**Study Title**

Autologous Stem Cell Augmentation in Arthroscopic Cuff Repair: a Prospective Randomized Controlled Trial

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**Autologous Stem Cell Augmentation in Arthroscopic Cuff Repair: a Prospective Randomized Controlled Trial**


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## 1. Statement of Objectives

The primary research objective is to determine whether patients who undergo a repair of the rotator cuff with arthroscopic technique using autologous stem cell augmentation with a pre-surgical trephination have improved disease-specific quality of life as measured by the Western Ontario Rotator Cuff Index (WORC) at 24 months post-operatively. Secondary objectives include functional outcome as measured by the Constant score and the ASES score in patients who undergo cuff repair with the two aforementioned techniques; determination of the re-tear rates as determined by ultrasound imaging at 6 and 24 months; determination of the degree of healing reaction in the early post-operative period by MRI; and determination of the composition of the healing matrix following trephination.

It is our hypothesis that rotator cuff repair with a pre-operative trephination technique will yield improved disease-specific quality of life compared with historical controls. Demonstration of superiority of the trephination technique will lead to significant improvement in function, strength, earlier return to employment and recreational activities and a decreased cost to the health care system compared with traditional rotator cuff repair.

## 2. Background and Rationale

Tears of the rotator cuff tendons are a very common entity. Uhthoff and associates(1) found a 20% incidence in a series of cadaver dissections. Lehman and associates(2) found an incidence of 17% in a large series of cadaver dissections with an incidence of 30% in those older than 60 years of age. Surgical repair of the rotator cuff is the preferred treatment with failure of conservative therapy. The results of repair of the rotator cuff have shown that function and strength can be successfully restored, and that pain is effectively relieved.(3-6)

Failure of cuff repair can occur as a result of infection, failure of the deltoid muscle reattachment, and re-tearing of the rotator cuff.(7) Failure of the rotator cuff repair is the most frequently observed complication, and has been estimated between 20 and 68%. (8) Failure of the repair of the rotator cuff often occurs secondary to lack of tendon to bone healing.(9-11) The high incidence of rotator cuff repair failure provides the rationale for seeking new methods to improve healing.

In the interest of minimizing the surgical morbidity associated with open rotator cuff repair, minimally invasive arthroscopic techniques have evolved. These techniques do not require detachment in the deltoid muscle, and thus deltoid detachment is not seen as a complication in arthroscopic cuff repair. Advantages of the arthroscopic method include smaller skin incisions, glenohumeral joint inspection, treatment of intra-articular lesions, and more rapid rehabilitation.(12) Weber and associates have shown that the rate of infection seen in arthroscopic cuff repair is lower than that of open repair. Failure of the repair itself however does occur with arthroscopic methods.(13)

Various reports have shown that a correlation exists between the anatomical integrity of the cuff as determined by various imaging modalities and the functional outcome following open repair. (5, 6, 14-16) Harryman et al. in a study of 105 patients, demonstrated a 20% re-tear rate by ultrasound in repairs of isolated supraspinatus tendons. In patients with tears involving more than one tendon, over 50% had re-torn. Patients with a healed tear had better function during activities of daily living, greater range of motion and strength compared with patients in whom the cuff had re-torn.(5) Gazielly et al. in a study of 100 patients with surgically repaired full thickness tears found a close correlation between the anatomic integrity by ultrasound and the functional outcome as measured by the Constant score. Patients in whom the repair had not healed had poorer range of motion, strength, and lower activities of daily living outcome.(6) In a study of 30 patients with rotator cuff repairs, post-operative MRI demonstrated recurrent tears in 20% of shoulders. The authors demonstrated a correlation between the anatomical integrity of the tear, and final Constant functional outcome scores and final strength. In patients with non-healed tears, abduction strength never exceeded 4 kg.(14) In a study of 65 patients with an arthroscopically repaired cuff tear by Boileau et al., only 71% of patients had complete healing. The healing rate was even lower (43%) in patients over the age of 65. There was a significant difference in the Constant score and final strength in favour of patients in whom the cuff head healed, as demonstrated by MRI or CT scan.(15) In an ealier study by Galatz et al., 17 of 18 patients who underwent an arthroscopic cuff repair had recurrent tears. At a minimum of two year follow-up, the American Shoulder and Elbow Surgeons (ASES) score was 79.9 points.(16)

Despite recent advances in arthroscopic minimally invasive surgical technique, the re-tear rate following rotator cuff repair remains unacceptably high. Failure of the cuff to heal following repair is associated with poorer functional outcomes and loss of strength with corresponding costs to individuals and society due to loss of productivity and impairment of function. Thus, research into methods to improve healing rates must be sought.

### 2.1 Present state of Knowledge

Following cuff repair in the animal model, the insertion site of the rotator cuff does not return to its normal state; the structure, composition and organization of a normal insertion site does not regenerate(17-19)

There are a number of possible reasons for this: insufficient gene expression that directs insertion site formation; insufficient numbers of undifferentiated cells at healing interface, excessive loads on tendon, or the insufficiency of appropriate molecular signals (gene expression) and cell differentiation. The end result is that the cuff heals by scar formation, and not by regeneration as seen in the embro.(20) The inflammation that follows repair and the recruitment of inflammatory cells may result in cellular and molecular signals that ultimately lead to fibrosis rather than tissue regeneration.

It has been previously suggested that surgical repair is necessary to initiate the healing process(21) It is possible that gap formation occurs early following repair, resulting in lack of contact between the rotator cuff and the tendon insertion area. It is likely that tissue contact between tendon and bone is necessary in order for appropriate tissue differentiation to occur. Uhthoff et al.(22) have demonstrated in a rabbit model that the portion of tendon in contact with the bony trough influences the quality of healing. Fibrocartilage formed at sites where transected tendon was in contact with bone but not where the articular or bursal tendon surface contacted bone.

The process of tendon healing similar course to all soft tissues: 1) immediate postinjury phase 2) inflammatory phase 3) proliferation phase 4) reparative phase 5) remodeling phase.(23, 24) Significant proliferation of reparative tissue around the edges of chronic torn tendon of human cuff has been observed(25, 26) With tissue damage, blood vessels rupture and signaling molecules released by intrinsic cells trigger a coagulation cascade that coordinates the formation of clot in area; the clot contains cells and platelets that begin to release molecules (growth factors); intrinsic and extrinsic cells can potentially produce these molecules.(27)

As this cascade occurs, a number of molecules are necessary in order to healing to occur. Growth factors are known to appear during wound healing and include betaFGF, IGF-1, PDGF, and TGF-beta(28). Kobayashi et al.(29) studied the timing of expression of growth factors in the early supraspinatus tendon healing in rabbits. After full thickness cuff defects were produced in rabbit shoulders, basic fibroblast growth factor appeared with its peak on days 7 and 9, Insulin-like growth factor 1 peak day 5, platelet-derived growth factor had mild expression between days 7 and 14 and transforming growth factor B (beta) appeared with constant mild expression throughout the observation period. In addition, fibroblast-like cells appeared in the defect on days 7 and 9, and filled the defect to a full extent on day 14. Vascularization increased on day 7 and decreased as the fibrolast-like cells increased. The authors concluded that growth factors likely play a role in early phase of healing of SSP tendons.

Wurgler-Hauri et al. demonstrated the temporal expression of 8 growth factors in tendon-bone healing in a rat supraspinatus model. Immunoassays showed an increase in expression of all growth factors at 1-week, then return to control levels by 16 weeks in both insertion and midsubstance.(30)

In addition to growth factors, various cells are recruited to the healing site. Galatz et al. studied the sequence of the healing response of rat supraspinatus tendon following tendon to bone re-insertion.(31) The repair tissue demonstrated an inflammatory response with multinucleated cells present at 1 and 3 days, lymphocytes and plasma cells present at 7 and 10 days, and capillary proliferation began at 3 days and peaked at 10 days. The ultimate strength of the repair increased over time. There was a large presence of type III collagen in early cuff healing in the initial disorganized scar material at the insertion site. By 56 days of healing, large amounts of type I collagen were also found. TGFbeta-3 was not seen at healing insertion site. TGFbeta-1 was localized to repair tissue and coincided with the peak in cell proliferation and cellularity. The repair sites remained disorganized histologically and biomechanically inferior in comparison to uninjured insertion sites. The observations concerning the inferior biomechanical strength of the healing repair has been corroborated by other authors; St Pierre et al. found that the strength a healed repair increased over time but was only 1/3 of control by 12 weeks(32)

In the rat model, Kawamura et al. studied the accumulation of hematopoietic lineage cells in the early phase of tendon-bone healing during anterior cruciate ligament (ACL) reconstruction. Neutrophils, recruited phagocytic macrophages and resident anabolic macrophages accumulate sequentially in the

healing tendon graft with progressive cell ingrowth towards the inner tendon(33). Neutrophils and recruited macrophages were seen after 4 days, and resident macrophages not until 11 days. Infiltrating macrophages likely contribute to scar tissue formation by producing inflammatory cytokines. Bone marrow derived mesenchymal stem cells (MSCs) could improve cuff tendon to bone repair due to their capacity for self-renewal and totipotency(20)

In the rabbit model with ACL reconstruction, tendon grafts coated with MSC's in fibrin glue carrier demonstrated large areas of immature fibrocartilage cells at the tendon bone junction at 2 weeks. By 8 weeks, MSC treated grafts resembled chondral entheses of normal acl insertions with the presence a of mature zone of fibrocartilage blending into the adjacent bone and tendon substance rather than disorganized fibrovascular granulation tissue. This tissue had a higher failure load than fibrin glue treated grafts at 8 weeks post-surgery(34)

The ideal substrate for delivery of stem cells and growth factors to the repair site is not known and requires further study. (20)

Rodeo et al.(18) studied the effect of augmentation of rotator cuff tendon-healing with osteoinductive growth factors. Seventy-two skeletally mature sheep underwent detachment of the infraspinatus tendon followed by repair. Three treatments were studied: osteoinductive bone-protein extract on a type-I collagen sponge carrier; collagen sponge carrier alone; and no implant. Testing occurred at 6 and 12 weeks. Outcomes included MRI, xrays, histology and biomechanical testing. MRI demonstrated that the volume of newly formed bone and soft tissue in the tendon-bone gap were greater in the growth factor treated animals compared with collagen sponge control group . Histology demonstrated that the fibrovascular tissue in the interface between tendon and bone had a more robust fibrocartilage zone between bone and tendon in the growth factor-treated animals. Mechanical testing did not demonstrate any differences between groups, suggesting treatment with growth factor results in formation of poor-quality scar tissue rather than true tissue regeneration. However, repairs treated with collagen sponge carrier alone had significantly greater stiffness than the growth factor-treated group at twelve weeks

Seeherman H,(35) et al. studied the effect of rhBMP-12 in the healing of rotator cuff repairs in a sheep model. The authors demonstrated that sponge carriers had better local retention of rhBMP-12 than did the buffer of paste carriers in a rat pilot study. Rhbmp-12 with paste and sponge combinations were evaluated in 8 sheep each with unilateral infraspinatus tear and reattachment. Contralateral normal shoulders from 16 sheep shoulders were repaired without rhBMP12. Rhbmp12 with type I and type I/III collagen sponge combinations were evaluated in 8 additional sheep on basis of superior efficacy. Type I/III collagen sponge alone evaluated in 10 sheep to examine effect of collagen carrier. Ultrasound evaluation was carried out at 4 and 8 weeks. Plain radiographs, mechanical testing and biochemical evaluation was performed at 8 weeks, along with histological analysis. The mechanical properties of repairs treated with rhbmp12 and hyaluronan paste were similar to untreated repairs. However, the delivery of rhbmp-12 in collagen or hyaluronan sponge resulted in accelerated healing of acute full-thickness rotator cuff repairs.

The effect of delayed reinsertion of tendon to bone has been studied by Koike et al. The supraspinatus reinsertion was delayed by 6 and 12 weeks and was compared with immediate reinsertion in a rabbit model. No difference was found in the three groups in terms of the number of non-chondrocytic cells, the number of chondrocytic cells, or the arrangement of collagen fibers. This data indicates that a delayed reattachment of the tendon does not compromise the ability of the tendon-bone interface to reconstitute an enthesis.(36)

**Restoration of an enthesis**

Currently, arthroscopic surgery for rotator cuff tendon repair includes debridement of the torn tendon, bursectomy and apposing the tendon onto a tendon insertion site or "footprint" with sutures anchored over the greater tuberosity of the humeral (Fig x). Sutures hold the construct together but in the long term, only the formation of a new enthesis would ensure anatomic continuity. The process of enthesis formation has been studied. Rotator cuffs were repaired in 89 rabbits and the restoration of a new 4-zone

enthesis was followed longitudinally.*(Koike JOR 2005, JOR 2006)* Cellular phases were initiated first and extracellular restoration followed. After 2 weeks, undifferentiated mesenchymal stem cells were concentrated in large numbers (68-fold increase) where the bone marrow had been exposed. The next phase included differentiation of some MSC into chondrocytes and involution of the majority of MSC by 12 weeks after repair. Chondrocytes then organized into rows, completing the cellular phase by 24 weeks after surgery. Extracellular matrix restoration was initiated later with presence of proteoglycan and alignment of collagen fibres less than 50% at 16 weeks. The process was still unfinished (less than 75% completed) by 24 weeks after surgery. Therefore, bone-marrow derived MSC migrating to the repair site appeared as the dramatic initial event, orchestrating orderly formation of a new enthesis. Current arthroscopic surgery does not involve MSC. From these basic observations, we designed the current clinical study and basic experiments to test trephination, and thus stem cell augmentation, to improve rotator cuff repair. Among the possible ways to augment the repair site with MSC, we selected the prior recruitment of autologous MSC.

**Timing**

Restoration of continuity requires biological integration and MSC appear essential in initiating and orchestrating this. At the time of arthroscopic repair, very few MSC are present. In the rabbit model, opening the bone marrow attracted a maximal number of MSC 2 weeks after repair. In these first 2 weeks, the pull on the tendon, exceeding the suture holding power may already have caused an early re-tear, also called dehiscence, that will cause the eventual failure of the surgery. Timing is critical; if remaining dehisced, tendon-bone continuity will never be established. Review of the literature indicates that dehiscences occur rather early since the prevalence of re-tears varies little between studies with a follow up of 9 months (Postel=40%) and studies with a follow up of 4 years (Gazielly=41%). The presence of MSC in large numbers at the time of repair could significantly accelerate biological integration, prevent early dehiscence and achieve lasting continuity. One way is to attract bone-marrow derived MSC to the site of repair by opening a communication between bone marrow and the future tendon insertion site. In addition to regain access to MSC during arthroscopic repair, we propose to accelerate the repair with recruited, proliferated and activated MSC already present in large numbers at the time of repair.

Given the poor healing rate in surgically treated rotator cuff tears, novels techniques to improve healing rates should be sought. There is accumulating evidence that growth factors and pluripotential stem cells have a positive influence on tendon to bone healing. As the proximal humerus has an autologous source of red marrow and corresponding stem cells, this represents a potential source of such cells for the enhancement of tendon to bone healing. There are several potential benefits to using local, autologous cells in this fashion compared with the use of a scaffold materials and any of the available “carriers”; lower cost, technical ease, and most importantly the availability and recruitment of all growth factors, cytokines and stem cells rather than selecting individual factors in isolation. It is possible that the interplay between various growth factors and cytokines is as important as the presence itself of such individual cells and molecules. As we have demonstrated a significant healing reaction by T1 MRI ten days following surgical reinsertion of the rotator cuff in the rabbit model, it is biologically plausible that stimulating the tendon insertion area or cuff tendon prior to surgical repair will have two benefits. The first is the recruitment of MSC’s and associated cytokines and growth factors to the repair site prior to the repair. This may allow for a more vigorous healing response as MSC’s are present in greater numbers during healing. Second, by stimulating the bone or the tendon prior to repair, the healing rate may be accelerated leading to a lower re-tear rate. Acceleration of healing may be beneficial as a delay in healing can result in gap formation(37-39), which may in turn lead to fibrosis at the tendon insertion rather than healing with chondrocytes. This provides the rationale for study of adjunctive soft tissue or bone trephination for biologic augmentation of rotator cuff repair. Our primary hypothesis is that adjunctive bone trephination prior to arthroscopic cuff repair will lead to higher quality of life outcomes, as measured by the Western Ontario Rotator Cuff score, than soft tissue trephination. Our secondary hypotheses are that bone trephination will lead to higher functional outcomes, strength, lower re-tear rates, and a greater healing reaction (including recruitment of stem cells, cytokines, and growth factors) than soft tissue trephination. `

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## 4. Research Design, Methods and Analysis

**Primary research question**
Do patients who undergo a repair of the rotator cuff with adjunctive, pre-operative bone trephination have an improved disease-specific quality of life, as measured by the Western Ontario Rotator Cuff Index, (WORC), compared with adjunctive, pre-operative soft tissue trephination, at 24 months post-operatively?

**Secondary Research Questions**

1) What is the difference in functional outcome as measured by the Constant score, and the ASES score, at 24 months post operatively?
2) What is the difference in re-tear rate for cuff repair with adjunctive bone trephination, as measured by ultrasound, at six months and 24 months post-operatively, compared with adjunctive, pre-operative soft tissue trephination?
3) What is the difference in the early healing reaction, as measured by T1 quantitative MRI, at 6 weeks post operatively?
4) What is the histological, cellular and molecular composition of the soft tissue and bone healing reaction following soft tissue and bone trephination?

**Response variables**
The primary outcome measure is the Western Ontario Rotator Cuff Index (WORC).(40)

The secondary outcome measures are the Constant Score(41), the American Shoulder and Elbow Society standardized assessment of shoulder function (ASES)(42). Ultrasound will be used to determine re-tear rates. MRI evaluations will be carried out to determine the healing status of the rotator cuff. The histological, molecular and cellular composition of the healing matrix, harvested at the time of the cuff repair, will be analyzed.

**Null Hypothesis**
There will be no difference in quality of life outcome in patients who undergo pre-operative bone trephination compared with pre-operative soft tissue trephination prior to arthroscopic rotator cuff repair at 24 months post-operatively.

**Why is a trial needed now?**
Rotator cuff repair carried out with current techniques has shown favourable results in terms of pain relief. However the re-tear rates remain high and are associated with significant morbidity in terms of functional outcome and shoulder strength. As rotator cuff disease becomes ever more prevalent with our aging population, it is imperative to determine if healing rates can be improved with autologous stem cell enhancement with pre-surgical preparation of the tendon insertion site through trephination. This trial is necessary both to provide optimal care of our patients, and to do so in a fiscally responsible fashion.

**Give references to any relevant systematic review and discuss the need for your trial in the light of these reviews**
An advanced search of the clinical databases in Medline and Pubmed was undertaken.
There have been no systematic reviews or human comparative studies and only animal studies have been carried out to date. Favorable results in animal studies have been reported demonstrating the efficacy of growth factors, MSCs and cytokines to the insertion site in cuff repair. Hence the need for a study comparing the two different types rotator cuff insertion site preparation that may allow the benefit of local pluripotential stem cells as well as cytokines and growth factors to stimulate an increased healing response.

**How will the results of this trial be used?**

The results of the trial will provide valuable information regarding the best technique for managing the rotator cuff via repair. The data obtained from retear rates and quality of life measurements will enable

the authors to suggest recommendations that will lead to maximizing function and quality of life in patients undergoing rotator cuff repair. The information will be presented at national and international shoulder meetings, and publications will be sought in major orthopaedics journals.

### 4.1 THE PROPOSED TRIAL

**What is the proposed trial design?**

Single center, randomized controlled trial.

**Recruitment:** Up to 180 consecutive men and women, aged 18 or older with surgical indication for surgical repair of a full-thickness rotator cuff tear consulting one of two Ottawa shoulder surgeons (P. Lapner or J. Pollock). Both surgeons have extensive experience with arthroscopic cuff repair, and are both shoulder fellowship-trained subspecialists. When meeting inclusion and exclusion criteria and providing informed consent, they will be included in this randomized controlled trial. Up to 90 patients will be randomized in blocks of 10 consecutive patients to either a bone trephination group or a soft tissue trephination group. Treatment allocation will be stratified by surgeon. We require a sample size of 90 participants who have been randomized *and* received the intervention, and thus we will need to recruit up to 180 participants, as we have experienced a high percentage (~50%) of participants who were lost to follow up or excluded prior to randomization (reasons include cancelling surgery, not being available for the pre-operative trephination and withdrawing consent).

### 4.2 What are the planned trial interventions?

Standard arthroscopic repair of the rotator cuff tear will take place. Ten to 14 days prior to the repair, one of two techniques for preparation of the cuff insertion site will be used; either bone trephination or soft tissue trephination.

Ten to 14 days following the experimental procedure, the cuff repair operation will be carried out with standard technique. The two surgeons in the trial have adopted a standardized approach to arthroscopic cuff repair. Prophylactic antibiotics will be administered with either cefazolin or in the case of penicillin allergy, Clindamycin. An examination under anesthesia will be performed and documented. All will undergo a standard diagnostic arthroscopy. All shoulder pathology encountered will be documented on a standardized form. The surgical repair will proceed using standard arthroscopic technique. Peek suture anchors will be used to carry out the repair. The number of anchors used is at the discretion of the surgeon, and will be based on the size and complexity of the tear. Duration of the surgery will be between 60-120 minutes.

**Preoperative site preparation: Bone Trephination or Soft Tissue Trephination**
Both pre-operative procedures will be performed under local anesthesia. A mixture of lidocaine (5 mL, 2% and Marcaine 5 mL, 0.5%) will be injected into the subacromial space under sterile technique. The skin site will also be infiltrated.

After the local anesthetic is infiltrated, a 14 gauge core biopsy needle will be introduced percutaneously and under ultrasound guidance to the exposed area of the cuff insertion site. For the bone trephination, the needle will be advanced into the insertion site through the cortex and into the metaphyseal bone of proximal humerus. This procedure will be repeated such that a grid pattern of 4 holes in the insertion site will be created in a rectangular pattern.

The soft tissue trephination will be carried out in a similar fashion with percutaneous introduction of the needle. The needle will be advanced through the rotator cuff tissue stump at the insertion site but will not be advanced through the cortical bone. This procedure will be carried out in a grid pattern with 4 holes through the soft tissue created in a rectangular pattern.

An arthroscope will be used in both the soft tissue and bone trephination procedures, to further assist in guiding the needle to the precise location during the trephination procedure.

A 14 gauge needle was chosen for the trephination technique as this is large enough to create a tunnel through soft tissue or bone, can be used manually and does not require the use of power equipment, is small enough to allow for 4 trephination points without weakening the bone of the greater tuberosity but large enough to allow for bleeding and communication with the marrow. Such needles are typically used for core biopsy of tumours localized in bone. Ultrasound was chosen to guide the needle to the insertion site as this is a simple and cost effective method to provide needle localization. Its use has been well-established for use for needle localization in other disciplines.(43) The depth of the needle for bone trephination will be established by direct measurement on plain shoulder xrays.

If patients are interested in enrolling in the study, but are not willing to consent to an adjuvant procedure, patients will be offered the option of undergoing the trephination procedure at the time of the cuff repair. In this case, the intervention would be as follows:

Standard arthroscopic repair of the rotator cuff tear will take place. Immediately prior to tendon repair, one of two techniques for preparation of the cuff insertion site will be used; either bone trephination or soft tissue trephination.

The cuff repair operation will be carried out with standard technique. The two surgeons in the trial have adopted a standardized approach to arthroscopic cuff repair. Prophylactic antibiotics will be administered with either cefazolin or in the case of penicillin allergy, Clindamycin. An examination under anesthesia will be performed and documented. All patients will undergo a standard diagnostic arthroscopy. All shoulder pathology encountered will be documented on a standardized form. The surgical repair will proceed using standard arthroscopic technique. Peek suture anchors will be used to carry out the repair. The number of anchors used is at the discretion of the surgeon, and will be based on the size and complexity of the tear. Duration of the surgery will be between 60-120 minutes.

**Preoperative site preparation: Bone Trephination or Soft Tissue Trephination**
As part of the surgical preparation of the tendon insertion site, a 2 mm K-wire will be introduced under direct arthroscopic visualization to the exposed area of the cuff insertion site. For the bone trephination, the wire will be advanced into the insertion site through the cortex and into the metaphyseal bone of proximal humerus. This procedure will be repeated such that a grid pattern of 4 holes in the insertion site will be created in a rectangular pattern.

The soft tissue trephination will be carried out in a similar fashion. The wire will be advanced through the rotator cuff tissue stump at the insertion site but will not be advanced through the cortical bone. This procedure will be carried out in a grid pattern with 4 holes through the soft tissue created in a rectangular pattern.

A 2mm K wire was chosen for the trephination technique as this is large enough to create a tunnel through soft tissue or bone, is small enough to allow for 4 trephination points without weakening the bone of the greater tuberosity but large enough to allow for bleeding and communication with the marrow. The depth of the needle for bone trephination will be established by direct measurement on plain shoulder xrays.

**Post-operative Care and Physiotherapy**
All procedures will be carried out on an out-patient basis. Post-operative care will be identical in both groups and occur with close guidance from their physiotherapist.

Following repair of the rotator cuff, early passive motion of the shoulder is initiated. Both passive forward flexion and external rotation are implemented, as are passive pendular motions. The rehabilitation protocol will occur as follows:

- 0 to 6 weeks: pendulum exercises with progression to passive (assisted) exercise. A sling is worn for the first 4-6 weeks for protection.
- 6 -12 weeks: stretching and continuation of active-assisted exercise, including forward elevation and external rotation. Patients will be encouraged to begin gentle use of the shoulder (brushing teeth, combing hear etc).
- after 12 weeks: active/resistive exercise will be undertaken. Full use of the arm will be allowed. Restrictions will include heavy lifting below shoulder level, and lifting above shoulder level.
- After 6 months: no further restriction will be placed. Full home and work activity allowed.

**4.3 Proposed practical arrangements for allocating participants to trial**
A treatment allocation schedule will be produced under the supervision of the orthopedic research study coordinator. Allocation to either bone trephination or soft tissue trephination will occur in blocks of 10 in a randomized fashion. Treatment allocation will be determined when the patient is scheduled for surgery. Treatment allocation will be stratified by surgeon.

**4.4 What are the proposed methods for protecting against sources of bias?**
**Blinding:** Due to the nature of a surgical trial, the surgeon may not be blinded to the intervention. However, a trained MSK radiologist will carry out the post-operative imaging, both ultrasound and MRI, and will be blinded to the nature of the treatment. Further, an independent assessor will carry out the follow-up functional assessments and will be blinded. This will minimize the potential for biases introduced by the examiner when performing the physical assessment and recording data. The assessor will not have access to the patient chart prior to the examination. The patient will also be blinded to the treatment assignment. To help reduce the potential for observer bias, the physical examination and the administration of study questionnaires are standardized.

**Control of contamination and co-intervention:**
Co-interventions will be documented. These are to include physiotherapy including the number of sessions and the nature of the physiotherapy intervention. The type and frequency of pharmaceutical agents used by the patient post-operatively will also be documented. In addition, all intraoperative adjunctive procedures will be documented, as well as details of the treatment method and implants used.

**Ensuring complete follow-up:** The following measures will help to ensure completion of follow-up: a) study patients will supply their own address, telephone, and email information, and the name, relationship, address, telephone, and email information of someone who does not reside with the patient, but is likely to have contact with them should they move or change telephone information, b) patients will receive a copy of the consent form which will outline the purpose of the study, the importance of their individual participation and attendance for follow-up assessments, and c) the research coordinator will maintain regular contact with the patients.

**4.5 What are the planned inclusion/exclusion criteria?**

**Patient Population**
The target population is both men and women of any 18 or older with full-thickness tears of the rotator cuff who have failed 6 months of conservative management.

**B. Inclusion Criteria**
1. Patients who have failed standard non-surgical management of their rotator cuff tear, and who would benefit from a surgical repair of the cuff.

Failed medical management will be defined as persistent pain and disability despite adequate standard non-operative management for 6 months. Medical management will be defined as:
a) The use of drugs including analgesics and non-steroidal anti-inflammatory drugs
b) Physiotherapy consisting of stretching, strengthening and local modalities (ultrasound, cryotherapy, etc)
c) Activity modification

2. Imaging, and intra-operative findings confirming a full thickness tear of the rotator cuff.

**C. Exclusion Criteria**
**Preoperative**

1. Characteristics of the cuff tear that render the cuff irrepairable: fatty infiltration in the muscles grade III (50%) or greater; superior subluxation of the humeral head; retraction of the cuff to the level of the glenoid rim.
2. Partial thickness cuff tears.
3. Significant shoulder comorbidities e.g. Bankart lesion, osteoarthritis
4. Previous surgery on affected shoulder e.g. Previous rotator cuff repair.
5. Patients with active worker's compensation claims
6. Active joint or systemic infection
7. Significant muscle paralysis
8. Rotator cuff tear arthropathy
9. Charcot's arthropathy
10. Significant medical comorbidity that could alter the effectiveness of the surgical intervention (eg. Cervical radiculopathy, polymyalgia rheumatica)
11. Major medical illness (life expectancy less then 1 year or unacceptably high operative risk)
12. Unable to speak or read English/French
13. Psychiatric illness that precludes informed consent
14. Unwilling to be followed for 24 months
14. Advanced physiologic age

**4.6 What is the proposed duration of treatment period?**
The insertion site preparation procedure is approximately 15 minutes in duration in total length. All patients follow the same surgical procedure to repair the cuff 10-14 days following preparation, and the same post-operative protocol and a follow-up period of 24 months following cuff repair.

**4.7 What is the proposed frequency and duration of follow-up?**
Patients are to be assessed in the clinic by the blinded evaluator at post-operative intervals of 3, 6, and 12 and 24 months post operatively. The primary outcome evaluation occurs at the 24 month evaluation. At each clinical follow up, the patient will be assessed with the clinical outcome measures. It is anticipated that at each clinic visit approximately 20 minutes will be spent with the assessor. However, as in all doctors' clinics, some waiting can be anticipated and this can be variable depending on clinic loads and nature of cases.

Radiographic analysis will be done with a high-resolution ultrasound at 6 and 24 months following surgical repair. An MRI T1 quantitative sequence will be carried out 6 weeks following surgical repair. An independent investigator trained in MSK radiology will perform evaluation of the imaging.

**4.8 What are the proposed primary and secondary outcome measures?**
**PRIMARY:**
2) The Western Ontario Rotator Cuff Index (WORC)(40) is a disease specific evaluation that has proven to be an accurate and valid assessment of function after rotator cuff repair. Because it is specific for rotator cuff disease of the shoulder, it is highly sensitive to small but clinically significant changes in patient function.

**SECONDARY:**

1) The American Shoulder and Elbow Surgeon's (ASES) score is a shoulder specific assessment tool developed by the American Shoulder and Elbow Society for use in all types of shoulder problem(42). It consists of both patient self-assessment and physician assessment. The patient self-evaluation is divided into two sections: pain and activities of daily living (ADL). Pain is recorded on a visual analogue scale and ADL's are recorded on a numeric scale. The overall score is an equal weight of the two sections and produces a score out of 100. The higher the score, the better the outcome. The physician assessment is divided into four segments: range of motion, physical signs, strength and instability. The results of the physician assessment do not provide a score.

Europeans favor the Constant Score(41). It has been validated, and normalized in comparison to disease free patients and places greater emphasis on range of motion and strength The European shoulder society has adopted the Constant Score for functional assessment of the shoulder. The Constant Score records a variety of shoulder measurements including an objective test of strength using a spring loaded measuring device. The Constant Score reflects an overall clinical functional assessment. This instrument is based on a 100-point scoring system calculated from a self-assessment portion that evaluates pain and ability to perform tasks of daily living, and a clinical assessment which tests active range of shoulder motion and strength. The higher the score the better the outcome.

2) High-resolution ultrasound will be used as the primary outcome measure to determine the re-tear rate at 6 and 24 months following repair. Ultrasound was chosen as it has been shown to have a high degree of accuracy for the diagnosis of rotator tears that is equivalent but less expensive than MRI.(44)

3) Further secondary outcomes which will be monitored during the post-operative course include: operative times of the two procedures, complications, and the incidence of revision surgery in each procedure.

4) Quantitative T1 MRI will be used to determine the degree of early healing reaction of both procedures. Additional sequences will be carried out to assess the degree of proteoglycan and collagen within the healing substrate.

5) Samples: X grams of tissue will be harvested at the surgical tendon insertion site with a curette. This will include, in the trephination group, an organized blood clot, and superficial bone removed to prepare the surgery. This tissue will be representative of the cellular and extracellular environment at the time of attachment.

Cell identity at the enthesis:
1. Combination of RT-PCR and immunocytochemistry.
1A. Cell isolation and culture: tissue will then be cut into 2mm pieces and digested with 3 mg/ml colleganase type I and 4 mg/ml dispase to generate single-cell suspensions.
1B. Real time PCR: Single-cell suspension of tendon-derived cell will be used to establish the gene expression profile. For each suspension, total RNA will be isolated (expected yield 20 ng and 70 ng RNA/mg wet weight, consistent with the low cellularity of tendon). The quantity and quality of isolated mRNA will be assessed using a Bioanalyzer available in our Department to measure the ratio of absorbance at 260 nm to 280 nm. Isolated RNA will be diluted to 1 ng/ml and stored at -70oC as aliquots, which will be thawed once only. Complementary DNA (cDNA) will be prepared using SuperScript II (Invitrogen), and primed using random hexamers according to the manufacturer's instructions. Two hundred fifty ng RNA will be used for cDNA preparation. The cDNA will be stored at -20oC until required for quantitative real-time PCR. Specific primers and fluorogenic probes for PCR amplification were chosen to detect gene expression profiles related to tendon, cartilage and bone as already published (Table I). To control against amplification of genomic DNA, primers were chosen, where possible, so that amplicons crossed intron-exon boundaries. The 18S ribosomal RNA gene will be used as an endogenous control to normalize for differences in the amount of total RNA in each sample. PCRs will be performed using the ABI Prism 7700 Sequence Detection System according to the manufacturer's protocol.

Table I. List of genes for expression measurement

Bone: osteopontin (Spp1), bone sialoprotein (Ibsp), alkaline phosphatase (AKP1), OSTEOCALCIN (BGLAP1).
Cartilage: Collagen type II and aggrecan
Tendon: scleraxis (Scx), cartilage oligomeric protein (Comp), Sox9, Runt-related transcription factor (Runx2), tenomodulin (TNMD), Tenascin C, fibronectin, type I collagen.
1C. Immunocytochemistry: Single cell suspensions of tendon-derived cells will be fixed with 4% paraformaldehyde in PBS at 25oC for 20 min and immunostained with primary antibodies for 1hr at room temperature or overnight at 4oC. An immnoperoxidase assay will then be used to detect the immunoactivity after incubation with a secondary antibody. Presence of stem cells will be associated with immunoreactivity positive for: collagen type I, alpha- smooth muscle actin, Comp, tenascin C, fibronectin and negative for: collagen type II and aggrecan.
2. Colony-forming efficiency: Single-cell suspensions will be cultured in a-MEM supplemented with 20% FBS, 100 mM 2-mercaptoethanol, 100U/ml penicillin and 100mg/ml streptomycin for 8-10 days at 37oC under a 5% CO2 atmosphere. Cells will be cultured in 25-cm2 flask and inspected daily under the microscope for 9 days. At the end of the 9-day period, colonies that had formed from single cells will be visualized using methyl violet staining and counted as an indication of the potential clonogenicity.
3. Extracellular matrix: the unique tendon-specific parallel alignment of collagen fibers is able to reflect polarized light. Goldner's trichrome staining. Sharpey's fibers are condensed collagen fibers that insert into the bone.
4. Indicators of tendon matrix formation: the ratio of collagen types I and III and decorin (expect increases). Glutamate production (produced and released by tenocytes) is increased in tendinosis and can be detected by measuring mRNA and proteins corresponding to glutamate transporters VGluT1 and VGluT2. Excessive glutamate production is associated with changes in extracellular tendon matrix metabolism. Decorin regulates assembly of collagen fibrils and acquisition of biomechanical properties during tendon development.
5. Dynamic equilibrium between synthesis and degradation of the tendon extracellular matrix. Degradation of the tendon ECM is principally mediated by proteinases of the metalloproteinase group; MMP, ADAM, ADAMTS families. Five members of the MMP family including MMPs 1, 2, 8, 13 and 14, have been associated with activity against fibrillar collagen of the tendon. The ADAM family members may participate in inflammatory processes. The ADAMTS family consists of procollagen propeptidases (ADAMTS-2, -3, AND -14) and aggrecanases (ADAMTS-1, -4, -5, -8, -9, and -15) are implicated in tendon-matrix turnover. Of interest, ADAMTS-4 has been shown to cleave other, nonproteoglycan ECM components such as cartilage oligomeric matrix protein, fibromodulin, and decorin. The tissue inhibitors of metalloproteinases (TIMPs) family contain 4 human gene products that are physiologic inhibitors of metalloproteinases. TIMP-3 is the most potent inhibitor of members of these families. The local balance of metalloproteinases and TIMP proteins is likely to be of importance in the correct maintenance of tendon ECM.

**4.9 How will the outcome measures be measured at follow-up?**
The collection and administration of all outcomes and examinations are standardized and are clearly outlined in the Study Protocol Manual. Surgeons and research assistants will have met on several occasions to discuss and review this protocol.

**PRIMARY:**
The patients will complete the WORC Score questionnaire pre-operatively and at 3, 6 12 and 24 months post-operatively. The research assistant, blinded to treatment allocation, will be available to answer any questions. The patient will be examined by the blinded research assistant in a standardized fashion. The surgeon is the last person to examine the patient.

**SECONDARY:**

The patients will complete the ASES and Constant Score questionnaire pre-operatively and at 3, 6 12 and 24 months post-operatively. The research assistant will be available to answer any questions. The patient will be examined by a blinded assessor in a standardized fashion. The surgeon is the last person to examine the patient and is blinded to the results of the outcomes.

The interpretation of the high-resolution ultrasound is based on healing status and will be carried out by a trained MSK radiologist. Healing status will be documented at both 6 and 24 months as either completely healed, partially healed, or not healed. For tendons partially healed or not healed, the size of the defect will be compared with the size of the tear pre-operatively.

The quantitative T1-MRI will be interpreted by a trained MSK radiologist.

Analysis of the healing matrix will be carried out as described above.

**4.10 What is the proposed sample size and what is the justification for the assumptions underlying the power calculations?**
The sample size calculation was based on a scale score of 71.31 and standard deviation of 30.43. The authors are assuming superiority from historical controls. Superiority would be considered a difference of more than 30%, or 21.4 points on the WORC scale, from the expected mean. With alpha at 0.05 and power 0.80, the sample size was determined at 33 per group. With a foreseen dropout rate of 25%, we would therefore seek 45 patients per group.

We have experienced a much higher than anticipated rate of withdrawal (~50%) which has mainly been due to 'loss to follow up', or being excluded at the time of surgery, in particular, there has been a large number of participants who signed the consent and completed baseline measures, but never booked a surgery, were not available for the pre-operative trephination procedure, or withdrew consent prior to randomization. Given that we require a sample size of 90 participants who have been randomized *and* received the intervention, we would like to recruit up to 180 participants, however, recruitment will be ceased once 90 participants have been randomized and received the pre-operative intervention.

**4.11 What is the planned recruitment rate?**
With two surgeons enrolling patients, we plan to recruit 60 patients per year. Recruitment will be completed in a 18 month time-frame. This recruitment rate is expected based on two previous RCT studies conducted at our center with a similar patient population.

**4.12 Are there likely to be any problems with compliance?**
This being a surgical trial, there is no opportunity for patients to avoid complying with their assigned intervention. It is unlikely that any crossovers would occur from one surgical treatment to the other. It is also unlikely that conversion to open surgery will occur based on the surgeons' previous experience with this procedure and patient population.

**4.13 What is the likely rate of loss to follow-up?**
Patients are called by the research assistant two to four days before their appointment. Patients will normally reside within 90 minutes traveling time of their surgical centre. Patients who do not attend their appointment are rescheduled. If the patient misses their re-booking then the surgeon will phone the patient to encourage their attendance. In the event that a patient chooses not to return for a follow-up, the questionnaires are mailed out with a stamped return envelope. Patients that can no longer be followed by their original surgeon may be followed at another collaborating center. Research assistants in both cities will communicate to arrange follow-up appointments and maintain contact with the patient.
It has been our experience that these patients are compliant with their clinic follow-ups. The sample size calculation takes into account a 10% loss to follow-up rate. Every effort will be made to minimize this occurrence.

**4.14 Details of planned analyses**

**Primary:**

Primary analyses involve a comparison of the mean WORC scores with control data from patients who have undergone an arthroscopic cuff repair, without trephination, obtained through our prospective database. This analysis is a two-tailed unpaired t-test to assess whether there is a statistically significant difference between groups for the mean WORC scores at all time points. The 5% significance level is employed. The underlying assumption for the WORC score data is that there is a normal distribution. If the sample distribution is determined to depart from normal, then a Wilcoxon rank sum test will be performed.

**Secondary:**

Similar analysis will be carried out for the functional outcome scores. The ASES, Constant Score, and U/S healing rates will be analyzed for differences at 24 months. The planned secondary analyses are performed using a 5% significance level. The secondary outcomes will be analyzed using appropriate statistics; t-tests for continuous and chi-square for dichotomous variables.

Interpretation of the MRI data will involve a comparison of the quantitative T1 signal intensity.

**4.16 What is the proposed frequency of analyses?**

The analysis will occur at 24 months post-surgery. An interim analysis of data will take place once 6 months follow data is available for 50% of the cohort, in order to monitor for adverse events in the study group. Possible adverse events include hematoma formation in the shoulder, infection, and fracture of the greater tuberosity. Adverse events will be documented on standardized forms, including the severity of the adverse events. A data safety monitoring committee has been set up. The committee will consist of two surgeons, Dr. Joel Werier and Dr. Alan Giachino, both with extensive knowledge and experience in the area of shoulder and cuff surgery. Neither surgeon is involved in the trial. Any severe adverse events will be reported to the committee within one week of occurrence. At the time of interim analysis, the committee will determine, based on their collective experience, whether the trial should be stopped based on the frequency or severity of adverse events. The committee will review the interim analysis data primary outcome with the assistance of a statistician from the methods center. It is unlikely that the trial will be stopped due to demonstration of superiority, given the relative small numbers in the trial, but may be recommended by the committee if a difference is demonstrated at $p>0.0001$.

**4.18 What is the estimated cost and duration of the trial?**

The duration of the trial will be 48 months total – 24 months of recruitment and 24 year for patients to reach the endpoint of the study. Please see attached budget for associated costs.

**DETAILS OF TRIAL TEAM**

**Trial management:**

**What are the arrangements for day to day management of the trial?**

The orthopedic research study coordinator is responsible for the day to day management of the trial. This includes: general administrative details, implementing randomization, collecting, monitoring, tracking and analyzing data. The Study Research Coordinator (SRC) has experience in biostatistics, computer technology, epidemiology and study management. He/she is available to answer questions on a daily basis. **Quality Monitoring: Forms**: All forms are checked by the SRC for completeness, consistency and extreme values. **Appointments**: The SRC is responsible for monitoring participant visits **Equipment**: The scales used to measure power are calibrated. **Data Management:** is supervised by the study biostatistician. Data is collected on standardized Case Recording Forms (CRF). Any revisions to the CRF's are dated to maintain an audit trail of these changes. CRF's are signed and dated by the clinical investigator.