A Pilot Study to Assess the Amnesic Properties of Propofol in Pediatric Patients

PROTOCOL FACE PAGE FOR
MSKCC NON THERAPEUTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

The goal of this study is to extend findings of propofol's effects on memory, as measured in volunteer research studies, to a clinical setting. Standard memory tasks utilized in clinical drug studies do not readily differentiate between effects on memory from sleepiness alone (sedation) or from a specific effect of certain drugs (e.g. benzodiazepines, propofol) on memory itself (amnesia). We have been able to differentiate these effects in adult volunteers using a visual picture task where intravenous infusion produced increasing drug concentrations over a period of approximately 10 minutes. We wish to assess the feasibility of using this behavioral paradigm in a clinical setting.

Very little research on the immediate memory effects of anesthetic drugs in pediatric patients has been done, as many tasks that test memory function are not suitable for pediatric patients, particularly in a busy clinical setting. The visual picture task used in our volunteer studies, on the other hand, is simple in nature and should be able to be performed easily by younger patients with minor disruption in procedure traffic.

We wish to assess the feasibility of a similar picture naming task in pediatric patients who require sedation for minor therapeutic procedures, principally MRI scans of the brain. Pediatric patients who are old enough to be able to name pictures will be offered inclusion in the study. Before the therapeutic procedure is begun, during induction of sedation, pictures will be shown to the child while they name them. This procedure will form memories as propofol concentration is increasing. After awakening following completion of the therapeutic procedure, recognition memory will be tested for the pictures presented as propofol sedation was being induced.

A control group of children of similar age and undergoing similar minor therapeutic procedures will be recruited to perform memory tasks as for the children who receive propofol.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

1. The primary objective is to determine the feasibility of using the visual picture naming task in pediatric patients in the clinical setting. Feasibility will be defined as being able to accrue an average of 2 patients a week who successfully name and recognize sufficient numbers of pictures so that the thresholds for sedation and memory can be determined in each individual (as described in Section 11.0, Aim 1).

2. The strength of propofol amnesia (the effect of propofol on memory not related to sedation) will be estimated as a difference between thresholds for amnesia (loss of memory) and sedation (loss of verbal responsiveness)

Hypothesis 1: The threshold effect for memory will occur significantly sooner, i.e. at lower drug concentrations, than the threshold effect for sedation, as illustrated in Fig 2 (the threshold for memory effect is illustrated by the light gray curves in the Figures, and for sedation by the dark curves).

3.0 BACKGROUND AND RATIONALE

Amnesia versus Sedation

One of the critical components of anesthesia is amnesia (lack of recall) for events during surgery or therapeutic procedures. The failure of this anesthetic effect, i.e. conscious awareness and recall of events during anesthesia, known as 'awareness', occurs at a low, but predictable frequency of ~0.5% both in adults and children. (1) In fact, the incidence of this complication may be higher in the pediatric population. (2) (3) Serious psychological sequelae may occur after an episode of awareness, with symptoms similar to those of post-traumatic stress disorder. (4) (5) (6) This eventuality may be particularly distressing for patients with cancer, who frequently require repeated therapeutic procedures. The fact that the incidence of awareness is so low makes it difficult to conduct systematic studies to address this issue. Thus, practice aimed at prevention of this complication is frequently based on expert opinion. One common recommendation is to use drugs with specific amnesic properties during anesthesia.

A more precise definition of an amnesic drug is one that is able to prevent recollection of memories at low or minimal levels of sedation. Amnesic drugs are useful adjuncts to other anesthetic agents, most of which prevent recall of intra-operative events on the basis of sedation alone, i.e. no conscious memories are formed because the patient is unable to experience and process stimuli from the outside world. However, periods of inadequate anesthetic level may occur for any number of reasons e.g. individual response to medications, sudden painful stimulus, hemodynamic instability necessitating decreased drug doses, refilling the drug delivery device, 'stormy' induction or emergence, etc. The rationale for the routine use of an amnesic drug is that it will prevent recall of any events occurring during periods of inadvertently light anesthesia. Midazolam is such an amnesic drug, and is frequently used in the therapeutic setting for this reason. Relative disadvantages of midazolam include relatively prolonged duration of action, of particular concern in the outpatient setting, and the inability to act as a suitable anesthetic agent when given alone. Propofol has been shown in many studies in adults to possess specific amnesic properties, both in the research and clinical settings. (7) (8) (9) (10) To date, propofol provides the most desirable qualities for an 'all-purpose' anesthetic agent, as it possesses amnesic properties, has a short duration of action, and can be administered as the sole anesthetic agent.

Sedation for therapeutic procedures in children

As propofol has desirable pharmacokinetic properties that allow deep levels of sedation commensurate with rapid recovery, it is the most common sedative agent given to pediatric patients for therapeutic procedures. However, almost no research has been done to determine if propofol is indeed an amnesic, as opposed to a purely sedative drug when

given to pediatric patients. (11) There is evidence that the pharmacodynamics for propofol are different in children than adults, so the amnesic effects present in adults need to be confirmed in children. (12) Recently dexmedetomidine, an agent with a similarly favorable pharmacologic profile to that of propofol, has been introduced for sedation in pediatric patients. (13,14) Similarly to propofol, there is no research in pediatric patients regarding the memory effects of dexmedetomidine. In adult patients, the amnesic effect of dexmedetomidine is unclear, but there are some data to indicate that dexmedetomidine has few amnesic properties. (15) (16) (17) Interestingly, when dexmedetomidine was used for sedation in pediatric patients, improvement in the quality of sedation was noted when a known amnesic agent (e.g. midazolam or ketamine) was co-administered. (18,19) Whether this improvement may have been a result of the additional amnesic effect of these drugs, or some other property is unknown.

Thus, the possibility exists that using agents with amnesic properties may provide better quality of sedation in pediatric patients. The only way this hypothesis can be critically assessed is to have some measure of the amnesic effect of a given drug when given to pediatric patients in a clinical setting.

Measures of amnesic versus sedative effects

Sedative effects of anesthetic drugs can be measured in real time, for example by assessing reaction time, or presence of an adequate behavioral response while the drug is being given (e.g. keeping eyes open, or performing a simple task such as naming a picture). However, the assessment of memory is by definition retrospective. The memory effect of amnesic drugs develops over 10-30 minutes, and the full extent of memory impairment is only evident after this time interval has elapsed. (7,16) Measures of memory impairment due to a drug use recognition performance at some distinct time after the sedative effect of a drug was measured during administration. Thus, comparison of the amnesic and sedative properties of a drug represent behavioral responses obtained at two distinct time points. Modulation of the memory effect of a drug is related back in time to conditions present when the memory was being formed, i.e. at encoding. For the purposes of this study we are assessing modulation of memory by the degree of sedation present at encoding. (20) (21)

The methods used to assess the amnesic properties of drugs in the clinical setting are quite limited in comparison to controlled research settings. (22) Frequently measures of memory are used which cannot differentiate among the various factors that impair memory in the clinical setting. For example, anxiety in the peri-operative setting can itself impair memory for events before the administration of anesthesia. (23) Other difficulties in translation of methods to the clinical setting include the use of other drugs, timing of measurements, the presence of painful treatments, etc. (24) One of most difficult issues to address is the ability to separate the amnesic and sedative effects of drugs on memory. (25) (21) A behavioral paradigm that could separate sedative and amnesic effects of drugs easily applied in the clinical setting would allow the ability to measure the influence of the amnesic properties of a given drug on outcome, for example patient satisfaction with anesthesia or recall of procedure events. Over the past decade we have developed

methods to measure amnesic versus sedative effects, in particular with propofol, in the research setting using volunteers. (7,16,21)

The drug ramping paradigm

A simple paradigm that allows amnesia to be differentiated from sedation is to infuse drug in increasing concentrations over a period of ~10 minutes. During this time period, as drug concentration and sedation are increasing, visual stimuli are presented. Importantly, these stimuli are attended to by performance of a task, in this case by naming a picture. A positive response on the task, naming the picture either correctly or incorrectly, confirms that the stimulus was processed sufficiently to be learned and allow testing for subsequent recognition.

The full range of sedation effects is achieved by administering the drug at a rate so that no sedation is present initially, with levels of sedation present that allow the naming task to be performed during the bulk of the infusion period. By the end of the infusion period sedation appropriate for the therapeutic procedure is present, namely, unresponsiveness to voice. Analysis of subsequent recognition memory and sedation at the time of encoding allows one to determine the time of picture presentation at which 50% memory effect occurs and compare it to the time at which 50% sedation occurs. The larger the separation between these two dose-response points, the greater are the amnesic properties present for the drug. This is illustrated below using exemplars from volunteer studies we have previously conducted.

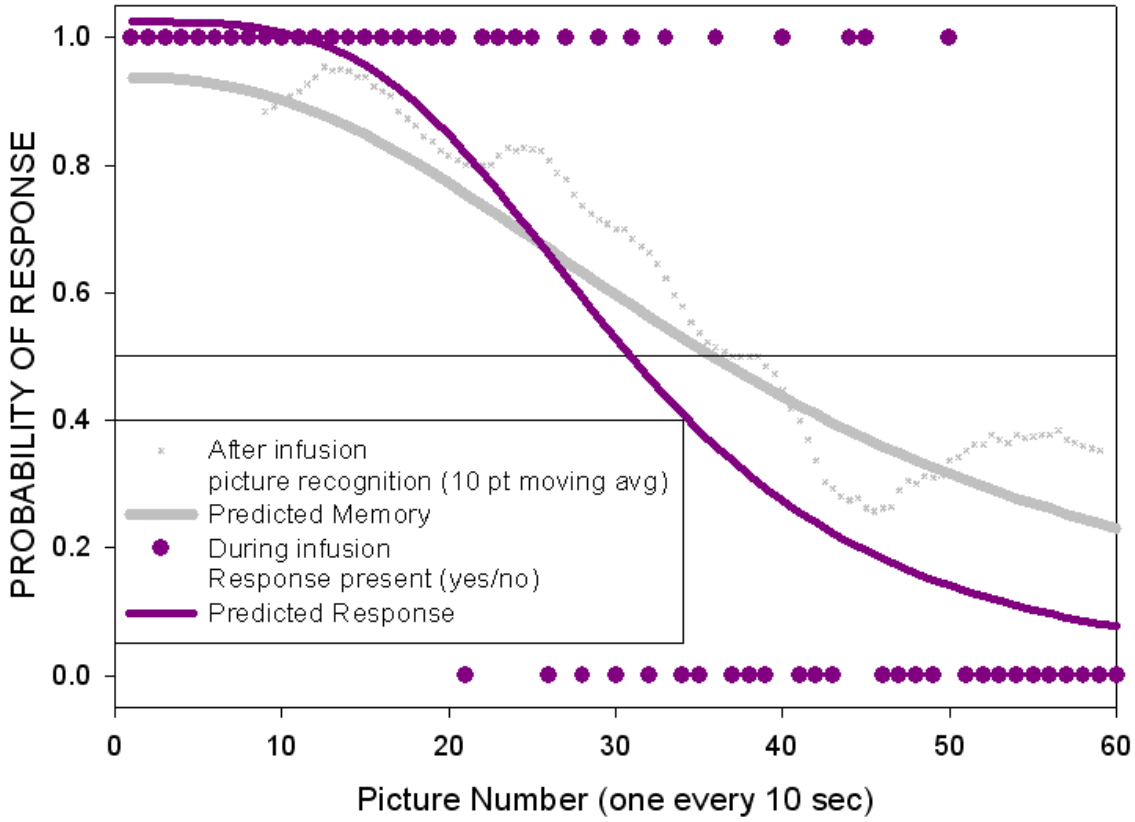

FIG 1 Infusion of a typical **sedative** drug (**thiopental**) over 10 minutes, during which time 60 pictures were shown. As time increased (higher picture number), sedation increased, and fewer responses occurred (dark dots). Response data (response to picture task during infusion (yes/no) and subsequent recognition of picture, gray crosses) were fitted to regression curves. For sedative drugs, the subsequent lack of recognition memory parallels the increase in sedation, i.e. there was no specific amnesic effect (a **small difference in 50% effect** (horizontal black line) for memory and sedation)

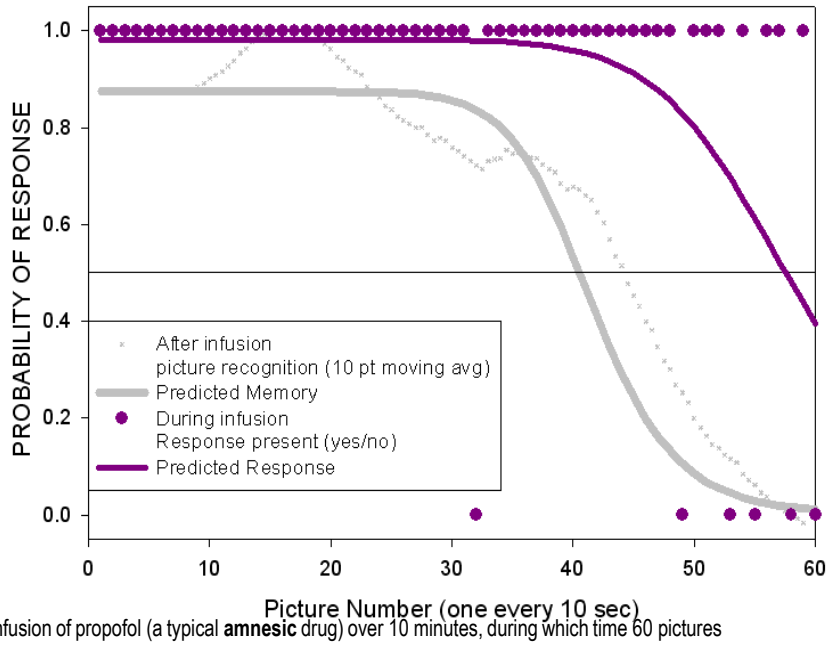

FIG 2 Infusion of propofol (a typical **amnesic** drug) over 10 minutes, during which time 60 pictures were shown. As time increased (higher picture number), sedation increased only at the end of infusion (dark line). The hallmark of amnesia is the lack of subsequent recognition which begins well before any increase in sedation (dark line, **a large difference in 50% effect** for memory and sedation).

As there is substantial evidence that propofol is amnesic in adults and propofol is the most common sedative agent used for pediatric procedures, we wish to initially test the drug ramping paradigm as a measure of amnesic effect using propofol in pediatric patients. The main goal of this study is to determine the feasibility of patient accrual and ability to define the relationship of amnesia to the level of sedation.

In summary, a rationale exists, but is not proven, for the desirability of specific amnesic properties for drugs used during sedation/anesthesia. The development of an instrument to detect the amnesic effect of a given drug in a clinical setting would not only confirm results from previous volunteer studies, but would provide an opportunity to measure an important variable in patient outcome in terms of recall of the surgical/therapeutic experience, or of patient satisfaction. If the quality of amnesia does indeed relate to outcome, then this measure applied in the clinical setting would provide a rational basis for drug selection. Future studies could be used to compare drugs with similar pharmacokinetic profiles, for example, propofol with dexmedetomidine or various inhalational agents.

A protocol using the same methodology as in the current one is now open at Boston Children's Hospital, where dexmedetomidine is used for pediatric sedation. Accrual demographics are nearly identical with the patients accrued so far to the MSKCC protocol. Inclusion of a control group at both sites will validate a more direct comparison of memory effects from propofol with those of dexmedetomidine.

Post-Operative Cognitive Dysfunction

Another important clinical issue is the presence of cognitive dysfunction after anesthesia in the elderly with impaired cognitive reserve. (26-28) (29,30) Memory impairment is an important component of post-operative cognitive dysfunction, which in turn is associated with a higher incidence of post-operative delirium, and poorer outcomes. (31) Of importance, patients of all ages who have received chemotherapy demonstrate varying degrees of cognitive impairment. (32) Thus, in theory, this patient population may be at similar risk to elderly patients with diminished cognitive reserve in terms of post-operative cognitive dysfunction. In fact, age, cognitive reserve and chemotherapy are all important determinants of cognitive performance. (33) If feasibility is demonstrated in the current protocol, the proposed behavioral paradigm could then be tested in a more heterogenous adult patient population. The drug ramping paradigm could be a useful tool to assess the sensitivity of different patient populations to acute memory impairment by drug administration. The paradigm could be easily modified to assess memory function at various time points before and after intervention (as we have done to define memory decay characteristics in volunteers after receiving sedative and amnesic agents (16)). Substantial improvement in patient outcome may be possible if anesthetic management could be modified to decrease the incidence of POCD or delirium. Development of a behavioral measure of amnesia / memory dysfunction that can be easily applied in the clinical setting is a key component of this process.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

Children either requiring sedation or not for therapeutic or diagnostic procedures will be offered inclusion in the study. Sedation will be induced over a period of 10 minutes by administering propofol at an infusion rate that will produce suitable conditions for the procedure at the end of infusion (heavily sedated or asleep). During the infusion pictures will be shown to the child who will be encouraged to name the item in the picture. After completion of the procedure, when the child is awake and being assessed for discharge, memory will be tested using forced choice recognition of pictures previously shown intermixed with novel pictures. The child will indicate yes/no whether the picture was seen during induction of sedation. Children not requiring sedation will perform exactly the same tasks as described above, but without any drug infusion.

4.2 Intervention

During induction of sedation, or in the case of no sedation, before the therapeutic procedure, children will be encouraged to name the items shown in pictures displayed, one every 5 seconds, as drug concentration is increasing. Naming pictures will ensure that items are being attended to and memory systems are engaged. The child's response will be used to assess the degree of sedation present (response present / response absent). After recovery from sedation, or after a similar time period after the therapeutic procedure

(approximately 40 min) for children in the control group memory for the previously presented pictures will be tested using a yes/no response. The recognition testing set will contain both previously seen and novel items.

5.0 CRITERIA FOR SUBJECT ELIGIBILITY

Describe the characteristics of the subject population.

5.1 Subject Inclusion Criteria

- The patient must be between 4 and 14 yrs of age and be undergoing a therapeutic or diagnostic procedure with or without sedation
- The patient must be able to comprehend and perform the task (naming pictures)
- The patient must have a minimum weight of 8 kg

5.2 Subject Exclusion Criteria

- Allergy to propofol (for those patients requiring sedation)
- Procedure of short duration (< 15 min)
- Pregnancy
- Recent use (within 5 half-lives) of centrally acting medications that could affect concentration (e.g. diphenhydramine)

6.0 RECRUITMENT PLAN

Pediatric patients undergoing therapeutic or diagnostic procedures that might require sedation will be offered inclusion in the study on the day of the procedure upon arrival to the Pediatric Day Hospital. It is anticipated that between 2 and up to 5 patients a week will participate in this study.

7.0 ASSESSMENT/EVALUATION PLAN

The recognition memory task will consist of simple line drawings selected from a larger stimulus data base (http://crl.ucsd.edu/experiments/ipnp/method/getpics/getpics.html) based on their age appropriateness and identifiability by children in the target age range. Stimulus items are presented by means of a bound stimulus book with one black and white line drawing presented on each page. A brief test will be performed to familiarize the child with performing the picture naming task, using different pictures from those that will be shown in the study. If the child is not able to cooperate sufficiently with the test task, then he/she will be withdrawn from the study and propofol will then be administered as per normal clinical practice for their procedure. If sedation will be needed, propofol infusion will be started at a rate to deliver 3mg/kg over a 10 minute period. During this learning phase of the study, pictures will be presented to the participant and the participant will be asked to name each object pictured with accuracy and non responses will be recorded by the examiner. If sedation is being given, the drug infusion rate will be adjusted according to clinical observation (e.g. excessive sedation/no drug effect apparent) so that the patient will be appropriately sedated for the planned procedure by the end of the 10 minute infusion period. After conclusion of the initial infusion, propofol will be administered as per usual practice. Following the procedure after awakening in the PACU, when no apparent sedation is

present, or after a similar time period, if no sedation was used, the picture recognition phase of the study will be performed. Patients will again be presented the original pictures with an equal number of pictures not seen during the infusion phase. The order of pictures in the learning (propofol infusion) and recognition phases(PACU) will be the same for every patient. The child will indicate whether the picture was seen before (yes/no). The study is complete. The child will be discharged form the PACU as per standard clinical criteria."

8.0 TOXICITIES/SIDE EFFECTS

As is normally used for pediatric sedation, propofol will be used. As the length of sedation for the procedure is anticipated to be more than a few minutes, propofol will be infused using a drug infusion pump, as is routinely done now. Thus, no additional toxicities/side effects beyond those associated with the clinical administration of propofol as currently practiced are present.

9.0 PRIMARY OUTCOMES

Several factors affect the feasibility of the proposed study design, including 1) accrual rate in the proposed 4 – 6 months study period, 2) drop-out rate (children who complete the picture naming task during infusion but fail to complete the memory task post recovery), and 3) sufficient data (e.g., few observations during the picture naming task because the child falls asleep quickly; few accurate responses during the memory task).

The accrual and dropout rates will be addressed by keeping a running tally of the number of recruited participants to monitor the recruitment numbers. Our target is to recruit at least an average of 2 out of the anticipated 4 – 6 children per week. However, it would be impractical to set a fixed recruitment target for a pilot study of this nature.

Factors associated with data sufficiency will have to be determined after the data have been collected. For example, we have to wait until the data have been collected before we can begin calculating the proposed threshold statistic (Section 14 below). The statistical computer packages may or may not be able to derive a stable estimate of the threshold measure per child. This will have to be determined after each child's data have been collected, entered, and fitted for the threshold statistics.

It is premature to anticipate a statistically reliable difference between the two threshold measures, one for the *sedative* effect threshold and the other for the *memory* effect threshold. These will have to be ascertained after the data have been collected, entered, fitted, and plotted in the manner similar to Figures 1 and 2 above. It is plausible that the threshold values are similar in some children and quite different in some other children. An important goal of this study is to examine the variability between the two threshold values among the sample of children.

10.0 CRITERIA FOR REMOVAL FROM STUDY

If the patient cannot adequately perform the picture naming task (defined as verbally responding to >80% of the pictures presented before falling asleep, or half way through the list in the case of no sedation) through a significant portion of the initial 10 minute

infusion, data collection will be stopped, the patient withdrawn from the study, and no further testing be performed. Similarly, if the patient is unable or unwilling to perform the recognition task, he/she will be withdrawn from the study. In the extremely unusual circumstance of severe or unanticipated toxicity from the administration of propofol (e.g. allergic reaction), the participant will be withdrawn from the study. Any participant who is removed from the study prior to the start of their procedure for reasons other than toxiticity (i.e., inability or unwillingness to complete the practice or actual task) will then be administered propofol as per normal clinical practice for their procedure.

11.0 BIOSTATISTICS

Overview. This study is a pilot project to separately examine the *amnesic* and the *sedative* effects of the drug propofol. The plan is to recruit a pilot sample of 40 children who will undergo sedation as part of their clinical management and give them a memory encoding task during propofol infusion to measure the effects of *sedation*. The mere task of naming a picture will encode that picture into memory. When the anesthesia has worn off (at approximately 1 hour later), children will be given a memory recognition task to measure the *amnesic* effects of propofol. We will also recruit a total of 30 children who will not undergo sedation to serve as a control group. This brings out total number of participants to 70.

Analytic Plans for the Specific Aims:

Aim 1: The primary objective is to determine the feasibility of using the visual picture naming task in pediatric patients in the clinical setting. Feasibility will be defined as, at the conclusion of the study, 25 or more of the pilot sample of 30 (control) or 35 (propofol) per group complete the recognition memory task and yield usable parameter estimates for the psychophysics function. The probability of declaring the study design feasible is 0.51 when the true population feasibility is 0.70; and the probability of a feasible study increases to 0.92 when the true population feasibility is 0.80.

Descriptive statistics will be sought to examine study feasibility. A running tally of the number of recruited participants will be kept to monitor the recruitment numbers during the anticipated 4 – 6 months study period. Due to the complex nature of this research, many factors affect study feasibility. It would be impractical and unrealistic to set an a priori feasibility target. Rather, we will monitor several factors, including patient volume, rate of study consent, the proportion of patients who can complete the experimental tasks and the practicality of fitting the psychophysical Weibul model described below. Study feasibility will be evaluated holistically at the end of the study by the study investigators.

As for the minimally sufficient number of responses, the 10-events-per-parameter rule of thumb may apply here. (34) Although that rule was developed for logistic regression, which may or may not be too restrictive for the SAS NLMIXED procedure we intend to use to fit the threshold functions.

Aim 2. Illustrative Examples. Aim 2 involves the calculation of a "sedation threshold" and a "memory threshold" for each child. Figures 1, and 2 provide illustrative examples on how the separate sedative and amnesic effects will be estimated statistically. An example is provided below to explain the procedures and the analytic plan.

1. "Sedation threshold": During the 10-minute infusion of propofol, children will be presented with pictures at 5-second intervals and asked to name the picture. They will be asked to name each picture (e.g., cat, tree, pencil, etc.). A valid response is naming of the picture within 5 seconds, either correctly or incorrectly.The important response measure is whether the child is awake enough to perform the naming task. Though the picture list is a validated set of stimuli, as described in Section 7.0, some stimuli may end up being too difficult to name for children of this age group. Thus no response due to sedation may be confounded by no response due to an inappropriately difficult stimulus. Responses from the control group of children will be used to eliminate problematic stimuli which reach a given criterion of no response at both sites.

In Figures 1 and 2, the dark circles with a value of 1 on the y-axis represent that the participant is making valid responses. The dark circles with a value of 0 on the y-axis represent lack of a valid response because the participant is sedated to the point of impaired response performance as propofol concentration continues to increase. As the child gets sedated and becomes gradually sleepier as the infusion continues, he/she is less likely to make a valid response (thus the increased frequency of dark circles at the bottom of the Figures as image number increases). The dark line in Figure 1 represents the estimated sedative effects over time.

There is a vast literature in psychophysics on modeling the shapes of these curves. Since the seminal paper by Quick (1974; *Kybernetik*, 16: 65-67: PMID: 4453110), the model below has been used extensively in modeling various psychophysical functions. We will use an asymmetric Weibull cumulative density function *F(x)* to model in the overall probability of a valid response *G(x)* over time *x*:

$$G(x) = 0.5 + 0.5 \cdot F(x)$$

$$= 0.5 + 0.5\left[1 - \mathrm{e}^{-(\alpha \cdot \mathrm{x})^{\beta}}\right],$$

where $\alpha > 0$ and $\beta > 0$ are the scale and shape parameters, respectively, and $x \geq 0$. (35) The constant of 0.5 assumes a 50-50 chance of a random response in a psychophysical task. Conventionally, the median of *F(x)* is called the "threshold" of the underlying psychometric function (the value of x for which *F(x)* = 0.5). Because of the assumed 0.50 constant in *G(x)*, and the 0.5 times the median of the Weibull, the threshold estimate is the *x* value of an overall 75% response probability given the Weibull parameters. The threshold of a psychometric function generally represents the strength of stimulus that elicits a sensation or a noticeable difference. In this case the sedation threshold represents the time value of *x* when sedation is actuated. We will estimate one sedation curve and its corresponding threshold for each child.

2. “Memory threshold”: When the anesthesia has worn off at approximately 1 hour later, the child will be presented with another list of 120 pictures with half having been presented during the initial infusion of propofol. At the presentation of each picture, the child will be asked whether or not he/she remembers having seen it previously. Each response will be coded as correct (true positives and true negatives) or incorrect (false positives and false negatives). A curve may be fitted to the memory recognition data to estimate the average memory decay function for each child. In Figure 1 and 2 this is represented as the light gray curve, which can be modeled as 1 – *G(x)* above. Similarly, a threshold represents the time value (picture number) when memory fades below threshold.

The *sedation* threshold in Figure 1 is at image 25 (250 seconds), while the *memory* threshold is at approximately image 28 (280 seconds). This 30-second / 3 picture difference is taken to represent that sedation occurs concurrently with memory decay. Alternatively, in Figure 2, the *sedation* threshold is at image 58 (580 seconds) while the *memory* threshold is approximately at image 40 (400 seconds).This larger difference of 180 seconds / 18 pictures is a measure of how much sooner amnesia occurred in this instance than sedation. In this latter case, a measureable amnesic effect of 180 seconds can be inferred from the two threshold values.

Calculations of the sedation and memory thresholds. The overall statistical paradigm will involve non-linear regression modeling to estimate *G(x)* functions for the memory and sedation curves for each child in order to address the main hypothesis:

“The threshold effect for memory will occur significantly sooner, i.e. at lower drug concentrations, than the threshold effect for sedation”.

Sample Size Considerations. The proposed pilot sample of 35 children accrued to the propofol group is primarily determined by our plan to complete the study within 4-6 months. In our experience we have a pool of approximately 10 children who undergo anesthesia for clinical scans each week who would meet the eligibility criteria. Among them an anticipated 50% would agree to participate in this study. If half of these (2-3/week) produce data of sufficient quality to be able to perform curve fitting as described above, we expect to complete recruitment within 5 months.

A sample of 35 children will also yield an 80% power in a one-sample t-test against the null that the difference in the sedation and memory thresholds is zero (null ~ $N(0, 1)$), assuming a two-sided Type-I error rate of 0.05, and an alternative population distribution with a mean of 0.50 and a standard deviation of 1.0. The statistical power was estimated by the G*Power computer program.

12.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

12.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the written consent/verbal script and a completed Eligibility Checklist must be faxed to PPR.

12.2 Randomization

This study does not require randomization.

13.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinating the activities of the protocol study team. The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record. All data will be maintained by the RSA under the direct supervision of the principal investigator.

13.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

13.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Essential Elements of a Data Safety and Monitoring Plan for Clinical Trials Funded by the NCI” which can be found at: http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb5.mskcc.org/intranet/_assets/_tables/content/359709/DSMPlans07.pdf.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center’s Research Council and Institutional Review Board. During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation.

14.0 PROTECTION OF HUMAN SUBJECTS

As is routinely performed, a medical doctor will be present during drug administration and performance of the therapeutic procedure (usually MR scanning) and vital signs will be monitored by clinical monitoring equipment. After sedation is established, propofol dosing will be adjusted as per clinical routine during the therapeutic procedure. Each patient will be observed for as long as necessary after the conclusion of the procedure, and will meet the usual clinical discharge criteria used for ambulatory surgery.

Side effects of sedative agents are more pronounced with bolus administration than continuous infusion. Using a continuous infusion to obtain targeted concentrations will minimize the potential side effects of propofol.

No direct benefit to the participant is expected from participation in the study and participants will not be reimbursed for participation in the study.

All members of the research study team will have current certification in HIPAA Regulations and Human Subjects Protection as required by the NIH. Every effort will be made to ensure that this study is conducted within the federal, state, local and institutional guidelines regarding research involving the use of human subjects. To this end, the following will be done:

The potential risks including adverse drug reactions will be discussed in detail with patients. No patient will be required to participate in the study and participation or lack of participation will not affect the patient's subsequent care or treatment.

The patient will not incur any financial cost as a result of participation in the study.

Throughout the study, patient confidentiality will be maintained. No results of the study will be presented or discussed in a fashion that will allow identification of a particular patient in the study. Any protected health information used for the study will be maintained in a secure drive (as described in Section 13.0) and handled only by those individuals authorized by the patient to do so as indicated by their signature on the Research Authorization (as described in Section 15.0).

All adverse events will be fully disclosed to the MSKCC IRB in a timely fashion as required. SAE reporting procedures will be carried out as described in Section 14.2.

Participation will be purely voluntary and informed consent will be obtained for all patients who choose to participate in the study. This informed consent process will be documented as described in Section 15.0.

14.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

14.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)

- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

We expect that our patients may be hospitalized in relation to their cancer. However, due to the nature of our non-therapeutic study, we will not report hospitalizations or any other events unrelated to the procedures outlined in our protocol as SAEs.

14.2.1

N/A

15.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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17.0 APPENDICES

Appendix 1. Gallery of images to be shown to protocol participants