RePPAIR –Reducing Procedural Pain and Improving Recovery of Quality of Life in Pediatric Neuroblastoma Patients Undergoing Bone Marrow Procedures: A Prospective Randomized Cross-over Clinical Trial

PROTOCOL FACE PAGE FOR
MSK THERAPEUTIC/DIAGNOSTIC 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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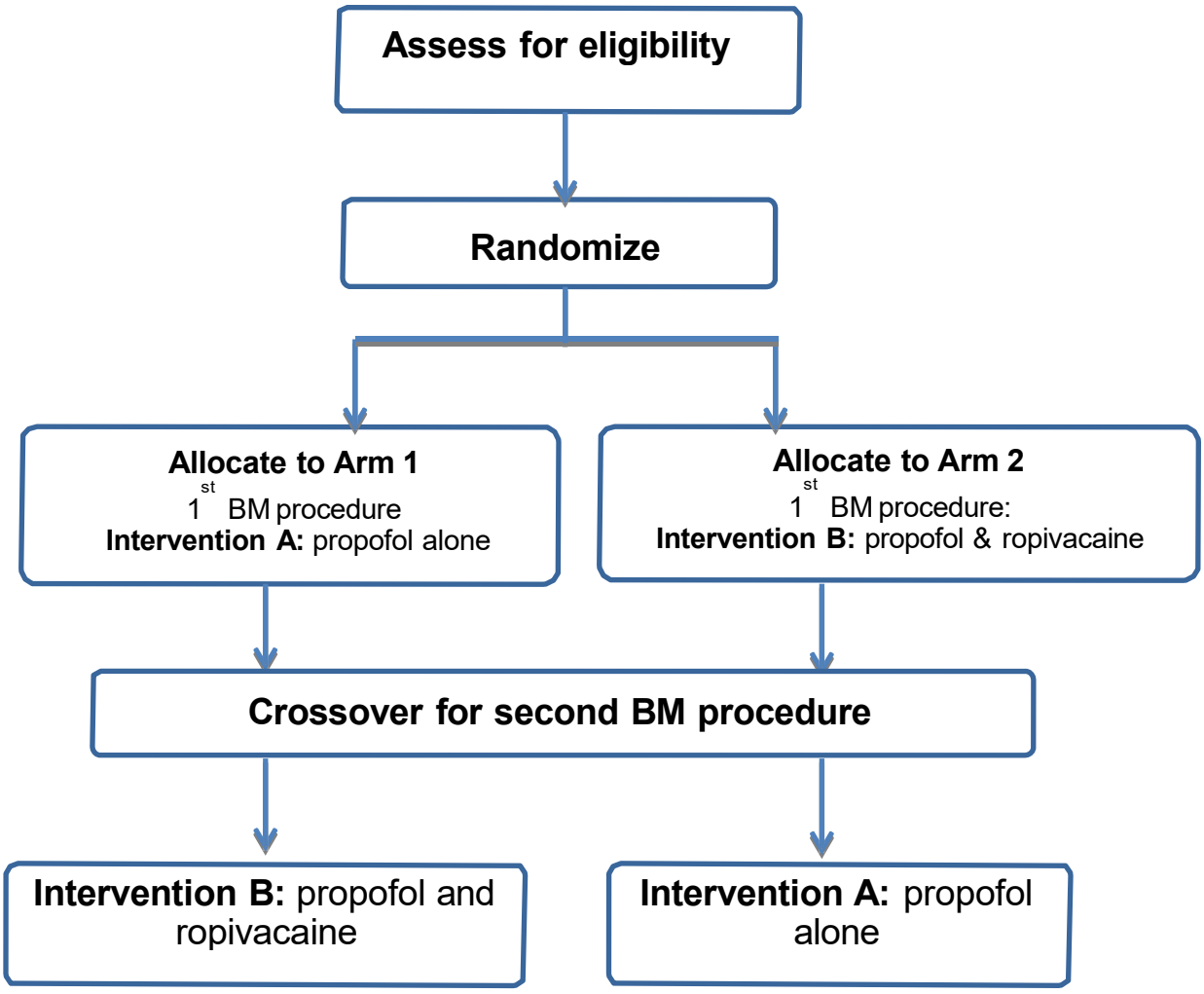
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is prospective double-arm, randomized cross-over clinical trial that will assess whether the addition of a local analgesic agent, ropivacaine, to the standard of care of propofol will reduce the percentage of pediatric neuroblastoma patients who require opioid analgesia after bone marrow procedures compared to propofol alone. A "bone marrow procedure" will be defined as 4 bone marrow aspirations *and* 2-4 bone marrow biopsies. Pediatric neuroblastoma patients will receive the standard of care (Intervention A) or the standard of care with the addition of subcutaneous and periosteal infiltration of ropivacaine (Intervention B). We will compare the percentage of patients requiring post-procedural opioid analgesia in each Intervention as the primary endpoint, as well as total opioid consumption, time to first opioid, percentage requiring non-opioid analgesia, standardized pain scores and quality of life metrics. Based on statistical considerations and extrapolation from an informal needs assessment, we expect to enroll enough patients for adequate power within 6 months of study opening.



2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

- Determine whether there is a reduction in the percentage of pediatric neuroblastoma patients undergoing a bone marrow procedure who require post-procedural opioid analgesia within 24 hours (+/- 4 hours) of the procedure with the addition of local ropivacaine.

Secondary Objective:

Determine whether there is a difference in:

- 24 hours (+/- 4 hours) post-procedure opioid consumption in morphine equivalents (mg/kg/day)
- Percentage of patients requiring non-opioid analgesia within 24 hours (+/- 4 hours) of procedure
- Standardized pain scores (Wong-Baker FACES® Scale)
- Time to first opioid medication
- Short-term quality of life
- Adverse outcomes with the addition of local ropivacaine

3.0 BACKGROUND AND RATIONALE

3.1 Background

Pediatric neuroblastoma patients undergo bone marrow aspiration (BMA) and biopsy (BMB) procedures as a part of their extent of disease evaluation at regular intervals during treatment and surveillance. Many studies of both pediatric and adult oncology patients have shown that bone marrow aspirations and biopsies are painful procedures.[1-3] Not only do patients report procedural pain, but health care professionals and parents also acknowledge that these procedures are painful. A study asked Italian Pediatric Hematology-Oncology health professionals (medical directors, physicians, nurses, psychologists) their perceptions of procedural pain and found that providers considered BMA and BMB to be above 5 on a scale of 0-10 in 97.5% and 99.5% of cases, respectively.[4] Another study looking at pediatric oncology patients and their parents showed procedures to be the most frequent cause of distress.[5] Exposure to repeated painful procedures has been found to exacerbate anxiety and distress in children.[6,7]

The American Academy of Pediatrics (AAP) developed a report in 1990 stating that strategies to reduce pain and anxiety are integral to the care of pediatric oncology patients.[8] Pediatric oncology departments such as the Memorial Sloan Kettering Cancer Center (MSKCC) Department of Pediatrics have adopted institutional practices in an effort to reduce bone-marrow procedure-related pain and anxiety. The standard of care at MSKCC for pediatric patients undergoing BMA and BMB is to receive propofol. While propofol has amnestic and anesthetic properties, it lacks any analgesic properties.[9]

3.2 Needs assessment

In order to better understand bone marrow procedural pain for pediatric patients at MSKCC, we conducted a needs assessment of 25 pediatric patients and 1 adult patient, asking about their experience with BMA and BMB, done with the standard of care administration. We found that 8/26 = 30.7% of patients required opioid analgesia within 24 hours of the procedure - 7/8 post-procedurally and one patient with systemic opioid given with anesthesia. We also discovered that many children had persistent pain and reduced activity level the day following the procedure - 12/26 = 46% and 8/26 = 31%, respectively. Based on this data, we identified a need to improve the experience of pediatric neuroblastoma patients with bone marrow procedures. Although there are no standard clinical guidelines, the AAP recommends an individualized and age-based approach and encourages the use of both non-pharmacologic and pharmacologic interventions that includes both anesthesia and analgesia.[8] We also conducted an informal survey of seven other major pediatric oncology centers and found that each of these centers uses analgesia, either systemic or local, in addition to general anesthesia for bone marrow biopsy procedures.

3.3 Rationale

The purpose of this study is to investigate whether subcutaneous and periosteal infiltration of a local anesthetic agent, ropivacaine, will reduce the percentage of patients requiring post-procedural opioid analgesia and improve quality of life in the day following the procedure. A similar study recently demonstrated that topical analgesia for lumbar punctures reduced the amount of propofol used in pediatric oncology patients.[9] However, no study has been done to investigate the efficacy of local analgesia in combination with propofol for bone marrow procedures. For this reason, a trial evaluating the effect of the addition of local analgesia is both justified and necessary. Local analgesia acts to limit the initiation of nociceptive pathways prior to the traumatic insult, in this case, subcutaneous and periosteal infiltration by a bone marrow aspiration or biopsy needle. Ropivacaine is an example of a local anesthetic agent that blocks both the initiation and conduction of nerve impulses by decreasing the neuronal membrane"s permeability to sodium ions.[10] It is an amino-amide local anesthetic that is a pure S-(-)-enantiomer with lower lipid solubility than racemic mixtures; these features allow ropivacaine to have a higher safety profile with less cardiovascular and central nervous system toxicity than racemic lidocaine and bupivacaine.[10] Its onset of action is listed as “fast” with infiltration. i.e. within 3 to 15 minutes.[11] Its duration of action is 3 to15 hours.[11] Therefore, due to its effect on nociceptive pathways, rapid onset and moderate duration of action while maintaining a low toxicity profile, ropivacaine is a reasonable option for local analgesia for bone marrow procedures. This is the first time ropivacaine will be directly injected into the bone marrow site at MSKCC Pediatrics.

Primary and secondary outcome measures were carefully selected after reviewing pediatric pain literature. Within pain clinical trials, analgesic efficacy can be measured by the ability to reduce or eliminate the need for rescue analgesia. “Rescue analgesia-sparing” has been identified as practical and feasible surrogate primary endpoint[12,13]. A systematic review of

33 pediatric trials that used opioid as the study drug showed that percentage requiring rescue medication was a useful outcome measure in small procedures when the time and amount of rescue medication needed was low relative to surgical procedures.[13] This will be the primary outcome in the current study. Time to first rescue opioid and total opioid dose were alternate outcomes that are commonly studied;[13] in this protocol, they are selected as secondary outcomes. Relative differences in pain scores, either over time or with an intervention, are frequently used as an outcome measure in pain clinical trials and will be a secondary outcome in this study.[1 2,15] We selected the Wong-Baker FACES® Pain Rating Scale (WBFPRS) (Appendix 1) for this study because it is a validated scale intended for use for our patient population.[14,15] Advantages of this scale include its reliability over time, ease of administration, and children have been shown to prefer this scale over others.[15] It is routinely used clinically at MSKCC Department of Pediatrics. An extensive review of various pediatric pain scales concluded that many of the pain scales in use are equivalent, and encouraged the use of a scale familiar to the institution for clinical purposes.[16]

This study will use a pain management algorithm for consistency in post-procedural pain management (Appendix 2.1 and 2.2). This algorithm relies on the WHO Analgesic Ladder for escalation of therapy. We referred to the previously mentioned needs assessment as well as commonly used categories for pain severity to determine the interventions starting from heat packs, moving to the non-opioid analgesic: acetaminophen and escalating to a low dose strong opioid for moderate pain as defined as pain greater than but not equal to a 4 on the WBFPRS. The decision to use a low dose strong opioid instead of a weak opioid as suggested by the WHO Analgesic Ladder is based both on institutional practice and recent multi-center study in patients with cancer and moderate pain demonstrating better pain relief with a low dose strong opioid instead of weak opioid.[17]

Groups such as the Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (PedIMMPACT) have recommended multidimensional outcome domains and measures for pediatric pain clinical trials.[15,18] The PediIMMPACT consensus guidelines for investigators conducting clinical trials addressing acute pain include 6 domains including pain intensity, physical recovery and emotional response.[18] We aim to incorporate these additional domains into this study by utilizing a quality of life metric adapted from a validated pain interference inventory. We will use an abbreviated version of the National Institutes of Health (NIH) Patient Reported Outcomes Measurement Information System (PROMIS®) Parent Proxy measure for pain interference.[19,20] This full item bank has been validated for use by the parents of 8-17 year olds and has been extended for use in 5-7 year olds.[19,20] We will extrapolate its use for our patient population and have selected 4 of the 13 items from the item bank to assess how procedural pain affects physical recovery in the context of activity and sleep as well as social and emotional functioning (Appendix 3).

This study is clinically relevant in the care of pediatric neuroblastoma patients who undergo repeated painful procedures in an effort to optimize pain alleviation and reduce the potential for distress related to procedures. We specifically selected pediatric neuroblastoma

patients since they undergo repeated bone marrow procedures during the course of their care and these procedures often involves four sites. Therefore, it would benefit these young patients to identify pain associated with recurrent procedures and optimize its management. We have selected a single patient population to allow for better standardization in our assessment and outcome measures. As a result of this study, we hope to improve standard institutional practice for any pediatric patient undergoing a bone marrow procedure.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This study will be a prospective double-arm randomized controlled single-blinded crossover design. The two interventions are:

- Intervention A: MSKCC standard of care
- Intervention B: MSKCC standard of care *plus* local analgesia with ropivacaine.

Pediatric neuroblastoma patients will be enrolled based on eligibility criteria and randomized to one of two arms representing a specific sequence of each intervention.

- Arm 1 (AB): standard of care only during the first procedure, then standard of care plus ropivacaine during the second procedure.
- Arm 2 (BA): Standard of care plus ropivacaine during the first procedure, then standard of care only during the second procedure.

Each patient will serve as his or her own control. The patients and parents will be blinded to the study arm. The procedural attending physicians and pharmacy will have to coordinate and administer the treatment agent (ropivacaine), and they will not be blinded to the study arm. The registered nurse (RN) in the procedure room will similarly not be blinded to the study. The Pediatric Day Hospital (PDH) Procedure Recovery Room (PRR) RNs will be blinded as they will also be responsible for data collection as described below. The study investigators who will be responsible for post-procedural data collection will similarly be blinded to the study combination.

4.3 Intervention

Intervention A: The standard of care agent will be administered intravenously by an anesthesiologist as per current institutional practice. An empty decoy syringe will be provided by the pharmacy and taken to the procedure room by appropriate staff as sometimes parents accompany their children into the procedure room prior to anesthesia administration. The empty syringe will be clearly marked and discarded.

Intervention B: The standard of care agent will be administered intravenously by an anesthesiologist as per current institutional practice. Once the anesthetic effect is achieved as determined by the anesthesiologist, the proceduralist physician will inject subcutaneous and periosteal ropivacaine prior to bone marrow aspiration and biopsy at each site (bilateral anterior and posterior iliac crests). Ropivacaine will be provided by the MSKCC PDH Pharmacy and will

be administered at standard dosing of 2mg/kg of a 0.5% solution (5mg/ml) and delivered to the procedure room by appropriate staff.

The following process occurs after every procedure. Patients will complete the procedure and recover in the PRR for an approximate time of 30 to 90 minutes. In the PRR, trained RNs who are blinded to the study combination will assess patient pain based on a validated self-report pain scale and administer pain medication when necessary based on a standard pain management algorithm (Appendix 2.2). After recovery in the PRR, patients will be discharge home. Parents/parents will assess their child"s pain on a validated self-report pain scale and administer pain medication when necessary based on a standard pain management algorithm (Appendix 2.2).

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Study agent: ROPIVACAINE[11, 25-28]

5.1.1 Source and Pharmacology: A local anesthetic. Mechanism of action is by blockade of both the initiation and conduction of nerve impulses by decreasing the neuronal membrane's permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction. The half-life is 5 to 7 hours when used as an epidural infusion and has a terminal half-life of 111 ± 62 minutes. It is metabolized by the liver and excreted through the urine.

5.1.2 Formulation and Stability: Supplied in single-dose containers in 2 mg/ml (0.2%), 5 mg/ml (0.5%), 7.5 mg/ml (0.75%) and 10 mg/ml (1%). Store at 20°C to 25°C.

In this study, the PDH pharmacy will prepare four (4) syringes from a single vial of the 5mg/ml (0.5%) ropivacaine at a dose of 2mg/kg/patient divided evenly into 0.5mg/kg/syringe with a maximum dose of a single 20 ml vial = 100 mg.

5.1.3 Guidelines for Administration: Doses are administered via local infiltration.

5.1.4 Supplier: Commercially available. See package insert for further information.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

- Diagnosis of neuroblastoma as defined by the International Neuroblastoma Risk Group Staging System (INRGSS)[22]
- 3 - 18 years of age
- Patient has had prior bone marrow procedures
- English speaking

6.3 Subject Exclusion Criteria

- History of allergy to investigational agent: ropivacaine or other amino amide analgesics
- History of allergy to standard agent: propofol
- Chronic daily opioid requirement
- Lansky/Karnofsky Score < 60
- Inability to comply with protocol requirements including refusal to forego pre-procedural opioid use
- Patient is receiving additional potentially painful interventions (e.g. central line insertion/removal) concurrent with the bone marrow procedure

7.0 RECRUITMENT PLAN

All consecutive eligible patients will be offered participation in this study by a physician in the Department of Pediatrics at Memorial Sloan Kettering Cancer Center. No patients will be identified by chart review or direct advertising. Every week, the Neuroblastoma Personal Office Assistant (POA) will circulate an email to the consenting investigators on this study that includes the name and medical record number of every neuroblastoma patient receiving a bone marrow procedure in the following week. Every day, the consenting investigators on this study are included on an email notice of new patients being seen by the Pediatric Neuroblastoma service. In this way, potential study participants will be identified for recruitment. The consenting professional will be responsible for explaining the study and obtaining written informed consent. Participants in the study will receive neither financial payment nor reimbursement. Eligible patients of all genders and racial groups will be equally offered enrollment in the study.

8.0 PRETREATMENT EVALUATION

Before each bone marrow procedure, the patient will be re-evaluated for continued eligibility. If the patient does not meet eligibility at the time of the scheduled bone marrow procedure, the intervention may be postponed until a subsequent bone marrow procedure when the patient meets eligibility criteria.

9.0 TREATMENT/INTERVENTION PLAN

Each enrolled patient will serve as his/her own control. On two bone marrow procedures, patients will receive either **intervention** A or B.

Each procedure will occur at approximately a two to four month interval. The timing of bone marrow procedures will be determined by the patient's clinical course.

In Intervention A, standard of care dosing and administration will be at the discretion of the anesthesiologist according to standard of care in the Department of Anesthesia at Memorial Sloan Kettering Cancer Center. In Intervention B, 2mg/kg of 0.5% ropivacaine will be drawn into

pre-filled syringes with a maximum dose of 20ml = 100mg. The physician performing bone marrow procedures will administer ropivacaine.

Ropivacaine will be injected into the subcutaneous tissue in an area approximately 1 cm in diameter. Subsequently, the ropivacaine will be administered to the periosteum in an area approximately 2-3 cm in diameter. Four pre-filled syringes will be provided and proceduralist physicians will be advised to administer one full syringe volume for each site (0.5mg/kg) with equal distribution between the subcutaneous and periosteal injection per site. Currently, propofol alone is the standard of care in the Department of Pediatrics at Memorial Sloan Kettering Cancer Center. While ropivacaine is a well described local anesthetic agent, the addition of ropivacaine to propofol to minimize post procedure pain is an experimental intervention.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Pain will be assessed in the post-anesthesia care unit (PRR). Directly upon emergence from anesthesia after the procedure and every 15 minutes subsequently, PRR nurses will use the Wong-Baker FACES® Pain Rating Scale (Appendix 1). Nurses will record patient-reported pain scores and administered analgesia in the Electronic Medical Record (EMR). Analgesia doses will be recorded at the time of administration. The PRR nurses will follow a standardized post-procedural algorithm (Appendix 2.1). Patients will recover in the PRR for approximately 30 to 90 minutes prior to discharge from MSKCC. In some instances, patients will be discharged from the PRR to the Neuroblastoma Clinic in the Pediatric Day Hospital (PDH). We anticipate that all patients will be discharged from MSKCC before 6 hours from the end of their procedure. In the unexpected case that a patient is admitted to the hospital for any reason during the study period (28 hours post-procedure), study investigators will provide the inpatient RN with the post-procedural opioid management algorithm (Appendix 2.1). Only if the admission is due to a study related life-threatening grade 4 toxicity, will the admitted patient be removed from the study as described in Section 13.0.

Families will be provided a 2 part, 12 item written questionnaire with 4 items and 8 items in each part, respectively (Appendix 3). They will be asked to complete Part 1 at 6 hours (+/- 1 hour) and Part 2 at 24 hours (+/- 4 hours) following the procedure. This questionnaire will have items regarding pain intensity and management to be answered at both time points. Families will be asked to follow a post-procedure pain management plan (Appendix 2.2). Post-procedural quality of life (QOL) will be assessed using a four-item questionnaire (Appendix 3) adapted from the NIH PROMIS® Parent Proxy Item Bank for Pain Interference and approved for use by the MSKCC Behavioral Research Methods Core Facility. These four questions will include the domains of physical recovery, emotional and social functioning. QOL will be assessed about 24 hours (+/- 4 hours) following the procedure. Principal Investigators, Co-Investigators, Investigators or appropriate clinic staff will call families 24-72 hours following procedure to obtain answers to the questionnaire.

11.0 TOXICITIES/SIDE EFFECTS

11.1 DEFINITION OF TOXICITIES:

- Common - Happens to 20-100 patients out of every 100
- Occasional - Happens to 4-20 patients out of every 100
- Rare - Happens to 3 or fewer patients out of every 100

11.2 LOCAL INFILTRATION OF ROPIVACAINE[11, 25-28]

Common	Occasional	Rare
None	None	• Allergic reaction with any route of administration • Arrhythmia with intravascular administration* • Seizure with intravascular administration* **Reported with inadvertent intravascular administration*

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 To assess primary objective, we will determine and compare for each study intervention the percentage of patients who required opioid analgesia between the time of bone marrow procedure and 24 hours (+/- 4 hours) after the procedure.

12.2 For the secondary objectives:

a) We will determine and compare for each study intervention the percentage of patients who used any non-opioid analgesia within 24 hours (+/- 4 hours) after bone marrow procedure.

b) We will calculate and compare for each study intervention the total dose of opioid consumption within 24 hours (+/- 4 hours) of the bone marrow procedure using mg/kg/day morphine equivalent.

Drug	IV conversion factor	PO conversion factor
Morphine	10mg	30mg
Fentanyl	0.250mg (250mcg)	—
Hydromorphone	2mg	8mg
Oxycodone	—	20mg
Oxymorphone	1mg	10mg
Codeine	75mg	130mg
Methadone	1mg	2mg
Hydrocodone	—	30mg

c) We will also determine the time to the first opioid administration. The starting point for this time will be the time of transfer to the PRR which will be documented by the PRR RN. This time will be recorded on the parent worksheet by the PRR RN.

d) We will assess standardized pain scores at 3 time points: (1) the maximum recorded pain score in the PRR, (2) at 6 hours (+/-1 hour) and (3) 24 hours (+/- 4 hours) after the bone marrow procedure. Pain scores 2 and 3 will be recorded by the parent after discharge from MSKCC. We will use the following validated pain scales: Wong-Baker FACES® Pain Rating Scale for patients between 3-18 years of age for patient-reported pain when asked by post-anesthesia recovery room nurses upon emergence from anesthesia and by inpatient nurses or family members in the outpatient setting upon discharge from the post-anesthesia recovery unit. We will compare pain scores between study interventions.

e) The QOL metric is a brief instrument that will assess post-procedural quality of life within 24 hours (+/- 4 hours) of the bone marrow procedure. This instrument assesses the following domains: sleep, physical functioning, emotional functioning and social functioning. This brief measurement tool will be adapted from a validated metric for pain interference in pediatric patients: NIH PROMIS® Parent Proxy Item Bank v1.0 – Pain Interference, which is a 13-item questionnaire. However, given that our study has rapid, frequent assessments, we will use an

abbreviated version for feasibility purposes and to minimize participant burden. Parents will be asked to assess QOL at 24 hours (+/- 4 hours) following the procedure by completing the questionnaire at that time. Principal Investigators or Research Staff will call families 24-72 hours following procedure to obtain answers to survey. This phone call will be for the purposes of data collection only and not for survey administration.

f) Patients will be under medical observation during the expected time when most adverse effects from ropivacaine will be experienced. Families will be advised to call the hospital for any symptoms beyond this time period.

13.0 CRITERIA FOR REMOVAL FROM STUDY

a) A patient will come off study if the patient/parent administers an opioid or any analgesic within 24 (+4 hours) after the bone marrow procedure that is not in accordance to the algorithm provided to them.

b) If at any time the patient develops life-threatening grade 4 toxicity during the study period, he/she will be removed from study.

c) If a patient is found to be ineligible for two sequential bone marrow procedures as designated in Section 6, the patient will be removed from study.

d)The patient may withdraw from study at any time if the patient/parent desires.

14.0 BIOSTATISTICS

This is a randomized two arm cross-over study investigating the effectiveness of the addition of ropivacaine to the standard of care on pain among pediatric neuroblastoma patients undergoing repeated procedures. The two drug combinations are standard of care (Intervention A) or standard of care plus ropivacaine (Intervention B, see Section 4.1). Patients will be randomized to either Arm 1 (AB sequence) or Arm 2 (BA sequence, see Figure in Section 1) to determine whether standard of care or standard of care plus ropivacaine will be administered in the first of two procedures. Patients will cross over during the second procedure. Sample size calculation is based on the primary outcome: the proportion of patients requiring post-procedural opioid analgesia (“rescue opioids”) within 24 hours (+/- 4 hours) post procedure. A needs assessment conducted in pediatric patients at MSKCC suggests that this proportion is about 30% under Intervention A (standard of care). We plan to enroll 50 patients (total of 100 procedures).

This is a crossover study in which we assume that there will be no period effect (i.e., if patient"s response in the subsequent procedure is affected by the drug from the first procedure). Due to the estimated two month interval between the two procedures and the duration of action of less than 15 hours for either drug combinations, we can assume no period effect. The primary outcome (whether the patient received rescue opioids) will be evaluated with GEE (generalized estimating equations) for binary data with logit link function clustered by patients[23]. The model

will include the drug indicator, procedure order, and an exchangeable correlation structure to address the correlation between multiple observations from the same patient. GEE has the advantage of being able to include data from only one of a patient"s two procedures, in order to accommodate the (rare) case in which the patient drops out / withdraws prior to the second procedure. With complete data, however, this approach simplifies to a McNemar"s test. The power and sample size calculations will be based on McNemar"s test.

There is limited publication on the correlation among longitudinal measures of pediatric pain scores, particularly those reported by the parent instead of the child; one study reported correlation of 0.63 between times 1 and 2 (6 months apart) of parent-proxy reported pain scores[24]. Assuming a conservative correlation of 0.4 between the two outcomes (from two procedures) of the same patient, a sample size of 45 patients will allow 80% power to detect an absolute difference of 20% in proportions between the treatments at an alpha level of 0.05 (assuming rates of 30% in Intervention A and 10% in Intervention B). This sample size allows for an interim assessment of futility at the half way point (23 out of 45 patients with both procedures completed). If $p>0.703$, then the trial will stop for futility; if $p\leq 0.703$ then the study will continue until completion. The target enrollment of 50 patients allows for an anticipated drop-out rate (due to any reason) of 10% in the power analysis calculation. This power calculation was generated using the proc power procedure in SAS 9.4, specifying paired proportions and correlation for McNemar exact conditional test. Based on an accrual rate of 15 patients in month 1, 10 patients in months 2 and 3 and 5 patients per month in months 4, 5, and 6, we anticipate completion of enrollment in 6 months.

The potential variability between attending physicians performing the procedure will be explored by including specification of patients nested within physicians as clusters in the GEE models. Other potential factors to include in the GEE models as fixed effects may include total number of biopsies and aspirations per procedure and/or different dose of ropivacaine.

Secondary outcome of standardized cumulative opioid consumption within 24 hours (+/- 4 hours) (morphine equivalents, mg/kg/day) will be summarized and compared between the two drugs using linear GEE models with the same factors as described above, including of the other potential factors identified from the analysis of the primary outcome. Additionally, time to first opioid use within the first 24 hours (+/- 4 hours) post procedure will be estimated using the Kaplan-Meier method and compared between the two drugs using the clustered logrank test. This is appropriate as patients may never require any opioids and will hence be censored at 24-hours. The proportion of patients requiring non-opioid analgesia within 24 hours (+/- 4 hours) of procedure will be compared between the two drugs using GEE (for binary data) as described for the primary outcome.

Post-operative pain reported on the Wong-Baker FACES® Pain Rating Scale (converted to scale of 0-10) will be measured at 3 time points: in the PRR, at 6 hours (+/- 1 hour) and 24 hours (+/- 4 hours) after the procedure. If more than one pain score is recorded during the PRR,

then the maximum pain score during the PRR will be included in analyses. Pain scores will be compared between the two drugs using a linear GEE model with drug indicator, procedure order and the exchangeable correlation structure for the 3 time points. The GEE models appropriately account for correlation among within-individual repeated measures, sequence of drugs, and allow for missingness (i.e., if the respondent does not provide complete follow-up data). Short-term QOL and activity level will be reported based on the (NIH PROMIS® Parent Proxy Item Bank v1.0 – Pain Interference) as individual items. QOL measures will only be recorded once at 24-hours post-procedure. We will use a linear GEE model to analyze the differences in QOL item-measures between the two drugs. Drug indicator and procedure order will be included as covariates. Overall rate of any complications or major adverse events and the rates of specific adverse outcomes related to the addition of local ropivacaine will also be compared between drugs using GEE (for binary data) These analyses are exploratory because they are of secondary interest and we do not have prior data to estimate statistical power.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 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. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

The study arm will be assigned by randomization at the time of study registration.

16.0 DATA MANAGEMENT ISSUES

Data to be collected:

- Age
- Diagnosis
- Gender
- Opiates used during procedure
- Any analgesia used through 24 hours (+/- 4 hours)post procedure
- Pain scores
- Quality of life scores

Data will be collected via chart review post procedure, and personal phone calls to families/patients on the day after the procedure.

Data will be collected on a secured database and stored on an MSKCC server. Data will not be stored on personal devices or removed from MSKCC.

We expect to achieve the following accrual rate
Month 1: 15 patients
Months 2, 3: 10 patients/month
Months 4, 5, 6: 5 patients/month
We will need approximately 6 months to achieve our enrollment goal based on power analysis.

Given that each patient will complete two bone marrow procedures and there can be up to four months between procedures, we expect a study duration of approximately 10 months for all enrolled patients to complete both interventions.

16.1 Quality Assurance

Quality assurance is the responsibility of PI and Study team it will be achieved by frequent review of the data.

The data will be obtained from medical records and personal phone calls. The clinic team will educate the procedure room/recovery room on validated pain scales to ensure accurate capture of patients pain. The clinic team will also provide families with written validated pain scales to reference at home as well as a written form of questions to be asked on phone call.

Eligibility will be verified for all enrolled patients by secondary review of the eligibility checklist. This will be completed by the data team.

Registration reports will be generated by the RSA 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 extext 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 on an ongoing basis.

16.2 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 "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. 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: https://one.mskcc.org/sites/pub/clinresearch/Pages/protocol-review-committees/data-and- safety-monitoring-committee.aspx.

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.

Institutional monitoring plan for phase I and phase II trials: Memorial Sloan-Kettering Cancer Center (MSKCC) has established standard procedures for data safety monitoring of clinical research. For Phase II trials, these procedures include consideration of accrual rates, toxicity, adherence to dose-escalation schedules, adverse event notification and data recording. Therapeutic responses are logged on a central database and approximately 50% are reviewed by an independent committee. An annual report of the trial"s progress is sent to the IRB. All of the procedures for Phase II studies outlined in MSKCC"s policy are applicable to the current trial and will be followed by the investigators. The analysis of safety will include all patients who receive at least one dose of study medication. Adverse events, including all toxic effects of treatment, will be tabulated individually, and summarized by body system, according to study medication, and according to severity or toxicity grade. Laboratory data will be tabulated and summarized by descriptive statistics, as well as on the basis of MSKCC specified normal range.

17.0 PROTECTION OF HUMAN SUBJECTS

Patient participation in this protocol is completely voluntary. Patients will be provided with documentation explaining the protocol rationale and objectives, as well as its potential risks, benefits, toxicities/side effects, inconveniences and financial costs/burdens. Alternative options for therapy will also be discussed. Patients who choose to participate will sign an informed consent conforming to the MSKCC IRB guidelines. The protocol will protect the rights and privacy of all participants. Children, adolescents and young adults are eligible for this study. Patients of both sexes and all ethnic/racial backgrounds are eligible for this study. Alternative treatments are available and will be discussed with the patients and/or legal guardian.

It is not known whether this treatment will improve the overall survival of the patient. The potential risks of this therapy are described in Section 11 of this protocol and may outweigh the potential benefits in an individual patient. Reporting of serious adverse events is found in section 17.2.

Costs: Patients are responsible for the costs of physician visits and usual laboratory tests, hospitalizations, radiographic studies, drug administration and outpatient care. If there is an injury as a result of the research study, emergency care, hospitalization, and outpatient care will be made available by Memorial Hospital and billed to the patient as part of the medical expenses. No money will be provided by Memorial Hospital as compensation for research-related injury. Patients will not be paid for taking part in this study.

17.1 Privacy

It is the responsibility of the Research Staff to ensure that protocol subjects received the Center"s Notice of Privacy Practices. If the subject has not received one, MSK personnel must provide a Notice of Privacy Practices and obtain acknowledgment before the subject participates in the study.

MSK"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).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant‟s last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 „Reporting of Serious Adverse Events‟, the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject‟s initials
- 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
- The grade of the 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
- If the SAE is an Unanticipated Problem

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

18.1 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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20.0 APPENDICES

Appendix 1: Wong-Baker FACES® Pain Rating Scale
Appendix 2: Post-procedure pain management algorithm
- Appendix 2.1: For Procedure Recovery Room RNs
- Appendix 2.2: For parent/legal guardian

Appendix 3: Post-procedural quality of life (QOL) questionnaire