Medical University of South Carolina
Protocol

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Study Title: **Randomized Comparative Effectiveness Trial of Anesthesia/Analgesia Techniques for Primary Total Knee Arthroplasty (TKA)**
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A. SPECIFIC AIMS

The primary aim of this pilot study will be to develop a clinically meaningful, patient-centric, and pragmatic protocol to evaluate the comparative effectiveness of different modalities for achievement of the ideal balance between analgesia and functional mobility following total knee arthroplasty (TKA).

We propose a study by which focused ***patient-centered*** inquiry will quantify the relative value of various outcome measures believed to be most meaningful to this patient population. Emphasis on patient experience and guided reflection combined with objective data will establish the optimal methodology for comparing different techniques of perioperative analgesia. We will identify those outcome measures that most accurately reflect the overall patient experience as well as the clinical result. Patient input has been conspicuously absent from previously published work on this topic, and we propose a mechanism by which the patients in cooperation with the investigators will guide the research, and ultimately clinical care.

In addition to applying a patient-centric perspective towards the identification of meaningful outcome measures, we intend to establish the ***feasibility*** and ***cost-efficiency*** of our study design and protocol. Ease of implementation, and seamless integration of clinical measures and data collection into routine workflow is necessary in order for the protocol to be attractive to other centers as part of a future multi-center trial. Previous orthopaedic surgery randomized controlled trials have set the precedence that such studies can be completed in an economical manner when such aspects of design are carefully considered(21). Through promotion of collaborative relationships between and continued engagement of the orthopaedic, anesthetic, nursing, and postoperative rehabilitative teams, the final protocol will allow all participants – care givers and patients alike - to feel invested and unburdened by the process.

Though the primary goals of the project pertain to establishment and application of proper scientific methodology to the clinical query addressing the most efficacious method

of perioperative analgesia for TKA patients, we do expect to produce clinically meaningful, if not statistically significant findings. We expect the study to be adequately powered to establish estimates of variance that will help refine subsequent power analyses for outcome measures that may not yet have precedence in the literature.

At the conclusion of this pilot study, we hope to have compiled valuable experience and knowledge, established collegial relationships across a number of disciplines, and effected a mechanism of meaningful patient engagement in design of a study that will be well-positioned to compete for the expected Patient-Centered Outcomes Research Institute (PCORI) funding via the Large Pragmatic Studies to Evaluate Patient—Centered Outcomes opportunity in the Spring of 2016

B. BACKGROUND AND SIGNIFICANCE

According to the CDC, over 700,000 TKA's are performed in the United States annually. That number continues to rise exponentially, and is predicted to eclipse 3 million procedures by 2030(14). Though 98% of patients report pain relief following TKA, unfortunately up to one-third fail to achieve significant functional improvements (7). Nearly 20% of primary TKA patients report they are dissatisfied with their outcome, and up to 33% experience some residual symptoms (4, 17). Various associative factors have been suggested to influence outcome, ranging from socioeconomic factors, to depressed mood, age, gender, suCarolinargical technique, and comorbid conditions(3, 13).

The early postoperative period following total knee arthroplasty is widely believed to be critically important for regaining range of motion and mobility in order to optimize the ultimate clinical outcome and minimize the risk of complications including venous thromboembolic events(15). Perioperative analgesia for TKA patients has evolved considerably since the popularization of the procedure decades ago. Historically, perioperative interventions such as general anesthesia and patient-controlled analgesia pumps (PCAs) have aggressively treated postoperative pain, but have been associated with side effects including lethargy, somnolence, nausea, and mental status changes, all of which have a detrimental effect on early mobility. Furthermore, contemporary emphasis on value in healthcare has led to efforts to promote "rapid recovery" programs that facilitate early mobilization and discharge, thereby reducing total costs to the health care system. Recent trends in perioperative analgesic strategies may be related to these evolving priorities(5, 11).

Recently, with growing appreciation of the importance of early mobilization in addition to pure pain control, centers across the country have trended away from general anesthesia and PCA's in favor of regional anesthetic techniques(5). A wide range of strategies have emerged, most of which combine either spinal or epidural anesthesia with a spectrum of peripheral nerve blockade techniques and/or periarticular analgesic injection formulations(3). Unfortunately, the rate of institution of these varied modalities has outpaced the scientific evidence to support any one strategy over another. Multiple randomized trials have been published comparing one combination of interventions against another with little consistency, reproducibility, or generalizability in either methodology or results(1, 2, 8-10, 12, 16, 18-20, 22-24). The primary outcome measure

for most of these studies has been early post-operative pain levels, measured either directly via a visual analog scale (VAS), or indirectly via quantification of analgesic medication requirements(1, 2, 8-10, 12, 16, 18-20, 22-24). Most of these studies have failed to report outcomes beyond the typical 2 or 3 day hospital stay(1, 2, 8-10, 12, 16, 18-20, 22-24). Only one study that we are aware of has presented patient reported outcomes (PROs) using a validated measure, the Knee Society Score, and that was only recorded at discharge (22). Increasingly studies have reported secondary outcomes to include objective functional measures such as the Timed-up-and-go (TUG) (7, 19). Functional and patient reported outcomes beyond the immediate postoperative period are lacking in the literature. The proposed study will address these evidence gaps.

C. PRELIMINARY STUDIES/EXPERIENCE

During residency training at the University of Massachusetts Medical School, Dr. Drew elected to pursue a "research-track", which consisted of an additional year of training exclusively dedicated to research. Specifically, during that year Dr. Drew worked extensively to help develop the infrastructure that would ultimately become the NIH-funded FORCE-TJR. Additionally, he coordinated a prospective randomized control trial using radiostereometric analysis to quantify polyethylene wear and femoral stem migration differences between conventional and highly-cross-linked polyethylene liners in total hip replacement patients. Subsequently, productive research efforts have included an award-winning project resourcing the Nationwide Inpatient Sample database to characterize national trends in total joint replacement.

Dr. Bolin's interest in research began during his undergraduate years when he spent two years in a Drosophila lab. His primary project during that time involved isolation of a gene important in neural development in Drosophila. He presented this research at the North Carolina Academy of Science Meeting and received an award. During medical school Dr. Bolin worked on a project to culture human keratinocytes to produce skin grafts for burn patients. Currently Dr. Bolin has active projects that include development of a novel regional anesthetic technique and the evaluation of regional anesthetic techniques for post-operative pain management in mastectomy patients.

Dr. Pellegrini has previously served as a successful mentor for more junior faculty, and has demonstrated both interest and ability to secure extramural research funding. In support of this application as a mentor, Dr. Pellegrini has recommended quarterly mentorship meetings. These meetings will address study progress via benchmarks including the pace of recruitment, enrollment, and follow-up. Preliminary analyses will be prepared in advance of and reviewed at the mentorship meetings. Barriers, challenges, and opportunities for improvement in the process will be discussed, not only for the current project, but also with an eye towards optimizing subsequent study design in advance of planned application for PCORI funding. Of particular relevance, Dr. Pellegrini is the PI for a comparative effectiveness trial that has passed initial review for PCORI funding and is in the final stage prior to acceptance.

Dr. Drew & Bolin's strong foundational experiences combined with Dr. Pellegrini's exemplary track record of success suggests potential for a productive partnership and sound study leadership. With the proposed timetable of extramural funding during the calendar year following the pilot study, the expectation is that the mentor-mentee relationship will remain necessary for initiation of a multi-center trial, but investigator independence will gradually be achieved during the course of that trial.

D. RESEARCH DESIGN AND METHODS (including data analysis)

All ***primary*** TKA patients undergoing surgery at the Medical University of South Carolina (MUSC) will be offered the opportunity to participate in the study. Those with valgus deformity greater than 10 degrees on plain radiographs will be excluded from the study. Participants will be reflective of the population of TKA candidates at MUSC, and will include adults over the age of 18 of both genders and all races. Consenting patients will all receive spinal anesthetic, and will be randomized to one of three arms: 1) Continuous femoral nerve catheter plus single injection sciatic nerve block, 2) Adductor canal catheter plus selective tibial nerve block, and 3) Adductor canal catheter alone. Patients unable to receive spinal anesthetic will be excluded. All patients will receive a standardized multimodal pain regimen and early mobilization.

Preoperative data will include basic demographics, visual analog pain scale (VAS) score, range of motion, body mass index (BMI), primary insurer, coronal angular deformity, and baseline opioid use. Surgical data will include tourniquet time and implant type. Time spent in pre-operative holding area, the operating room, and the post-anesthesia recovery unit will be recorded. SF-12, Patient Reported Outcomes Measurement Information System (PROMIS), and Knee Injury and Osteoarthritis Outcome Score (KOOS) will be collected as part of our participation in the Function and Outcomes Research for Comparative Effectiveness in Total Joint Replacement (FORCE-TJR).

The primary outcome measure will be postoperative visual analog pain scale (VAS) score area under the curve (AUC) for 48 hours, recorded every six hours. Pain will be measured indirectly via total in-hospital opioid consumption. Functional outcome measures will be administered by members of the physical and occupational therapy team, who typically evaluate and treat patients once on the day of surgery and twice daily each day thereafter. They will document the patient's ability to perform independent terminal knee extension and grade knee buckling with ambulation on a scale of 0-2 during each encounter. Additionally, in the morning of postoperative day #1, a Katz Index of Independence in Activities of Daily Living score will be calculated. On the morning of postoperative day #2, the therapist will document distance walked by the patient, passive range of motion (flexion and extension), a timed up-and-go test (TUG), and calculate the AM-PAC (Activity Measure for Post-Acute Care) score. Patient reported outcome measures, specifically SF-12, PROMIS, and KOOS will be collected at 6 weeks and 3 months postoperatively. These time points are not included in the FORCE-TJR registry, and therefore will be independently collected and stored. Postoperative complications will be recorded. Finally, a brief survey will be administered at 3 months, presenting inquiries regarding satisfaction with the hospital stay, pain control, mobility, and the overall TKA experience. These inquiries will pose each question with a 0-10 scale, and respondents will be asked to select the number that corresponds to their level of satisfaction with each domain of their experience.

Via partnership with the FORCE-TJR, collection of patient-reported outcomes (PRO) data for arthroplasty patients at MUSC is both well-established and sophisticated. These data will be available as baseline measures for this project. Preoperative data are collected at a mandatory appointment 2-3 weeks in advance of elective arthroplasty. At that appointment and again at follow-up, our research coordinator facilitates patient recruitment and participation with the FORCE-TJR using validated computerized survey

instruments. Additionally, for this study, she will assist with enrollment, consent, extraction of clinical data from the EPIC-EMR, and coordination of prescribed follow-up. Postoperative SF-12, PROMIS, and KOOS are collected at 6 months and 1 year via the FORCE-TJR, therefore the coordinator will additionally facilitate collection of these instruments at 6 and 12 weeks, as well as the satisfaction survey. If, in the surgeon's opinion, the patient is doing well after surgery and does not have to return to clinic at the specified time points, the surveys will be mailed to the patient with instructions on how to complete them. The study coordinator will be available to field study-related patient questions in clinic and via telephone.

At three months, a random subset of four patients from each randomization arm will be invited to participate in a focus group. The purpose of the focus group will be to facilitate patient engagement with the hope of fulfilling our primary aim of this study, which is to identify the most meaningful outcome measures for perioperative analgesia among the TKA patients themselves. Qualitative data obtained during the recorded session will prompt discussion related to the overall patient experience in addition to individual experiences related specifically to analgesia, postoperative mobility, transitioning to the out-patient setting, and involvement in a randomized trial. The focus group will be held several months after surgery, on the MUSC campus in a private room. Audiotape of the focus group will be available to relevant study personnel only, and will be kept under lock and key within an office in the Department of Orthopaedics. A preference survey will be developed and distributed for additional patient feedback.

Though the main goal of conducting this pilot study is one of establishing the appropriate data points and testing the feasibility of such a design, we will conduct some preliminary hypothesis testing. Tests on the effect of treatment upon outcomes will be performed using an intent-to-treat analysis. Preliminary estimates suggest the study will be adequately powered to detect a significant VAS difference of 2 at 25 subjects per group. However, prior research suggests that the anticipated group differences may be much subtler, requiring a very large sample size to thoroughly address the issue of which treatment is superior to the others. As a preliminary step towards a larger, more definitive comparative effectiveness trial, we plan to enroll approximately 90 patients. This will allow us to reach our randomization goal of at least 75 patients while taking into account withdrawals. The 75 patients will be randomized into the three treatment arms over a 6-month recruitment period, with a 3 month follow-up for patient reported outcome and satisfaction data. This sample will allow us to estimate means relatively precisely, with 95% confidence intervals extending just 0.4 standard deviation units in either direction. We will also be able to make preliminary estimates of each treatment's effectiveness on the various outcomes of interest. Such estimates can be made using generalized linear mixed models (GLMMs)(6). Effect sizes will then be estimated from the GLMMs in a pairwise manner, and this information will be extremely valuable for use in designing a larger, more definitive trial in the future.

The study timeline calls for initiation in April of 2015, and completion of enrollment in October, 2015. Three-month follow-up data will be collected by the end of January, 2016, which will allow for data analysis and interpretation in advance of PCORI Letter of Intent, anticipated to be due in spring of 2016.

We expect to demonstrate sound scientific methodology and a fully invested multi-disciplinary team that will define clinically meaningful though perhaps not statistically significant differences in efficacy, safety, patient-reported and objective outcomes associated with various strategies of perioperative TKA pain management. With continued

patient engagement, this pilot study will support development of a multi-center randomized comparative effectiveness trial that we expect will be strongly considered for extramural funding through the Patient Centered Outcomes Research Institute (PCORI) via the "Large Pragmatic Studies to Evaluate Patient-Centered Outcomes" Funding Announcement. As a proposed randomized trial examining a poorly defined aspect of treatment that could affect nearly one million Americans per year, such a proposal meets the stated objectives outlined in the RFA. This pilot study will allow us to present a well-formulated, novel, scientific protocol supported by experience and data. Furthermore, it will allow us to demonstrate commitment and capacity for patient engagement in the study design process. The ultimate goal after procurement of extramural funding is to expand and establish this methodology as the generalizable gold standard for comparative effectiveness studies assessing perioperative TKA analgesia, and foster the development of a healthcare learning environment capable of identifying the most optimal strategy for perioperative TKA analgesia.

E. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

Targeted/Planned Enrollment Table

Total Planned Enrollment 90

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	4	3	7
Not Hispanic or Latino	53	30	83
Ethnic Category: Total of All Subjects*	9		
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	24	13	37
White	34	19	53
Racial Categories: Total of All Subjects*	58	32	90

We anticipate that patients recruited for this study will be reflective of the South Carolina population of candidates for total knee replacement in terms of ethnicity, race, and gender. All participants will be over the age of 18. No prisoners will be included.

b. Sources of Materials

Clinical data will be obtained from living human subjects for use in this project. This data will include basic demographic data in addition to the variables described above, including visual analog pain scale (VAS) score, range of motion, body mass index (BMI), primary insurer, coronal angular deformity, and baseline opioid use. Surgical data will include tourniquet time and implant type. Time spent in pre-operative holding area, the operating room, and the post-anesthesia recovery unit will be recorded. SF-12, Patient Reported Outcomes Measurement Information System (PROMIS), and Knee Injury and Osteoarthritis Outcome Score (KOOS) will be collected as part of our participation in the Function and Outcomes Research for Comparative Effectiveness in Total Joint Replacement (FORCE-TJR).

The primary outcome measure will be postoperative visual analog pain scale (VAS) score area under the curve (AUC) for 48 hours, recorded every six hours. Pain will be measured indirectly via total in-hospital opioid consumption. Functional outcome measures will be administered by members of the physical and occupational therapy team, who typically evaluate and treat patients once on the day of surgery and twice daily each day thereafter. They will document the patient's ability to perform independent terminal knee extension and grade knee buckling with ambulation on a scale of 0-2 during each encounter. Additionally, in the morning of postoperative day #1, a Katz Index of Independence in Activities of Daily Living score will be calculated. On the morning of postoperative day #2, the therapist will document distance walked by the patient, passive range of motion (flexion and extension), a timed up-and-go test (TUG), and calculate the AM-PAC (Activity Measure for Post-Acute Care) score. Patient reported outcome measures, specifically SF-12, PROMIS, and KOOS will be collected at 6 weeks and 3 months postoperatively. These time points are not included in the FORCE-TJR registry, and therefore will be independently collected and stored. Postoperative complications will be recorded. Finally, a brief survey will be administered at 3 months, presenting inquiries regarding satisfaction with the hospital stay, pain control, mobility, and the overall TKA experience. These inquiries will pose each question with a 0-10 scale, and respondents will be asked to select the number that corresponds to their level of satisfaction with each domain of their experience.

Data will be collected primarily by our study coordinator, but also by the PI. RedCap will be used to compile and store data. Collected data will be stored in a password-protected, MUSC network drive. Individual patient data will be linked to medical record number, but no other personal identifiers. These data and patient identifiers will only be accessible by study investigators. Most of the data collected are already part of the standard clinical care for total knee replacement patients, and are therefore already routinely available within the electronic medical record.

c. Potential Risks

Risks and side effects of nerve blocks may include elevated blood sugars, rash, itching, soreness at the site of injection, and localized bleeding. More serious complications, such as delayed recovery of nerve function, persistent numbness and/or tingling, or persistent weakness are extremely rare.

As a result of the randomization process, an individual patient may receive a treatment that ultimately proves less effective or otherwise inferior to the other study treatments or other available treatments.

The experimental treatments may have unknown side effects.

Other risks of anesthesia and total knee replacement are not expected to be affected by the experimental treatments in this study. These risks apply to all total knee replacement patients and are not specific nor exclusive to this particular study.

Risks of data breach and breach of confidentiality exist for participants in this study. In order to minimize such risks, data will be stored in a password-protected, MUSC network drive, and unlinked to personal identifiers other than medical record number. Only study investigators will have access to these data.

Current practice for perioperative analgesia for total knee replacement patients at MUSC, routinely includes arbitrary selection of one of the three treatments available in this study. Non-study participants will in all but very few cases receive one of the three experimental treatments in a non-random fashion, at the discretion of their surgeon. Patients may refuse to receive a nerve block of any type and still undergo total knee replacement. In our experience, a nerve block makes post-surgical pain much easier to manage, and therefore we recommend nerve blocks to all patients.

Spinal anesthesia is our default and preferred method of anesthesia for total knee replacement patients. For patients who are unable to receive spinal anesthesia, general anesthesia remains an option. Such patients will be excluded from this study. Spinal anesthesia is preferred over general for benefits in early recovery and a lower incidence of side effects such as nausea and postoperative confusion.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

In the outpatient clinic, at the time that the decision to proceed with primary total knee replacement is agreed upon, the surgeon will introduce the study to every primary TKR patient. If a patient decides to participate, the full informed consent process will be completed during a separate preoperative clinic visit (a mandatory visit for all elective TJR patients), which occurs 2-3 weeks in advance of surgery. A research coordinator will be responsible for the informed consent process.

Specifically, informed consent will include an explanation of the three possible treatment arms, all of which are currently available and common practice, though selection for an individual patient is per surgeon discretion. This discussion will be supported by a study description document. Potential risks and benefits of the randomized treatments will be addressed. Potential participants will also be educated on the additional surveys and functional tests that they will be asked to complete as a part of their study participation. They will be informed that deidentified data will be recorded and stored in a password-protected, MUSC network drive. It will also be explained that randomly selected individuals may be contacted and asked to participate in a focus group, though consent to participate in the study does not require participation in the focus group. Consenting

individuals will be required to sign a formal consent form, which will be kept in a secured file folder within a locked office in the Department of Orthopaedics. Patients who agree to participate in the focus group will be verbally consented prior to conducting any focus group procedures.

Any patient requiring re-consenting can be consented via telephone. The coordinator will mail the patient a consent form. Once the patient receives the form, the full informed consent process will be completed. The patient and the coordinator will each sign and date a consent form. The patient will mail the form back to the coordinator. Once the coordinator receives the form, the two signed forms will be combined as one fully executed informed consent form. The coordinator will then mail the patient a copy of the form.

No children or individuals under the age of 18 will be included in the study.

b. Protection against Risk

Risks of data breach and breach of confidentiality exist for participants in this study. In order to minimize such risks, data will be stored in a password-protected, MUSC network drive, and unlinked to personal identifiers other than medical record number. Only study investigators will have access to these data.

In the event of adverse effects to the subjects, necessary medical intervention will be provided in the routine manner. There will be no deviation from the routine postoperative protocol for a total knee replacement other than collection of additional data points mentioned earlier in this proposal.

Adverse events and complications will be recorded and monitored as a part of the study protocol. Any trend suggesting an association between treatment and adverse events will be noted, and study investigators will have the ability to stop randomization into any treatment arm seemingly associated with increased rates of adverse events at their discretion. Any such occurrence will be reported to the IRB.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

As it is unclear which of the three research arms may be superior, direct benefit to participating patients cannot be guaranteed. The results of this study are expected to inform design of a subsequent larger randomized comparative effectiveness trail that will be adequately powered to prove clinically meaningful differences between treatments. Ultimately, knowledge gained from this project will provide clinicians the ability to choose the most optimal treatment option for TKR patients, and therefore benefit future patients.

Current literature suggests equivalent risks among the three proposed treatment arms. The remaining risks inherent with major surgery, and TKR specifically, are not expected to be affected by randomization. All proposed treatments are currently available and in use for TKR patients at MUSC.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

We expect to demonstrate sound scientific methodology and a fully invested multi-disciplinary team that will define clinically meaningful though perhaps not statistically significant differences in efficacy, safety, patient-reported and objective outcomes

associated with various strategies of perioperative TKA pain management. With continued patient engagement, this pilot study will support development of a multi-center randomized comparative effectiveness trial that we expect will be strongly considered for extramural funding through the Patient Centered Outcomes Research Institute (PCORI) via the "Large Pragmatic Studies to Evaluate Patient-Centered Outcomes" Funding Announcement. As a proposed randomized trial examining a poorly defined aspect of treatment that could affect nearly one million Americans per year, such a proposal meets the stated objectives outlined in the RFA. This pilot study will allow us to present a well-formulated, novel, scientific protocol supported by experience and data. Furthermore, it will allow us to demonstrate commitment and capacity for patient engagement in the study design process. The ultimate goal after procurement of extramural funding is to expand and establish this methodology as the generalizable gold standard for comparative effectiveness studies assessing perioperative TKA analgesia, and foster the development of a healthcare learning environment capable of identifying the most optimal strategy for perioperative TKA analgesia. Identification and establishment of a new "gold standard" in perioperative analgesia for TKA patients has the potential to positively impact the perioperative experience and clinical outcomes for nearly 1 million Americans annually.

Each of the proposed treatments are currently commonly used in centers nationwide. There are no reports in the literature that we are aware of suggesting that any of the proposed treatments are associated with increased risk, and all are well-accepted as safe options for perioperative analgesia following total knee surgery. The safety and efficacy of each relative to the others is unknown.

5. SUBJECT SAFETY AND MINIMIZING RISKS (Data and Safety Monitoring Plan)

Complications thought to be directly related to the treatment will be assessed and documented at each patient encounter during and beyond the study period, beginning with the inpatient hospital stay, and continuing with the 3 week, 6 week, 3 month, 6 month and annual follow up visits. Such complications will include paresthesias, dysesthesias, motor weakness, neuroma, persistent pain, patient falls, and hematoma. Other serious adverse events that may be observed following total knee arthroplasty, but thought to be unrelated to the peripheral nerve block will also be noted. Such events might include wound infections, venous thromboembolic events, and cardiac events, among others. Individual surgeons will be responsible for such monitoring, and all adverse events and complications will be reported to the PI.

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G. CONSULTANTS

n/a.

H. FACILITES AVAILABLE

The setting for this study will be the campus of the Medical University of South Carolina, Medical University Hospital, and outpatient clinic settings within the MUSC system.