from a decreased risk of emergence delirium.

MONITORING AND QUALITY ASSURANCE

Monitoring the validity and integrity of the data and adherence to the IRB-approved protocol will be the primary responsibility of the Principal Investigator, Ken Solt, M.D. For each subject, he will confirm that written informed consent has been properly obtained, and that all data are appropriately recorded and maintained. The Principal Investigator will guarantee strict adherence to the IRB-approved protocol, and will monitor the integrity of the data collected. Should an adverse event need to be reported, the PI will be responsible for reporting in a timely manner according to the IRB regulations. All serious adverse events (including but not limited to myocardial infarction, a persistent and physiologically significant cardiac dysrhythmia, stroke, seizure, or any other life-threatening event) will be reported within 24 hours, and 10 working days in writing. Other, less severe adverse events will be reported within 30 days, or at the annual review, according to the IRB regulations. All outcome monitoring and adverse events will be reported through appropriate channels of the MGH Human Research Committee.

All data collected during the study will be recorded and stored in a de-identified form for offline analysis.

Data and Safety Monitoring Board (DSMB):

A Data and Safety Monitoring Board (DSMB) has been created as an independent body charged with ensuring that the safety of study subjects is protected and that the scientific goals of the study are being met. To support those purposes, the DSMB will perform expedited monitoring of all serious adverse events, perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure subject privacy and research data confidentiality.

Serious Adverse Events: Expedited review will occur for all events meeting the FDA definition of SAEs – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization. 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 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 the IRB will be done within 24 hours of the SAE

Other Safety-Related Reports: At twelve-month intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for drop-out, by treatment arm and study phase.

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.

Monitoring of Data Quality by the DSMB: At least on a yearly basis during the course of the study, the DSMB will receive a report on data quality and completeness
The Charter and Membership has been submitted to the IRB.

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