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NYU School of Medicine
NYU LANGONE MEDICAL CENTER

# Calcific Tendonitis Treatment: Barbotage vs. Barbotage with Cortisone Injection: A Randomized Controlled Double-Blind Study

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| **Principal Investigator:** | Mehul R. Shah, MD<br>NYU Hospital for Joint Diseases<br>Division of Sports Medicine<br>Mehul.Shah@nyulangone.org<br>616-501-7223 |
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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), any other applicable US government research regulations, and institutional research policies and procedures. 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.

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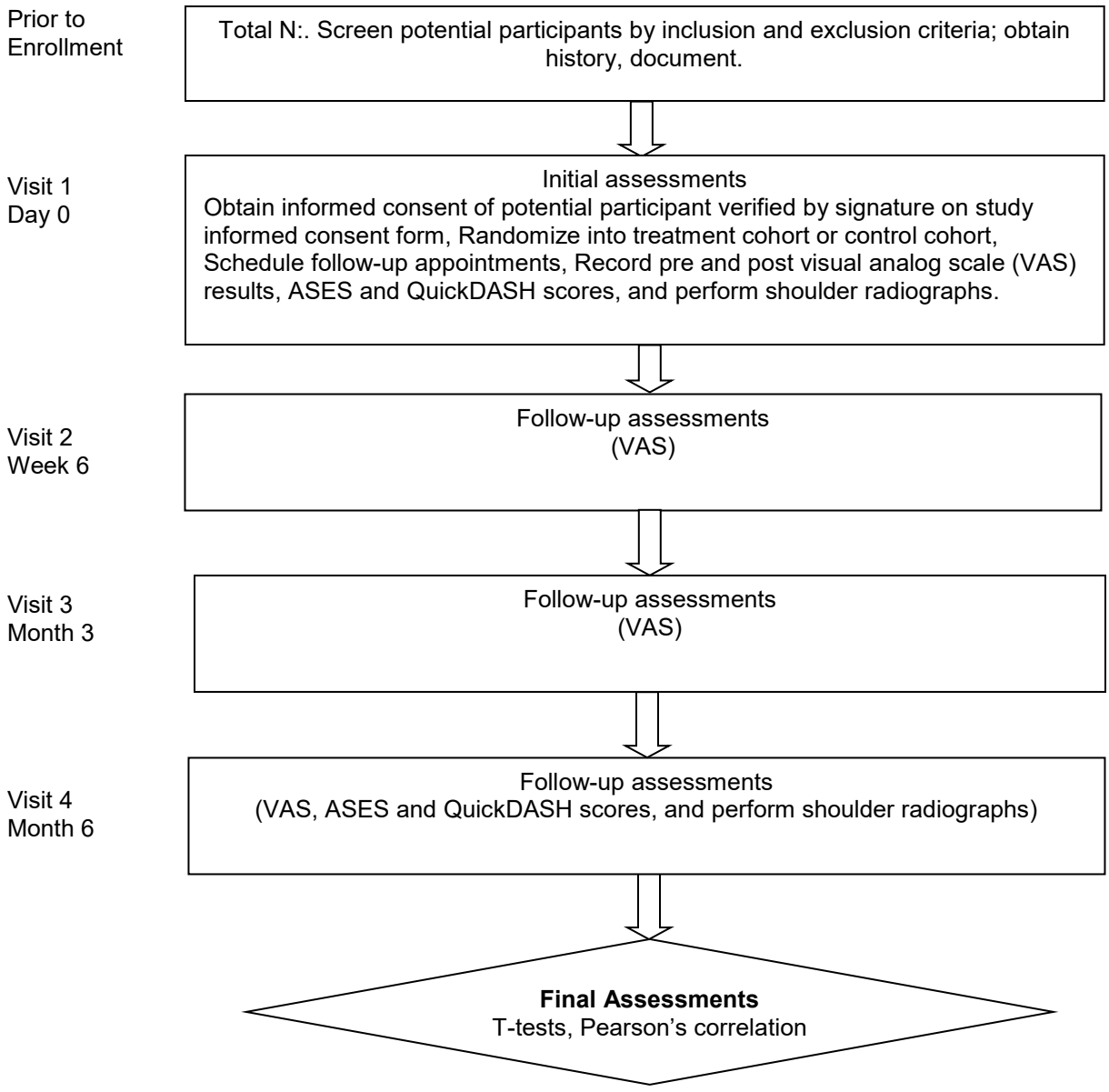
## List of Abbreviations

| | |
|---|---|
| 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 |
| 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 |

# Protocol Summary

| | |
|---|---|
| Title | **Calcific Tendonitis Treatment-Barbotage vs. Barbotage with Cortisone Injection: A Randomized Controlled Double-Blind Study** |
| Short Title | Calcific Tendonitis Treatment-Barbotage vs. Barbotage with Cortisone Injection |
| Protocol Number | S19-01299 |
| Population | A sample size of 140 patients belonging to NYU Langone Health with calcific tendonitis will be enrolled including both genders, ages 18-90. |
| Objectives | The purpose of this study is to determine the efficacy of barbotage therapy by comparing the clinical and sonographic changes in patients that solely receive barbotage to patients receiving the standard of care, barbotage with cortisone injection. |
| Study Center(s) | Single-center, prospective study |
| Number of Subjects | We will aim to enroll a total of 140 subjects. |
| Study Duration | The estimated duration of the study is 24 months. |
| Subject Participation Duration | Each patient will be present for the day of treatment and follow-up at: 6 weeks, 3 months, and 6 months. Patients will be in the study for 6 months. |
| Estimated Time to Complete Enrollment | The estimated time to completion of enrollment is 24 months. |
| Statistical Methodology | Statistical analysis will be performed using ANOVA or t tests. Pearson's correlation will be used to determine relationship between outcomes scores. |

## Schematic of Study Design



# 1 Introduction, Background Information and Scientific Rationale

## *1.1 Background Information and Relevant Literature*

Calcific tendonitis is a disorder characterized by pain and development of calcium deposits on one or more rotator cuff tendons and affecting normal sleeping habits and routine daily activities. Inflammation associated with the calcium deposit is theorized to contribute to the pain [1]. A few studies state the prevalence of the condition has been reported to be 3 to 10% in the general population [2, 3]. Several treatment modalities exist including anti-inflammatory and analgesic, extra-corporeal shockwave therapy (ESWT), ultrasound-guided needling and lavage (barbotage), and surgical treatment are in use. However, a consensus to which treatment is superior nor most effective does not exist.

## *1.2 Rationale*

Ultrasound-guided barbotage is a safe and efficient form of therapy for calcific tendonitis, with slightly more than half of the patients experiencing pain relief [4]. The procedure involves percutaneous insertion of a needle with saline, washing and aspirating the fluid content of the joint. By irrigating and aspirating the calcium deposit, symptomatic relief is achieved and signs of pathological resolution is seen on sonogram. All of this is achieved while preserving the native tendon, potentially avoiding surgery. Barbotage with cortisone injection continues to be the standard of care for calcific tendonitis resistant to physical therapy and cortisone injection, but it is not known if barbotage alone can provide the same amount of clinical and symptomatic resolution. We would like to evaluate and witness any significant difference from the standard treatment of care.

## *1.3 Potential Risks & Benefits*

### 1.3.1 Known Potential Risks

Associated Risks of Cortisol Injection: Some of the reported side effects of cortisone injection are joint infection, nerve damage, thinning of the skin and soft tissue around the injection site, temporary flare of pain and inflammation after injection and whitening or lightening of the skin around the injection site.

Associated Risks of Not Receiving Cortisol: Temporary pain and potentially prolonged inflammation following barbotage treatment.

Associated Risks of X-Ray: During this study, subjects will have exposure to radiation from a shoulder x-ray. This radiation exposure is not necessary for their medical care and is for research purposes only. This means subjects will be exposed to small doses or amounts of radiation. The risk from this amount of radiation is less than the risk from everyday exposure to the sun. The risks of receiving very small doses of radiation are thought to be low. These risks are not actually known.

Female subjects must have a negative pregnancy test before they can have an X-ray. This will be administered at the 6-month visit before the x-ray.

Potential Loss of Confidentiality: While every effort will be made to keep subjects' information confidential, there is the potential risk of loss of confidentiality. In order to minimize this risk, any information that can identify a patient will be removed and replaced with a unique study ID that only the study coordinator/investigators will know.

Psychological Risks: When completing the questionnaires, subjects may come across a question or answer choice they find unpleasant, unsure on how to answer or otherwise objectionable. We will tell subjects there is no right or wrong answer to minimize this risk.

### 1.3.2 Known Potential Benefits

We don't know if subjects will benefit from being in this study. There is a possibility the saline barbotage without cortisone may help some patients. However, we do not know for sure. We hope the results of this study will benefit future patients with this condition.

# 2 Objectives and Purpose

## *2.1 Primary Objective*

The primary objective of the study is to determine the efficacy of barbotage without cortisone on patients with calcific tendonitis by measuring their clinical improvement via VAS, QuickDASH, and ASES Shoulder scores and radiographic size of calcium deposit.

# 3 Study Design and Endpoints

## *3.1 Description of Study Design*

This will be a single-center, prospective, randomized study. This study will determine patient outcomes after minimally invasive treatment to determine the efficacy of barbotage therapy on patients with calcific tendonitis.

## *3.2 Study Endpoints*

### 3.2.1 Primary Study Endpoints

The primary study endpoint will focus on the decrease in pain of the affected shoulder measured by VAS scores. Based on their responses and their scores at the time prior to and after their barbotage therapy begins, we can determine a primary endpoint with a 10% change between baseline and their final visit. We would also like to observe the affected rotator cuff tendon and measure the efficacy of barbotage therapy via shoulder radiograph. Shoulder X-Ray is considered standard of care and we expect a resolution in size of the calcified deposit by at least 10% after aspiration and lavage.

### 3.2.2 Secondary Study Endpoints

The secondary endpoints will consist of questionnaires measuring the patients function. We will utilize the ASES Shoulder and QuickDASH scores. Based on their responses and their scores at the time prior to and after their barbotage therapy begins, we can determine a primary endpoint with a 10% change between baseline and their final visit.

# 4 Study Enrollment and Withdrawal

Eligible patients include patients at least 18 years of age, ASA class I-II, and patients diagnosed with calcific tendonitis.

## *4.1 Inclusion Criteria*

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

- Must be at least 18 years of age and younger than 90 years of age
- Diagnosed with calcific tendonitis and ruled out other shoulder-related pathologies
- Failed 1$^{st}$ line therapy (physical therapy and cortisone injection)
- Intention to receive barbotage with cortisone as standard of care
- 3 or more months of shoulder pain
- Finding of one or more calcifications ≥5 mm in size on either sonogram or radiograph, located on the supraspinatus tendon
- Positive Hawkin's test or Neer's sign for impingement

## *4.2 Exclusion Criteria*

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

- Legally incompetent or mentally impaired (e.g. minors, Alzheimer's subjects, dementia, etc.)
- Osteoarthritis of the glenohumeral joint of the affected shoulder
- Previous surgery or barbotage to the affected shoulder
- History of prior allergic/hypersensitivity reactions related to the study medication
- Shoulder instability, glenohumeral arthritis, AC pathology, inflammatory arthropathy, fibromyalgia, frozen shoulder or cervical radiculopathy
- Sub-acromial injection with a corticosteroid or treatment by ESWT during the last 3 months before inclusion
- Younger than 18 years of age or older than 90
- Any patient considered a vulnerable subject

## *4.3 Vulnerable Subjects*

We do not intend to enroll vulnerable subjects.

## *4.4 Strategies for Recruitment and Retention*

Patients identified by participating orthopaedic surgeons at NYU Langone Orthopedic Hospital with calcific tendonitis who meet inclusion criteria will be eligible for the study. When the patients arrive at the physician office for a standard of care visit, study team members will provide the potential patient subjects with information on the study and ask the patient for their consent to be in the study.

### 4.4.1 Use of DataCore/Epic Information for Recruitment Purposes

This study will utilize EPIC to identify subjects.

Patients will be identified by participating orthopaedic surgeons at NYU Langone Orthopedic Hospital.

- TP agrees to permit study team to directly contact potential subjects on behalf of TP.
- The patients will be contacted by the study team in person when patients arrive at the physician office for a standard of care visit

Subjects will be asked if they are interested in participating in this specific study. Should the potential subjects agree, the study team will provide the subjects with information regarding the next steps for participation.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research-contact-optout@nyumc.org or 1-855-777-7858.

## *4.5 Duration of Study Participation*

The study intervention phase of physical study will last for 24 months. The participants will require 3 follow-up visits.

## *4.6 Total Number of Participants and Sites*

Recruitment will end when approximately 140 participants are enrolled. All patients will be enrolled from NYULMC.

## *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

If patients withdraw from the study, we will remove their information from our REDcap database and we will enroll an additional patient to maintain the recommended sample size.

### 4.7.3 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor and/or IRB.

# 5 Study Procedures and Schedule

## *5.1 Study Procedures/Evaluations*

Once the study team member arrives to the physician office, they will provide the potential patient subjects with information on the study and ask the patient for their consent to be in the study. The patient will be given shoulder-related questionnaires (ASES and QuickDASH), asked to complete a VAS survey and will receive a shoulder radiograph prior to treatment and at 6 months post-treatment, to evaluate the state of the condition.

Patients in this study will receive the assigned form of treatment and have assigned follow-up appointments at 6 weeks, 3 months and 6 months post-treatment. The alternative treatment (barbotage with saline injection) will be administered in the same fashion as the control (barbotage with cortisone injection). If the patient desired to solely have the standard therapy, they will be ineligible for the study.

Patients will be randomized to one of two cohorts: receiving barbotage with saline injection or receiving barbotage with cortisone injection. Both groups will follow the same protocol for standard of care: 4 mg of dexamethasone (if receiving cortisone) and barbotage. Cortisone dosing is consistent with FDA-approved guidelines. The saline used for the barbotage and sham injection are the same, and readily available in the procedure room. The saline is manufactured by B. Braun Medical, available in the procedural room, and will be equivalent in volume to that of the cortisone injection, determined by the performing physician. Dr. Lauren Borowski will be performing the procedure. At each follow-up appointment, the patients will complete the questionnaires and VAS scores. Patients and physicians will be blinded to the cohort; patients will be randomly chosen by the research study members excluding the primary investigator (PI). The barbotage

and cortisone/saline (sham) injection will occur concurrently by a different physician from the PI, blinding the PI and patients. The study team members responsible for randomization will converse with the Dr. Borowski, who will be in charge of performing the barbotage and cortisone/saline (sham) procedure. The associated research members and the physician performing the barbotage excluding the PI and patients are the only individuals who will be aware of the blind. Blinding will be maintained until a patient experiences adverse effects, in which case the researchers will inform the primary physician.

### 5.1.1 Standard of Care Procedures

- Medical history (Past medical/surgical history, previous imaging)
- Medication history (e.g., previous medications)
- Follow-up at 6 weeks, 3 months and 6 months
- U/S guided barbotage
- Pre and post visual analog scale scores
- Pre and post ASES Shoulder Index
- Pre and post QuickDASH
- Baseline Shoulder X-Ray

### 5.1.2 Standard of Care Study Procedures

Patients with calcific tendonitis are prescribed a variety of treatment options including medicinal, procedural and operative. Barbotage with cortisone injection therapy is a standard of care treatment for patients with calcific tendonitis who fail primary, minimally invasive therapy. Both the control and experimental cohort will follow-up with their physician at the assigned times. Shoulder X-Rays are part of the standard of care.

## *5.2 Study Schedule*

### 5.2.1 Screening

**Screening (Day -7 to -1)**

- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.

### 5.2.2 Enrollment/Baseline

**Enrollment/Baseline Visit (Visit 1, Day 0)**

- Obtain informed consent of potential participant verified by signature on study informed consent form.
- Physical exam
- Randomize into treatment cohort or control cohort
- Schedule follow-up visits
- Record VAS, ASES Shoulder and QuickDASH scores.
- Perform Shoulder Series X-Ray

### 5.2.3 Intermediate Visits

**Intermediate Visits (Week 6, Month 3)**

- Follow-up visits
- Record VAS

### 5.2.4 Final Study Visit

***Final Study Visit (End of Month 6)***

- Record VAS, ASES Shoulder, and QuickDASH scores.
- Perform Shoulder Series X-Ray for Research Purposes

# 6 Assessment of Safety

## *6.1 Specification of Safety Parameters*

This study presents minimal risks as physical exams and barbotage do not generally present with serious associated risks.

### 6.1.1 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

### 6.1.2 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***.

### 6.1.3 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)
- <u>Related or possibly related to participation in the research</u> (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)
- <u>Suggests that the research places subjects or others at greater risk of harm</u> (including physical, psychological, economic, or social harm).

## *6.2 Classification of an Adverse Event*

### 6.2.1 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.

### 6.2.2 Relationship to Study Intervention

*The clinician's assessment of an AE's relationship to study intervention 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 intervention assessed. In a clinical trial, the study intervention must always be suspect. To help assess, the following guidelines are used.*

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

### 6.2.3 Expectedness

Dr. Mehul Shah will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

## *6.3 Time Period and Frequency for Event Assessment and Follow-Up*

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

## *6.4 Reporting Procedures – Notifying the IRB*

### 6.4.1 Adverse Event Reporting

Information about any breach of confidentiality 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 retrospective data collection to the Institutional Review Board (IRB) within the timeframe specified by NYU SoM.

### 6.4.2 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 and to the DCC/study sponsor. 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 and to the DCC/study sponsor within 1 week of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 2 weeks 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 1 month of the IRB's receipt of the report of the problem from the investigator.

# 7 Data Monitoring

Data monitoring will be done by Dr. Shah, the principal investigator. Data monitoring reviews will be conducted quarterly.

He will monitor:

1. Incidents of severe adverse effects (infection, bursitis, fainting or feeling of faintness)
2. Collection and storage of study data was performed as defined in the informed consent form and protocol
3. The risk/benefit to patients has remained the same throughout the course of the study.

4. If there is a greater than 10 percent difference in frequency of risks between the two study groups, the study will be stopped.

# 8 Statistical Considerations

## *8.1 Sample Size*

We will aim to enroll a total of 140 subjects. According to a post hoc power analysis calculating the effect size using our preliminary data, >128 patients are required with d=0.6 to obtain a power of 0.80 and an alpha value of 0.05. Therefore we are including an additional 10 patients per group to account for patients that may be lost to follow up. Statistical analysis will be performed using chi-squared and/or fisher's exact testing depending on size for binary variables. Continuous variables will be compared with paired t-tests if the data is approximately normally distributed. If the data is not normally distributed, Mann-Whitney tests will be used. All protected health information will be removed prior to statistical analysis.

## *8.2 Measures to Minimize Bias*

### 8.2.1 Enrollment/Randomization/Masking Procedures

Patients will be randomized (1:1) using REDCap. The physicians and patients will be blinded to their assigned treatment group.

As each patient receives the barbotage, the patient nor the PI will not know if they are receiving the cortisone in addition to the barbotage. Study team members and Dr. Borowski will not be blinded and in position to randomize the patients. Dr. Borowski will not be blinded to the study as she is performing the procedures. Dr. Shah, the PI, and his patients will be blinded from which combination of the two they receive (barbotage and cortisone or saline/sham).

### 8.2.2 Breaking the Study Blind/Participant Code

The study blind for a single patient will be broken if the patient reports severe adverse events. These events will be recorded and then reported to the PI. The information will be confidentially maintained by the PI and study team members. All information will be protected by REDCap.

# 9 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.

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.

# 10 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.

# 11 Ethics/Protection of Human Subjects

## *11.1 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.

## *11.2 Institutional Review Board*

The protocol, informed consent form(s), recruitment materials, 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.

## *11.3 Informed Consent Process*

### 11.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention. The consent form is submitted with this protocol.

### 11.3.2 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. 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. 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 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 from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

### *11.4 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.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

## 12 Data Handling and Record Keeping

### *12.1 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 REDCaps. 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.

## *12.2 Study Records Retention*

Study documents will be retained for the longer of 3 years after close out or 5 years after final reporting/publication. These documents should be retained for a longer period, however, if required by local regulations. 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.

## *12.3 Protocol Deviations*

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 7 days working days of identification of the protocol deviation, or within 7 days working days of the scheduled protocol-required activity. 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.

## *12.4 Publication and Data Sharing Policy*

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in

ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

# 13 Study Finances

## *13.1 Funding Source*

The study is funding by the Orthopedic Department and the Physical Therapy Department.

## *13.2 Costs to the Participant*

Subjects will not incur any additional financial costs as a participant in this study.

# 14 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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 Committee 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.

# 15 References

1. Moosmayer, S., et al., *KALK study: ultrasound guided needling and lavage (barbotage) with steroid injection versus sham barbotage with and without steroid injection - protocol for a randomized, double-blinded, controlled, multicenter study.* BMC Musculoskeletal Disorders, 2017. **18**(1).
2. Bosworth, B.M., *CALCIUM DEPOSITS IN THE SHOULDER AND SUBACROMIAL BURSITIS.* Journal of the American Medical Association, 1941. **116**(22): p. 2477.
3. Uhthoff, H.K. and J.W. Loehr, *Calcific tendinopathy of the rotator cuff: pathogenesis, diagnosis, and management.* JAAOS-Journal of the American Academy of Orthopaedic Surgeons, 1997. **5**(4): p. 183-191.
4. Lanza, E., et al., *Ultrasound-guided percutaneous irrigation in rotator cuff calcific tendinopathy: what is the evidence? A systematic review with proposals for future reporting.* European Radiology, 2015. **25**(7): p. 2176-2183.

# 16 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

- Consent form

# Attachment A

## *Schedule of Events*

| Activity | Visit 1 | Visit 2 | Visit 3 | Final Session |
|---|---|---|---|---|
| **Study team procedures** | | | | |
| Consent | X | | | |
| Medical History | X | | | |
| Physical Exam | X | X | X | X |
| Height | X | | | |
| Weight | X | | | |
| Vitals signs | X | X | X | X |
| Randomization | X | | | |
| Study intervention provided | X | | | |
| Subject Survey | X | | | X |
| ***Shoulder assessments*** | | | | |
| QuickDASH | X | | | X |
| ASES Shoulder | X | | | X |
| VAS | X | X | X | X |
| Shoulder Radiographs | X | | | X |

## Faces rating scale (FRS)


## Numerical rating scale (NRS)