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Protocol #: COMIRB 15-0036

**Project Title: Use of Ultrasonic Bone Scalpel in Adolescent Idiopathic Scoliosis – Randomized
Clinical Trial**

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Version Date: 7/6/2015

I. Hypotheses and Specific Aims:

The primary purpose of this randomized trial is to compare the efficacy of an ultrasonic bone scalpel (or osteotome device) with standard of care surgical instruments during posterior spine fusion with instrumentation. The primary outcome variable in this trial is estimated blood loss per spine level fused (EBL/level). Secondary outcome variables include the probability of meeting the intraoperative blood transfusion criteria, incidence of adverse events, and incidence of surgical site infections. Subjects with adolescent idiopathic scoliosis undergoing planned posterior spinal fusion with instrumentation will be recruited from a single tertiary recruitment center for this trial.

Primary Aim 1: Compare estimated blood loss per level fused

Hypothesis 1: The average estimated blood loss per level fused will be significantly lower in the ultrasonic bone scalpel (USBS) group compared to the standard of care group.

Secondary Aim 1: Compare the incidence of adverse events in the two groups.

Hypothesis 2: There will be no difference in the incidence of adverse events in the bone scalpel group compared to the standard of care group.

Secondary Aims 2-3: Compare the proportion of patients meeting intra-operative blood transfusion criteria in the two groups.

Hypothesis 3: The proportion of subjects meeting the intra-operative blood transfusion criteria will be significantly lower in the bone scalpel group compared to the standard of care group.

II. Background and Significance:

Adolescent idiopathic scoliosis (AIS) is a common spine deformity in children. In severe cases posterior spinal fusion surgery (PSF) is indicated to correct the deformity and prevent curve progression. Due to the duration and invasiveness of this procedure, PSF is associated with high intraoperative blood loss. On average, AIS patients typically lose 65-150 mL per vertebral level during spinal fusion surgery.[1] With regard to total blood volume, AIS patients typically lose 25-30% of their total blood volume during PSF.[1, 2] The percent of patients who receive an

intraoperative transfusion during PSF surgery is variable, but has been reported as low as 20-30% and as high as 50-75%.[2-6] The amount transfused also widely varies and ranges from 1-8 units of red blood cells.[2, 7] Minimizing intraoperative blood loss (EBL) is of great importance due to the association between increased blood loss and increased risk of postoperative complications.[8-10]

The utilization of an FDA approved ultrasonic bone scalpel (USBS) may help decrease EBL during PSF. The Misonix BoneScalpel® is a device that utilizes ultrasonic frequencies to “cut” through osseous structures. At the tip of the device is a blunt blade that vibrates longitudinally at a frequency of 22,500 times per second. This blunt, vibrating blade is selective between osseous tissue and softer, connective tissue. Further, the tip is irrigated by a sterile saline solution which helps to provide cooling and reduce the risk for thermal injury.[11, 12] This device has been used for various procedures in various specialties. It has been used in maxillofacial surgery in order to perform a more precise and controlled osteotomy.[13, 14] It has also been used in tumor resection and when performing surgery close to the spinal cord.[12, 15-18]

The literature surrounding the use of the USBS in pediatric spine surgery is more limited. Several retrospective studies cite the USBS as safe and effective for various procedures such as spinal decompression, posterior releases, posterior facetectomies, posterior osteotomies, and laminectomies.[16, 19-21] Bydon et al. (2014) reported that patients treated with the USBS showed a trend toward decreased complications. Bartley et al. (2014) observed a statistically significant difference in EBL between groups. Blood loss in the USBS group was 30-40% less than blood loss in the historical control group. The majority of studies involving pediatric spine surgery are retrospective in nature. The lack of randomization creates concern about potential for selection and/or indication bias. Therefore, the purpose of this randomized trial is to compare the safety and efficacy of the USBS relative to standard of care instruments in a pediatric population undergoing PSF.

III. Preliminary Studies/Progress Report:

No preliminary studies have been performed at this institution. Please see the above section for studies performed at other institutions.

IV. Research Methods not only

a. Outcome Measure(s):

Primary Clinical Outcome
Estimated blood loss/level [^]
Secondary Clinical Outcomes
Intraoperative and postoperative complications (events that cause a deviation from routine care) ^{^†‡}
Probability of meeting blood transfusion criteria (see section) ^{^†}
Procedure Time (first incision to close) [^]

Demographics/Covariates (potential confounding variables)	
Age at surgery*	BMI percentile at surgery*
Gender at surgery*	Weight (kg) at surgery*
Exposure to second hand smoke*	Preoperative Lenke Classification*
Preoperative major Cobb angle*	Preoperative hemoglobin/hematocrit*
Postoperative major Cobb angle††	Postoperative hemoglobin/hematocrit†
Intraoperative use of intrathecal narcotics^	Donor hematocrit^
Vertebral levels fused^	Intraoperative use of antifibrinolytic^

Exploratory Variables	
Unplanned return to OR††	Surgical site infection†
Procedure Time^	

* Collected preoperatively or day of surgery (before surgery)

^ Collected intraoperatively

† Collected postoperatively: short term follow-up, during initial hospital stay

‡ Collected postoperatively: long term follow-up, one year postoperative

I. Description of Population to be Enrolled:

All patients with a diagnosis of Adolescent Idiopathic Scoliosis who are scheduled for spinal fusion surgery and meet the following criteria will be eligible to participate in the study:

Inclusion Criteria:

1. 10-18 years of age
2. Diagnosis of AIS
3. Scheduled for a posterior spinal fusion (without Schwab Grade II or higher osteotomy)

Exclusion Criteria:

1. Plan for a posterior column osteotomy of Schwab Grade II or higher
2. Prior spinal surgery
3. MRI abnormalities (such as syrinx and/or chiari malformations)
4. Subjects with medical comorbidities (e.g. heart, lung, kidney disease)
5. Subjects with bleeding diatheses
6. Non-idiopathic etiology for scoliosis

II. Study Design and Research Methods

a. Power Analysis

The purpose of this single blinded, randomized, controlled, superiority trial is to compare the efficacy of an ultrasonic bone scalpel with standard of care surgical instruments during posterior spine fusion with instrumentation. The primary aim of this study is to compare differences in estimated blood loss per fusion level (EBL/level) between groups ($\theta = \theta_{standard\ care} - \theta_{USBS}$). We aim to test the null hypothesis that the difference between groups is less than or equal to 0 ($H_0: \theta \leq 0$). Based on a previous retrospective cohort study in a similar target population[21], we anticipate the EBL/level in the proposed study will be 48 mL/level (± 30) in the USBS group (θ_{USBS}) and 72 mL/level (± 28) in the standard instrument group ($\theta_{standard\ care}$). Although there are no universally established thresholds for defining a clinically meaningful difference in

EBL/level, the investigators are confident that the 33% reduction in blood loss per level observed in the previous study is representative of a clinically meaningful reduction in blood loss ($H_+ \theta \geq 24$ or $H_+ \theta \geq 33\%$). Based on a symmetric two sided, two stage group sequential design with O'Brien-Fleming stopping criteria and an alpha level of 0.05, we determined that a sample size of 62 subjects (31 subjects per group) would provide 90% power to reject the null hypothesis of no difference between groups (See Trial Monitoring section for information about the stopping criteria). This estimate assumes a group difference of 24 mL/level and a standard deviation of ± 28 in the standard instrument group and a standard deviation of ± 30 in the USBS group. Assuming a dropout rate of approximately 15%, we intend to enroll 36 subjects per group to achieve the desired statistical power. The estimated dropout rate is based on previous studies in a similar patient population, adolescents with idiopathic scoliosis.

b. Subject Screening:

All surgical patients under the care of two high volume pediatric orthopedic surgeons will be screened for study eligibility. All patients who elect to undergo spinal surgery at Children's Hospital Colorado under the care of the investigators of this study will be screened for study eligibility by the research coordinator (research assistant). Patients who are determined to meet the inclusion and exclusion criteria from above will be approached by the study team.

c. Enrollment and Consent:

After a patient is determined to be eligible for study participation, they will be approached by the study team. Most often consent will be obtained at the preoperative appointment. The preoperative appointment occurs before surgery, at least a day prior to surgery. During this visit, patients and their families meet with members of the surgical team, nurses from the spine team, orthopedic research team personnel, and relevant members from hospital support departments. The study will be presented by a trained member of the research team who is listed under the COMIRB approved personnel form (PI, Co-I, or research coordinator). Informed consent and assent will be obtained in this context. As patient schedules and preoperative appointments can vary, the timeline of obtaining consent will remain flexible. If a patient does not have a preoperative appointment or the study team is for some reason unable to meet with them during this time, the patient will be approached during an alternative preoperative appointment. If the patient cannot be approached during a preoperative visit, the patient will be contacted via phone, email, or mail ahead of their surgical date by the surgeon and issued a copy of the consent/assent forms. They will be given contact information for any questions and concerns. If interested and willing to participate in the study, an initialed and signed copy of the consent/assent form will be obtained before surgery. This method will be employed in order to allow the time for informed consent to occur as well as not to interfere with "on-time" start goals in the operative room.

Patients who elect to participate in the study will undergo the informed consent process. Assent will be obtained in one of two ways depending on the patient's age and understanding. If the participant is 7-12 years old, or if they are having trouble understand the details of the study, they will read and sign a separate assent form. If the participant is aged 13-17 years old, or if they understand completely the details of the study, they will initial and sign the consent form along with their parents, legal guardians,

or legally authorized representative. The patient's understanding of the protocol will be assessed by research team member who is obtaining consent.

d. Randomization and Blinding:

Patients will be randomized 1:1 into two different treatment groups using a block randomization scheme. Using the Proc Plan procedure within SAS 9.4 (SAS Institute, Carey NC), blocks will be constructed based on surgeon and patient gender. Each surgeon will have a randomization list generated, and patient assignment will be made after the informed consent process has been performed to the next assignment on the list. Randomization assignments will not be revealed to the study personnel until after the patient has been enrolled in the study so as not to unduly bias the consent process.

Blinded evaluators will be used to calculate the primary outcome variable of interest, estimated blood loss per level fused. All other study personnel, including the surgeons, will not be blinded to participant treatment assignment which is necessary to ensure the correct protocol is followed. Patients and their families will be blinded to study assignment to minimize the risk of assignment related study withdrawal. Patients and their families will not have the assignment revealed to them after the surgery as it will not affect their plan of care. If desired, treatment allocation may be revealed at the final study visit at one year following surgery.

e. Intraoperative Estimated Blood Loss

Estimated blood loss will be determined by 3 different methods. The first and primary method is to use the estimated blood loss listed on the cell saver report. This measurement is generated by the cell saver based on the blood collected. The other two methods determine blood loss through a calculation.

Method 2:

With this method, the EBL measurements will be based on the contents of the blood and fluid collection canisters as well as the volume reports generated by the cell saver system. To ensure blinding, final levels of fluid bags and canisters will be photographed by the study surgeon immediately after the procedure is complete. Photographs will be taken by the camera features from an iPhone 6. Photographs will be taken at a distance of two feet from the canisters and bags and such that the meniscus of the fluid is at eye-level with the lens. Photographs will be reviewed by blinded evaluators at two intervals, prior to the interim analysis and following final enrollment. Two blinded evaluators will be used for each measurement, and their measurements will be averaged for use in the final calculation.

EBL will be calculated in the following manner: First, the total fluid volume will be calculated: The volume of the contents of all of the blood and fluid canisters used during the course of the surgical procedure will be recorded based on the photographs. To this we will add the cell saver intake fluid, taken from a report generated by the cell saver system. Next, the total irrigation volume used during surgery will be calculated. The irrigation volume will be estimated as the difference in volume of the irrigation bag at surgery cut versus surgery close. For subjects in the USBS group, the total irrigation volume will also include the difference in volume of the USBS irrigation bag at surgery cut versus surgery close. Estimated blood volume will be calculated as total fluid volume minus irrigation volume.

Method 3:

To validate the above described method 2, the study personnel will also use the same method of calculated blood loss as was used in a study by Da Cunha et al (2015).[22] The blood loss calculation from this study was adapted from the method proposed in Brechter et al (1997).[23] This method calculates blood loss through the following mathematical model:

$$EBL = [EBV * (Hb_{pre} - Hb_{post}) / Hb_{pre}] + [Donor RBC_{normalized}] + [Cell Salvage RBC_{normalized}]$$

Where:

EBV = Estimated Blood Volume = Patient Weight (kg) x 70 ml/kg

Hb_{pre} = preoperative patient Hemoglobin

Hb_{post} = postoperative Day One Patient Hemoglobin

Donor RBC_{normalized} = [donor RBC volume] x [(donor Hct) / (Hct_{pre} + Hct_{post}) / 2]

Cell Salvage RBC_{normalized} = [cell saver RBC volume] x [(cell saver Hct) / (Hct_{pre} + Hct_{post}) / 2]

Hct_{pre} = Preoperative Patient Hematocrit

Hct_{post} = Postoperative Patient Hematocrit

Patient's weight will be measured the day of surgery. Hct_{pre} and Hb_{pre} will be taken by the lead anesthesiologist prior to first incision through an ISTAT. Hct_{post} and Hb_{post} will be taken 12-18 hours after the end of the procedure through an ISTAT. Donor and cell saver Hct will be taken by the lead hematologist before bags are sent up to the OR.

f. Intraoperative Transfusion Guidelines

Traditionally, CHCO does not have strict transfusion protocols for patients undergoing posterior spinal fusion surgery. Often these decisions are made at the discretion of the anesthesia provider in the operating room. This is due to the care involved and the differences between cases when caring for these incredibly complex patients. This is further complicated by differences in diagnosis, osteotomy procedures, and severity/flexibility of the scoliosis. Often in these complex surgeries, intangible variables such as estimated time remaining, perceived rate of blood loss, and trend of hematocrit levels all factor in to the decision. However, for this study, we have established guidelines for determining the need for intraoperative transfusion. The study team feels comfortable with these guidelines because all enrolled patients in this study will have a consistent diagnosis of adolescent idiopathic scoliosis, low rates of intraoperative bleeding, and no complex osteotomies such as a vertebral column resection. Our guidelines are below:

- Hematocrit will be checked every 30 minutes by the anesthesiologist
- Hematocrit levels below 23% will trigger a transfusion
- Hematocrit levels between 23-28% will trigger a transfusion if hypotension and/or tachycardia (>20% different from baseline) is present despite adequate fluid resuscitation

g. Study Interventions and Follow Up:

After patients have enrolled in the study and been randomized to a treatment group, study interventions will take place. The above outcomes will be collected at three different time points: preoperatively, intraoperatively, and postoperatively. Depending on the treatment randomization assignment, patients will undergo surgery with either the powered ultrasonic bone scalpel or with standard of care orthopedic surgical tools such as curettes, rongeurs, or high-speed burrs. These tools will be used in either treatment group for superior and inferior facetectomies, as well as to aid exposure of the pedicle for screw placement. All of these tools are commonly used at CHCO by facility pediatric orthopedic surgeons. Selection is most commonly made based on surgeon preference and familiarity. All surgeons involved in this study routinely use the surgical instruments being investigated. They have all received training and have experience with these instruments.

Study follow up will occur postoperatively. Enrolled patients will return for their one month and one year postoperative appointments with their spine surgeon as per their plan of care. No unique study interventions will take place, but the above postoperative outcomes will be collected from the medical records by research personnel. All visits and collected data are considered to be in line with the plan of care for these patients and not performed solely for research purposes. Interventions such as radiographs and laboratory samples are already performed for clinical purposes.

III. Description, Risks and Justification of Procedures and Data Collection Tools:

a. Associated Risks and Justification of Study Intervention and Procedures

The ultrasonic bone scalpel was approved by the FDA in May 2011 through application number K070313 for use in fragmentation and aspiration of hard and soft tissue in Orthopaedic surgery as well as a number of other specialties. The FDA found the safety profile of the device equivalent to an existing FDA approved device with the same indications.

Previous research has also validated the safety of the ultrasonic bone scalpel. Based on previous reports, risk for iatrogenic dural tears with the USBS is comparable to or less than the standard tools mentioned above.[13, 16, 18-20] Matsuoka et al. acknowledged the device as good for preserving surrounding soft tissue during bone dissection.[17] Concern for thermal injury appears minimal with this device. Brooks et al. found that the heat generated by ultrasonic tools in cadaver bone did not differ from previously reported temperatures generated by high speed drills and also credits the irrigation system with reducing potentially high temperatures that could be produced from ultrasonic devices.[24] Hu et al. cited one instance of dural tear associated with thermal injury, however also suggests that the USBS, if used properly, can decrease the risk of soft tissue injury. The authors of this study recommended not allowing the blade to sit too long in one position to avoid thermal injury.[20] One study comparing laminectomy procedures with and without the USBS on an ovine model found no evidence of thermal injury, attributing the irrigation system with the ability to adequately cool surrounding tissues during osteotomies.[12]

Research shows the USBS to be a safe alternative to historically standard tools with the potential for reduced blood loss (see section II. Background and Significance). Both methods are commonly employed by pediatric spine surgeons at CHCO for performing a variety of orthopedic procedures, including the procedures used in this study. Below is a table summarizing incidence of dural tear associated with the USBS in spinal surgery reported in previous studies.

All other study interventions and procedures (such as hospital visits, radiographic analysis, and laboratory procedures) are already performed by the physician care team as part of a surgical patient's normal plan of care. Data collected from these interventions will be extracted from CHCO's electronic medical record system.

Author	Year	Surgical Use	Number	Age (year)	Dural Tear in USBS	Dural Tear in Non-USBS
Al-Mahfoudh et al.[16]	2014	osteotomy, laminoplasty	62	Not Provided	1 (1.6%)	N/A
Matsuoka et al.[17]	2012	recapping hemilaminoplasty	33	4-74	0	N/A
Bydon et al.[18]	2014	spinal decompression	30	8-19	3 (30%)	9 (45%)
Bydon et al.[19]	2013	spinal decompression in achondroplastic patients	337	41-78	5 (5.7%)	9 (3.6%)
Hu et al.[20]	2013	osteotomy	128	12-85	11 (8.6%)	N/A

b. Data Collection Tools

Study data will be collected and managed using REDCap (Research Electronic Data Capture). REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). The system was developed by a multi-institutional consortium which includes University of Colorado–Denver and was initiated at Vanderbilt University. The database is hosted at the University of Colorado–Denver Development and Informatics Service Center (DISC), which will be used as a central location for data processing and management. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the DISC. This iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap also includes a powerful tool for building and managing online surveys. The research team can create and design surveys in a web browser and engage potential respondents using a variety of notification methods. REDCap is flexible enough to be used for a variety of types of research and provides an intuitive user interface for database and survey design and data entry.

c. Potential Scientific Problems:

One potential scientific problem in this study has to do with the quantification of estimated blood loss. Past literature has revealed this measurement to be variable.[2, 25] We hope to overcome this problem by strictly adhering to the EBL collection protocol outlined above. Two research coordinators will take measurements and their measurements will be averaged for a final EBL. In this way, although the measurement is prone to misclassification, we anticipate misclassification to be non-differential. A calculated blood loss will be performed to attempt to find reproducibility between the two types of measurements and reduce potential bias. Furthermore, the research assistants, who will be performing EBL measurements and calculations, will be blinded.

A second potential scientific problem could be obtaining 72 study subjects (36 for each group) to consent and enroll in the study protocol. Between the two protocol surgeons, approximately 80 patients with AIS undergo PSF each year. This population is actively involved in research at this institution and study personnel have been very successful in the past recruiting this patient population for research purposes. Based on the enrollment success rate of a current randomized clinical trial, the authors expect 80% of patients who are approached regarding this study to consent for participation. This requires 90 eligible subjects to be approached in order to reach the enrollment goal of 72. As such, it is expected that enrollment is completed within 2 years of study approval.

Finally, as this study involves long-term follow-up, there is potential for subjects to become lost to follow-up. To accommodate this, our enrollment goal factors in a 10% dropout. For subjects who are lost to follow-up, two certified letters will be sent two week apart following the first missed clinic visit. If there is no response, the subject will be contacted twice by phone. If study staff is unable to contact the subject, they will be considered lost to follow-up.

d. Data Analysis Plan

An intent to treat analysis of all randomized subjects will be performed. Descriptive statistics will be used to compare the distribution of demographics and clinical characteristics in the two groups. Baseline covariates significantly different between groups will be considered as potential confounding variables in subsequent statistical models. The primary aim of this study is to compare differences in estimated blood loss per fusion level (EBL/level) between the USBS and standard of care groups ($\theta = \theta_{USBS} - \theta_{standard\ care}$). We aim to test the null hypothesis that the difference between groups is less than or equal to 0 ($H_0: \theta \geq 0$). An independent sample t-test or multiple variable linear regression analysis, as appropriate, will be used to compare total EBL/level in the two study groups. For the secondary outcome variables, Chi-square tests will be used to compare differences in the categorical variables (the risk of adverse events, proportion of subjects meeting the intra-operative blood transfusion criteria) between the groups. Independent sample t-tests or Wilcoxon rank sum tests will be used to compare differences in the continuous variables (operative time, post-operative length of stay, and intraoperative irrigation volume).

e. Trial Monitoring/Human Subjects Research Consideration

Data Safety and Quality - All data will be collected and stored in a REDCap database. Access to the database will be restricted to investigators involved the study protocol per study personnel section of the COMIRB protocol application and/or the study delegation of duties log. Photographs obtained during surgery will be de-identified, assigned an appropriate study ID and will be stored on a secure departmental server that is managed by the IT department at Children's Hospital Colorado. The study coordinators will review data stored in the REDCap database on an ongoing basis. Potential outliers and/or biologically implausible data points will be identified and reviewed on an individual basis with the Principal Investigator.

Safety Monitoring – Based on the advice of our clinical trial study design consultant, Dr. John Kittelson, a Data Safety Monitoring Board (DSMB) will review the safety and efficacy of the study. The DMSB will consist of an orthopaedic surgeon not directly

involved in the study, an administrator, an anesthesiologist not involved in the study, and an independent biostatistician. The DSMB will meet a minimum of three times. During the first meeting (open session), the progress of the study will be reviewed and any issues regarding safety, study feasibility, and/or protocol compliance will be discussed. This meeting will occur 1 month after the enrollment of the first study subject. The second meeting (closed) will occur after 50% of the study enrollment has been achieved. Prior to this meeting, the investigators will send a clean, unblinded dataset to the independent biostatistician that includes information regarding the primary clinical outcome of interest, estimated blood loss per level fused. This dataset will be used to determine whether any of the study stopping thresholds has been met (see Decision/Stopping Criteria below). The DSMB will meet a minimum of one additional time once 100% of the study enrollment has been achieved. Similarly, a clean, unblinded dataset will be sent to the statistician to determine whether the decision thresholds have been achieved (see Decision/Stopping Criteria below). Although unlikely, additional, emergent meetings will be scheduled as needed. The formation of the DSMB and documentation of DSMB related meetings will be done in accordance with CHCO's DSMB policy. See DSMB Charter and DSMB Reporting Form for additional information.

Safety monitoring will also be performed on ongoing basis by the PI and members of the study team. All adverse events will be submitted to the DSMB and will be reported to COMIRB within 5 business days.

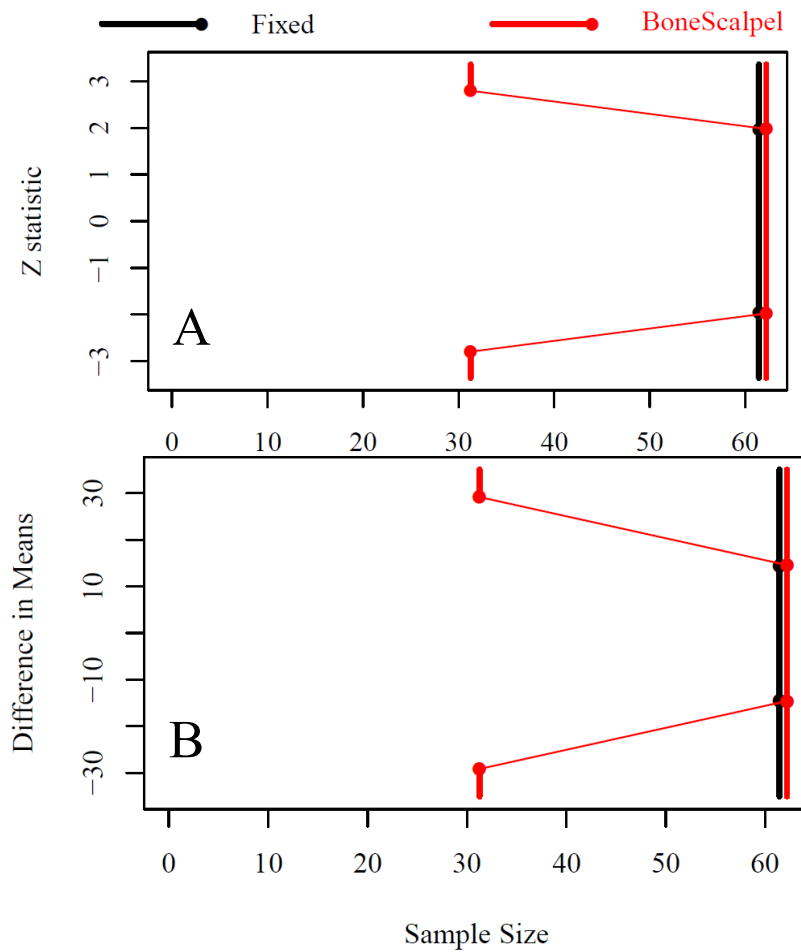
Decision/Stopping Criteria- This study will utilize a two-stage, group sequential design to monitor study progress. Under the alternative hypothesis, the two sided rejection boundaries at Stage 1 and Stage 2 were calculated according to the O'Brien-Fleming method (see Figures below). After 16 subjects per group have been enrolled, an interim analysis will be performed (Stage 1). If the standardized Z statistic representing the difference in estimated blood loss ($\hat{\theta} = \hat{\theta}_{standard\ care} - \hat{\theta}_{USBS}$) exceeds the upper or lower rejection boundary ($Z > 2.7965$ or $Z < -2.7965$), the trial will be stopped. Assuming the standard deviation of blood loss per level fused is 30 in the USBS group and 28 in the standard group, the trial will stop if $\hat{\theta} > 29.2$ mL/level or $\hat{\theta} < -29.2$ mL/level. If blood loss per level fused does not exceed the rejection bounds, the trial will continue until a total of 62 subjects have been enrolled (31 per group). At stage 2, the standardized Z statistic will be compared to the rejection bounds ($Z > 1.9774$ or $Z < -1.9774$). Assuming the standard deviation of blood loss per level fused is 30 in the USBS group and 28 in the standard group, we will conclude the USBS is superior to standard care instrument if $\hat{\theta} > 14.6$ mL/level or inferior to standard care instruments if $\hat{\theta} < -14.6$ mL/level. Sample size and stopping criteria were estimated using the RCTDesign package, R 3.1.2 (R Foundation of Statistical Computing, Vienna, Austria).

Summary of Decision Criteria - The decision criteria and potential corresponding conclusions are described in the table below.

Stage	Enrollment	Stop For Harm			Stop for Benefit		
		$\hat{\theta}_{\dagger}$	95% CI	pvalue*	$\hat{\theta}_{\dagger}$	95% CI	pvalue**
Stage 1	50%	-27.1	-42.2 to -8.55	0.005	27.1	8.55 to 42.2	0.005

Stage 2	100%	-13.9	-29.01 to 0.00	0.05	13.9	0.00 to 29.01	0.050
*Probability reject $\theta \geq 0$							
**Probability reject $\theta \leq 0$							
†Bias adjusted mean							

Figure 1. Plots of Rejection Boundaries (Red Lines) at Stage 1 and Stage 2 Relative to a Fixed Sample Design (Black Lines). 1.A Displays Rejection Boundaries on the Z Scale 1.B Displays Rejection Boundaries in Terms of EBL/level.



Probability of Stopping at the Interim Analysis To aid in the interpretation of the stopping criteria, the probability of stopping the trial at the interim analysis (for benefit or harm), under hypothetical scenarios in which theta is known, has been estimated in the table below.

True θ	Probability of Stopping for Harm	Probability of Stopping for Benefit
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-29	0.4930	0.0000
-14	0.0729	0.0000
0	0.0050	0.0050
14	0.0000	0.0729
29	0.0000	0.4930

Power/Type I Error Rate The power and type I error rate associated with this group sequential design, under hypothetical situations in which theta is known, is outlined in the table below.

True θ	Power for Lower Rejection Boundary	Power for Upper Rejection Boundary
-29	0.975	0.000
-14	0.470	0.000
0*	0.025	0.0250
14	0.000	0.470
29	0.000	0.975

*Under null hypothesis ($\theta = 0$), the design maintains a type I error rate of 0.05.

f. Summarize Knowledge to be Gained

This study will help to identify any potential advantages and disadvantages with regard to the use of an ultrasonic bone scalpel used in posterior spinal fusion surgery for patients diagnosed with Adolescent Idiopathic Scoliosis. A better understanding of the intraoperative outcomes such as estimated blood loss and surgical time compared between the two groups could reveal if one technique is able to provide significantly better results during surgery. If one method is determined to be more effective or efficient than the other, then it could have a positive impact on spinal fusion surgery. Decreased blood loss could lead to decreased need of intraoperative and postoperative transfusions and the risks associated with them. Further, shorter operative time would decrease wound exposure time, which could have an effect on postoperative complications. Decreased operative time could also decrease the financial burden of surgery.

V. References

1. Shapiro, F. and N. Sethna, *Blood loss in pediatric spine surgery*. Eur Spine J, 2004. **13 Suppl 1**: p. S6-17.
2. Thompson, M.E., et al., *Predicting excessive hemorrhage in adolescent idiopathic scoliosis patients undergoing posterior spinal instrumentation and fusion*. Spine J, 2014. **14(8)**: p. 1392-8.

3. Diab, M., et al., *Use and outcomes of wound drain in spinal fusion for adolescent idiopathic scoliosis*. Spine (Phila Pa 1976), 2012. **37**(11): p. 966-73.
4. Koerner, J.D., et al., *Blood loss during posterior spinal fusion for adolescent idiopathic scoliosis*. Spine (Phila Pa 1976), 2014. **39**(18): p. 1479-87.
5. Yoshihara, H. and D. Yoneoka, *National trends in spinal fusion for pediatric patients with idiopathic scoliosis: demographics, blood transfusions, and in-hospital outcomes*. Spine (Phila Pa 1976), 2014. **39**(14): p. 1144-50.
6. Yoshihara, H. and D. Yoneoka, *Predictors of allogeneic blood transfusion in spinal fusion for pediatric patients with idiopathic scoliosis in the United States, 2004-2009*. Spine (Phila Pa 1976), 2014. **39**(22): p. 1860-7.
7. Yu, X., et al., *Prediction of massive blood loss in scoliosis surgery from preoperative variables*. Spine (Phila Pa 1976), 2013. **38**(4): p. 350-5.
8. Jain, A., et al., *Smaller body size increases the percentage of blood volume lost during posterior spinal arthrodesis*. J Bone Joint Surg Am, 2015. **97**(6): p. 507-11.
9. Carreon, L.Y., et al., *Non-neurologic complications following surgery for adolescent idiopathic scoliosis*. J Bone Joint Surg Am, 2007. **89**(11): p. 2427-32.
10. Minhas, S.V., et al., *Assessing the Rates, Predictors, and Complications of Blood Transfusion Volume in Posterior Arthrodesis for Adolescent Idiopathic Scoliosis*. Spine (Phila Pa 1976), 2015. **40**(18): p. 1422-30.
11. Mixonix, *BoneScalpel with SonicOne Technology*, in *Ultrasonic Osteosurgery*, Misonix Surgical Devices.
12. Sanborn, M.R., et al., *Safety and efficacy of a novel ultrasonic osteotome device in an ovine model*. J Clin Neurosci, 2011. **18**(11): p. 1528-33.
13. Gilles, R., T. Couvreur, and S. Dammous, *Ultrasonic orthognathic surgery: enhancements to established osteotomies*. Int J Oral Maxillofac Surg, 2013. **42**(8): p. 981-7.
14. Gonzalez-Garcia, A., et al., *Ultrasonic osteotomy in oral surgery and implantology*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2009. **108**(3): p. 360-7.
15. Sun, S., et al., *Long-term outcomes of ultrasonic scalpel treatment in giant cell tumor of long bones*. Oncol Lett, 2014. **8**(1): p. 145-150.
16. Al-Mahfoudh, R., et al., *Applications of the ultrasonic bone cutter in spinal surgery--our preliminary experience*. Br J Neurosurg, 2014. **28**(1): p. 56-60.
17. Matsuoka, H., et al., *Recapping hemilaminoplasty for spinal surgical disorders using ultrasonic bone curette*. Surg Neurol Int, 2012. **3**: p. 70.
18. Bydon, M., et al., *Spinal decompression in achondroplastic patients using high-speed drill versus ultrasonic bone curette: technical note and outcomes in 30 cases*. J Pediatr Orthop, 2014. **34**(8): p. 780-6.
19. Bydon, M., et al., *Safety of spinal decompression using an ultrasonic bone curette compared with a high-speed drill: outcomes in 337 patients*. J Neurosurg Spine, 2013. **18**(6): p. 627-33.
20. Hu, X., D.D. Ohnmeiss, and I.H. Lieberman, *Use of an ultrasonic osteotome device in spine surgery: experience from the first 128 patients*. Eur Spine J, 2013. **22**(12): p. 2845-9.
21. Bartley, C.E., T.P. Bastrom, and P.O. Newton, *Blood Loss Reduction During Surgical Correction of Adolescent Idiopathic Scoliosis Utilizing an Ultrasonic Bone Scalpel*. Spine Deformity, 2014. **2**(4): p. 285-290.
22. Da Cunha, R.J., et al., *Intraoperative skull-femoral traction in posterior spinal arthrodesis for adolescent idiopathic scoliosis: the impact on perioperative outcomes and health resource utilization*. Spine (Phila Pa 1976), 2015. **40**(3): p. E154-60.

23. Brecher, M.E., T. Monk, and L.T. Goodnough, *A standardized method for calculating blood loss*. *Transfusion*, 1997. **37**(10): p. 1070-4.
24. Brooks, A.T., et al., *Effect of an ultrasonic device on temperatures generated in bone and on bone-cement structure*. *J Arthroplasty*, 1993. **8**(4): p. 413-8.
25. Adkins, A.R., et al., *Accuracy of blood loss estimations among anesthesia providers*. *AANA J*, 2014. **82**(4): p. 300-6.