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THE EFFECT OF BONE-VOID FILLER ON ANTERIOR KNEE PAIN FOLLOWING BPTB AUTOGRAFT ACL RECONSTRUCTION

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Table of Contents

List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

1 Introduction, Background Information and Scientific Rationale

1.1 Background Information and Relevant Literature

Anterior cruciate ligament (ACL) injuries are commonly seen and treated by orthopedic surgeons with approximately 400,000 reconstruction performed each year. Outcomes following ACLR are excellent with low rates of graft failure and high rates of return to pre-injury function. The surgery involves using a graft to replace the injured ACL in order to restore native knee biomechanics[1,2]. There are many graft choices including bone-patellar-tendon-bone (BPTB), hamstring tendon or quadricep autograft as well as several different allografts that the surgeon may choose from. Each graft has specific properties that contribute to surgeon choice. Graft-specific complications exist as well which further aid in the choice of graft.[3]

BPTB autograft is one of the most commonly used grafts worldwide especially in athletes and laborers. BPTB autograft is harvested through a midline incision over the patellar tendon that is carried down through the paratenon to expose the tendon[3]. Two parallel longitudinal incisions are made in the tendon to create a graft with the intended width. The incision is extended proximally to the distal pole of the patella where a segment of bone is removed in continuity with the tendinous insertion leaving a bone-void in the distal patella. Distally the incisions are carried down to the proximal tibia where a segment of bone is excised. The end product is a graft composed of tendon with bone plugs at both ends. The ACL reconstruction is then performed, incorporating the graft through femoral and tibial tunnels.[4, 5]

Like all autografts, BPTB has the advantage of having ideal biologic compatibility. Unlike other grafts, BPTB includes bone plugs at both ends of the tendons. These bone plugs can be customized to have good fit within the femoral and tibial tunnels and further secured with interference screws or suspensory fixation. This leads to predictable healing and early biologic graft incorporation of as little as 6 weeks postoperatively[4,5]. One of the advantages of the faster healing with BPTB autograft is that it allows for aggressive early rehabilitation. This results in earlier return to sport and pre-injury activity level[5].

BPTB autograft is not without complications. One of the graft-specific complications associated with BPTB autograft is persistent anterior knee pain postoperatively[3,4,5]. As a result, BPTB is often unsuitable for patients whose careers demand regular kneeling. Anterior knee pain can be a nuisance for patients and surgeons and in some circumstance be debilitating. The cause of anterior knee pain after ACLR has yet to be elucidated however the extensor tendon disruption and bone void from the harvest site is a likely contributory factor.

Currently, there is no consensus regarding management of the bone void after BPTB harvest. Existing literature is conflicting. Several studies report that bone grafting of the patellar defect can reduce the incidence of anterior knee pain and other complications, while Brandsson et al.[6] demonstrated that grafting bone at the site of the harvest did not reduce anterior knee pain. At this institution all surgeons fill the patellar bone void. There is no agreement on the material used to fill the void with surgeons using autogenous bone graft, calcium phosphate cement and demineralized bone graft[5].

Potential options for bone void filler include autologous bone graft, calcium phosphate cement, and demineralized bone matrix. Autologous bone graft is a byproduct of the customization of bone plugs during the BPTB autograft. In order to pass the graft through the tibial and femoral tunnels, the bone plus must be trimmed use bone cutters and other tools. The excess bone can be stored for use later in the operation for filling the bone defect of the patella. Autogenous bone graft is used often for its biologic compatibility and ability to incorporate into the boney defect. Most of the bone graft is cancellous bone which has osteogenic, osteoinductive and osteoconductive properties.

Calcium triphosphate is a bone-void filler used extensively throughout Orthopedic surgery. Calcium phosphate degrades slowly and is osteoconductive thereby new bone to replace it over time. Calcium

phosphate also has the highest compressive strength of synthetic bone grafts[8]. Calcium phosphate is commercially available and already used by the primary investigator as an option for filling the bone-void after the BPTB autograft harvest[7].

Demineralized bone matrix (DBM) graft is another commonly used bone void filler used throughout orthopedic surgery. DBM has osteoinductive and osteoconductive properties that facility bony ingrowth. DBM is commonly used by surgeons at this institution to fill the bone void after ACL[9].

1.2 Rationale

One of the common complaints after ACLR with BPTB autograft anterior knee pain. It is thought that this may be due to harvesting the patellar tendon for graft use. Specifically, this may be due to the bone defect that is left after graft harvesting. There is currently no consensus on a gold standard for treating the bone defect with surgeons using multiple commercially available bone void fillers as well as autologous bone graft in standard practice.

Potential Risks & Benefits

1.2.1 Known Potential Risks

The differing materials used will not prolong or significantly extend the time of surgery.

Possible adverse effects of using DBM include, but are not limited to: infection of soft tissue or bone, fever, deformity of the bone at the site of use, incomplete bone ingrowth, fracture of newly formed bone, hypercalcemia or transient hypercalcemia.

Possible adverse effects of using calcium phosphate cement include, but are not limited to: wound infection, wound dehiscence, fracture, loss of reduction, delayed or non-consolidation. While these risks are rare we will continue to monitor your condition to make sure these risks are minimized.

However, use of these elements are all considered standard of practice and used by surgeons at this institution and therefore, will not increase the level of risk for the patient beyond the normal surgery.

1.2.2 Known Potential Benefits

Potential benefits of being enrolled in this study may include reduced anterior knee pain after surgery. However, we cannot guarantee subjects will experience direct benefit as a result of participating in this study. We hope the knowledge gained from doing this study will inform surgeons in the future and, in turn, benefit other patients undergoing ACL reconstruction with BPTB autograft.

2 Objectives and Purpose

The purpose of the proposed study is to evaluate the effect bone-void filler on anterior knee pain following ACL reconstruction BPTB autograft.

2.1 Primary Objective

The purpose of the proposed study is to evaluate and compare the effect of three different bone-void fillers (autogenous bone obtained from graft preparation and bone plug customization; autologous bone plus DBM;

or autologous bone plus calcium phosphate cement) on anterior knee pain following ACL reconstruction BPTB autograft.

2.2 Secondary Objectives (if applicable)

Secondary outcomes include patient reported quality of life and functional outcome measures, rate (if any) of patella fracture, rate of return to activity, cost effectiveness and adverse events.

3 Study Design and Endpoints

3.1 Description of Study Design

This will be a single-center randomized controlled study. Patients will be randomized using RedCap using simple randomization. The study is comparing postoperative anterior knee pain after ACLR with BPTB autograft. There will be three cohorts that differ base on the bone-void filler used in the patellar boney defect. The three cohorts will include 1) autogenous bone obtained from the BTBPB graft harvest 2) Autologous bone plus demineralized bone matrix (Allosync DBM Putty, Arthrex, naples, FL) and 3) autologous bone plus calcium phosphate cement (Quickset, Arthrex, Naples, FL).

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

Primary endpoint will be based on the following postoperative surveys: KOOS, Kujala, IKDC, VAS for pain,

3.2.2 Secondary Study Endpoints

There are no additional secondary endpoints

3.2.3 Exploratory Endpoints

There are no exploratory endpoints

4 Study Enrollment and Withdrawal

Eligible patients include those indicated and scheduled for a BPTB ACL reconstruction. Patients will be identified from faculty surgeon case logs at the NYU Langone Health, Langone Orthopedic Hospital Sports Medicine Division.

4.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Patients undergoing ACLR with BPTB autograft
- Skeletally mature (as defined by closed growth plates on plain radiograph)
- At least 18 years of age
- Willing and able to provide consent

4.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- knee with intact ACL
- skeletally immature (as defined by open physis on plain radiograph)
- pregnant
- less than 18 years of age
- previous ACL repair or reconstruction
- unable to speak english or perform informed consent
- multiligamentous knee injury (two or more ligaments requiring surgical attention)
- varus or valgus malalignment greater than 3 degrees

4.3 Vulnerable Subjects

No vulnerable subjects will be included in this study.

4.4 Strategies for Recruitment and Retention

No additional recruitment or retention strategies will be implemented.

4.4.1 Use of DataCore/Epic Information for Recruitment Purposes

This study will utilize EPIC to identify subjects by viewing the operative schedule for the Department of Orthopedic Surgery Sports Medicine division. Surgeons will present the study information to eligible patients at a preoperative office visit, which will provide subjects sufficient time to ask questions about the study and make a decision whether they would like to participate prior to their surgery.

Commented [MR1]: Subjects should not be approached for study inclusion on the day of their surgery. Edit to indicate that subjects will be approached at a pre-operative visit.

4.5 Duration of Study Participation

Study participation with include the time of surgery to the final 1-year postoperative visit.

4.6 Total Number of Participants and Sites

Based on an effect size of 0.25 with 3 cohorts, a total of 159 patients are needed with 53 in each group. Assuming a 15% drop-out/lost to follow up rate, each group will enroll 60 patients for a total n of 180 subjects.

4.7 Participant Withdrawal or Termination

4.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

4.7.2 Handling of Participant Withdrawals or Termination

Patient visits will correspond to the standard of care postoperative visit schedule. Therefore, in the scenario that a patient withdraws from the study, they will still be seen and evaluated by the attending surgeon at regular intervals in accordance with their regular care. However, no additional data will be collected from subjects who withdraw from participating in this study.

5 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

The study agents in this study include Calcium phosphate cement (Quickset, Arthrex, Naples, FL) and Demineralized bone matrix (Allosync DBM Putty, Arthrex, naples, FL). The control group will receive autogenous bone graft to fill the bone void.

Commented [DP2]: Should this be autologous or autogenous?

Ensure the cohorts and agents used in the study are consistent throughout the protocol.

Commented [EH3R2]: Autologous

Commented [DP4R2]: Based on the background (p.9) and description of each cohort, the cohort that doesn't receive an agent gets autogenous bone (e.g. Sections 2.1 and 3.1 P.11)

5.1.1 Device Specific Considerations

Not applicable

5.2 Study Agent Accountability Procedures

The study agents are normally available (as part of standard of care) in the surgical suite. As per standard protocol, the study agents will be handled in a sterile manner, and the date of expiry will be checked and confirmed with the surgical staff prior to usage. If a product is opened but unused, it will be discarded.

5.2.1 Administration of Intervention

The use of the study agent will be done in-person, intraoperatively, by the surgeon. Nearing the end of the procedure, either autologous bone graft, DBM, or calcium phosphate cement will be used to fill in the site where the bone blocks were initially harvested (as part of the autograft). This intervention will only occur once, and will not be repeated.

5.2.2 Assessment of Subject Compliance with Study Intervention

N/A

5.3 Study Procedural Intervention(s) Description

The use of the study agent will be done intraoperatively, by the surgeon. Nearing the end of the procedure, either autologous bone graft, DBM, or calcium phosphate cement will be used to fill in the site where bone blocks were initially harvested from the patella and tibia (as part of the autograft).

5.3.1 Administration of Procedural Intervention

Administration of the study agent during the procedure will be completed by the lead surgeon. This is a one-time procedural intervention that will not be repeated.

6 Study Procedures and Schedule

6.1 Study Procedures/Evaluations

6.1.1 Study Specific Procedures

- Medical history (i.e. mechanism of injury, acuity of injury, co-morbidities, smoking status) will be collected by the surgeon during the first office visit
- Physical exam (i.e. height, weight, range of motion, points of pain, ability to bear weight, and assessment of ligamentous laxity) will be performed during the first office visit
- Radiographic images (which may include an X-ray, computed tomography scan, and/or magnetic resonance imaging scan, may be obtain as part of standard of care, independent of this study, to confirm the presence of a torn ACL and search for any concomitant pathology)
- A discussion of if the results of any study specific procedures (e.g., radiographic or other imaging or laboratory evaluations) will be provided to participant.
- If the patient is eligible for the study (i.e. meets inclusion/exclusion criteria), he/she will be informed of the study, and asked if they would like to participate (if yes, consent will be obtained by the surgeon or a study member)
- Once consented, the following questionnaires will be administered: VAS, KOOS, KUJALA IKDC
- On day of surgery, surgeon will ensure patient is aware of their participation in the study, and will consent them for the procedure
- Intraoperatively, when appropriate, the surgeon will use the appropriate graft (autologous bone graft, DBM, or calcium phosphate) based on the group to which the patient was randomized
- The patient will return for post-operative visits at the following intervals: 1 week, 4-6 weeks, 3 months, 6 months, 9 months, and 12 months. During each post-operative visit, the patient will be asked to complete the same survey as completed preoperatively; if unable to obtain during the office visit, patients will be contact via phone within 2 weeks of the visit.

6.1.2 Standard of Care Study Procedures

All of the above practices, aside from administration of the questionnaires, are standard of care.

6.2 Laboratory Procedures/Evaluations

N/A

6.3 Study Schedule

6.3.1 Screening

Screening (Day -28 to -1):

- Obtain informed consent of potential participant verified by signature on written informed consent form and provide patient with key information sheet regarding the study.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.

6.3.2 Enrollment/Baseline

Enrollment/Baseline Visit (Visit 1, Day 0)

- This is defined as the day of operation
- Obtain informed consent of potential participant verified by signature on study informed consent form (if consent was not already obtained during a pre-surgical visit)

- Provide the patient with a key information sheet regarding the study (if consent was not already obtained during a pre-surgical visit)
- Verify inclusion/exclusion criteria.
- Obtain demographic information, medical history, medication history, alcohol and tobacco use history.
- Obtain preoperative questionnaire of primary and secondary outcomes (VAS, KOOS, KUJALA IKDC)
- Record vital signs, results of examinations, other assessments.
- Administer the study treatment intraoperatively (i.e. use of autologous bone graft, DBM, or calcium phosphate)

6.3.3 Intermediate Visits

6.3.3.1 Visit 2

Visit 2 (1 week ± 4 days)
- Record adverse events as reported by participant or observed by investigator.
- Obtain questionnaire for primary and secondary outcomes (VAS, KOOS, KUJALA IKDC)

6.3.3.2 Visit 3

Visit 3 (4-6 week ± 2 weeks)
- Record adverse events as reported by participant or observed by investigator.
- Obtain questionnaire for primary and secondary outcomes (VAS, KOOS, KUJALA IKDC)

6.3.3.3 Visit 4

Visit 4 (3 months ± 3 weeks)
- Record adverse events as reported by participant or observed by investigator.
- Obtain questionnaire for primary and secondary outcomes (VAS, KOOS, KUJALA IKDC)

6.3.3.4 Visit 5

Visit 4 (6 months ± 4 weeks)
- Record adverse events as reported by participant or observed by investigator.
- Obtain questionnaire for primary and secondary outcomes (VAS, KOOS, KUJALA IKDC)

6.3.3.5 Visit 6

Visit 4 (9 months ± 4 weeks)
- Record adverse events as reported by participant or observed by investigator.
- Obtain questionnaire for primary and secondary outcomes (VAS, KOOS, KUJALA IKDC)

6.3.4 Final Study Visit

Final Study Visit (12 months ± 4 weeks)
- Record adverse events as reported by participant or observed by investigator.
- Obtain questionnaire for primary and secondary outcomes (VAS, KOOS, KUJALA IKDC)

6.3.5 Unscheduled Visit

In the event of an unscheduled visit, no questionnaire will be administered.

7 Assessment of Safety

7.1 Specification of Safety Parameters

7.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

7.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)

- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

7.2 Classification of an Adverse Event

7.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

7.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to type of graft used (i.e. isolated autologous bone graft, DBM, calcium phosphate) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

7.3 Reporting Procedures – Notifying the IRB

7.3.1 Adverse Event Reporting

Information about observed complications/adverse events will be documented in the electronic data collection system and/or on the paper CRFs, as appropriate. It will be the responsibility of the Principal Investigator to report any Serious Adverse Event (SAE) that occurs during the course of the outcomes data collection to the Institutional Review Board (IRB) within the timeframe specified by NYU SoM.

7.3.2 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB within 72 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the within 72 hours of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within<insert timeline in accordance with policy> of the IR's receipt of the report of the problem from the investigator.

7.3.3 Reporting of Pregnancy

Pregnant patients will not be included in this study.

7.4 Study Halting Rules

Administration of study agent will be halted when three grade 3 AEs determined to be "probably related" are reported.

7.5 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his site. The data safety monitoring plan will include careful assessment and appropriate reporting of adverse events as noted above, as well as quarterly review of enrollment, cumulative data from the patient-reported outcomes (pain scores), and adverse events. A yearly summary of adverse events and protocol deviations will be submitted to the IRB with the Continuation Submission in Research Navigator.

8 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by Eric Strauss.
- The monitoring will be on-site, early, for initial assessment and training, as well as throughout the study. This will be a quarterly review to ensure that:
    - collection and storage of patient data was performed in a sensitive and secure manner, as defined in the informed consent form and protocol
    - All study activities were conducted with primary emphasis on patient care and well-being
    - There were no adverse events
    - The risk/benefit to patients has remained the same throughout the course of the study
- This will be performed on a regular basis (every 3 months)

9 Statistical Considerations

9.1 Statistical Hypotheses

There is no difference in level of anterior knee pain, as defined by patient-reported functional outcome scores, between the three treatment groups.

9.2 Analysis Datasets

There will be 3 groups for analysis: group 1 will be control, receiving autologous bone graft; group 2 will receive autologous bone graft along with DBM; group 3 will receive autologous bone graft along with calcium phosphate cement. Patients will be randomized to these groups.

9.3 Description of Statistical Methods

9.3.1 General Approach

The general approach of this will be a 3-group study, without crossover. For descriptive statistics, categorical values will be described by percentages, and continuous variables will be described by means with standard deviations. To compare primary and secondary outcomes, an analysis of variance (ANOVA) will be performed, with a p-value of 0.05 set to determine statistical significance. Testing will be performed to determine whether sample distribution is normal; if not, non-parametric testing will be performed.

9.3.2 Analysis of the Primary Efficacy Endpoint(s)

To compare primary outcomes (anterior knee pain), an analysis of variance (ANOVA) will be performed, with a p-value of 0.05 set to determine statistical significance. Testing will be performed to determine whether sample distribution is normal; if not, non-parametric testing will be performed. Patients who do not complete at least 80% of follow-up visits will be considered lost to follow-up and will not be included in the analysis.

9.3.3 Analysis of the Secondary Endpoint(s)

To compare secondary outcomes (functional outcomes scores, complication rates), an analysis of variance (ANOVA) will be performed, with a p-value of 0.05 set to determine statistical significance. For categorical variables, chi-squared testing will be performed. Testing will be performed to determine whether sample distribution is normal; if not, non-parametric testing will be performed. Patients who do not complete at least 80% of follow-up visits will be considered lost to follow-up and will not be included in the analysis.

9.3.4 Adherence and Retention Analyses

Adherence will be defined as patients completing their post-operative visits at the following intervals: 1 week, 4-6 weeks, 3 months, 6 months, 9 months, and 12 months.

9.3.5 Baseline Descriptive Statistics

Intervention groups will be compared on baseline characteristics, including demographics and laboratory measurements, using descriptive statistics. These characteristics will be compared at baseline (pre-operative time point) and at final follow-up.

9.3.6 Planned Interim Analysis

Not applicable.

9.3.7 Additional Sub-Group Analyses

Not applicable,

9.3.8 Multiple Comparison/Multiplicity

Not applicable.

9.3.9 Tabulation of Individual Response Data

Individual participant data will be recorded by measure and time point, but will be reported in literature as means and standard deviations.

9.3.10 Exploratory Analyses

Not applicable.

9.4 Sample Size

Based on an effect size of 0.25 with 3 cohorts, a total of 159 patients are needed with 53 in each group. Assuming a 15% drop-out/lost to follow up rate, each group will enroll 60 patients. Outcome measures will include patient reported outcomes: VAS, KOOS, Kujala, and IKDC. Additionally, we will report on rates of complications post-operatively, if any. Type I error rate (alpha) will be set at 0.05. Power will be set at 0.80.

10 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12 Ethics/Protection of Human Subjects

12.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

12.2 Institutional Review Board

The protocol, informed consent form(s), and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.3 Informed Consent Process

12.3.1 Consent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol: consent form, key information form.

12.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families in a private office when they are being consented for their surgery. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise prior to their surgery. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw

Commented [MR5]: Edit to state that subjects will be consented prior to the day of their surgery.

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consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

12.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Data will be de-identified with a unique code and stored on password-protected computers behind the NYULH firewall as well as on REDCap, which is a HIPAA compliant and encrypted database managed by MCIT. Data will only be available to the investigators. The investigators will separately maintain the master list to reidentify subjects using RedCap.

12.5 Future Use of Stored Specimens

Not applicable, as this study does not involve the collection of samples or specimens.

13 Data Handling and Record Keeping

13.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source

documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by the home institution. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

13.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.3 Protocol Deviations

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14 Study Finances

14.1 Funding Source

This study will be financed by the Orthopaedics Department of NYU Langone Health.

14.2 Costs to the Participant

There will be no additional costs to the patient as a result of this study.

14.3 Participant Reimbursements or Payments

There will be no participant reimbursement or additional compensation provided on behalf of this study.

15 Study Administration

15.1 Study Leadership

This study, given that it will be a single-center study, will be led by the study PI, Dr. Eric Strauss. There will be no steering committee.

16 Conflict of Interest Policy

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management

plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULH investigators will follow the applicable conflict of interest policies.