IDE Number G150268: BEAR® Implant

A Prospective, Randomized, Controlled, Clinical Trial Evaluating the Non-Inferiority of Bridge-Enhanced ACL Repair (BEAR) to ACL Reconstruction with an Autologous Tendon Graft (ACLR)

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INVESTIGATIONAL PLAN

A Prospective, Randomized, Controlled, Clinical Trial Evaluating the Non-Inferiority of Bridge-Enhanced ACL Repair (BEAR) to ACL Reconstruction with an Autologous Tendon Graft (ACLR)

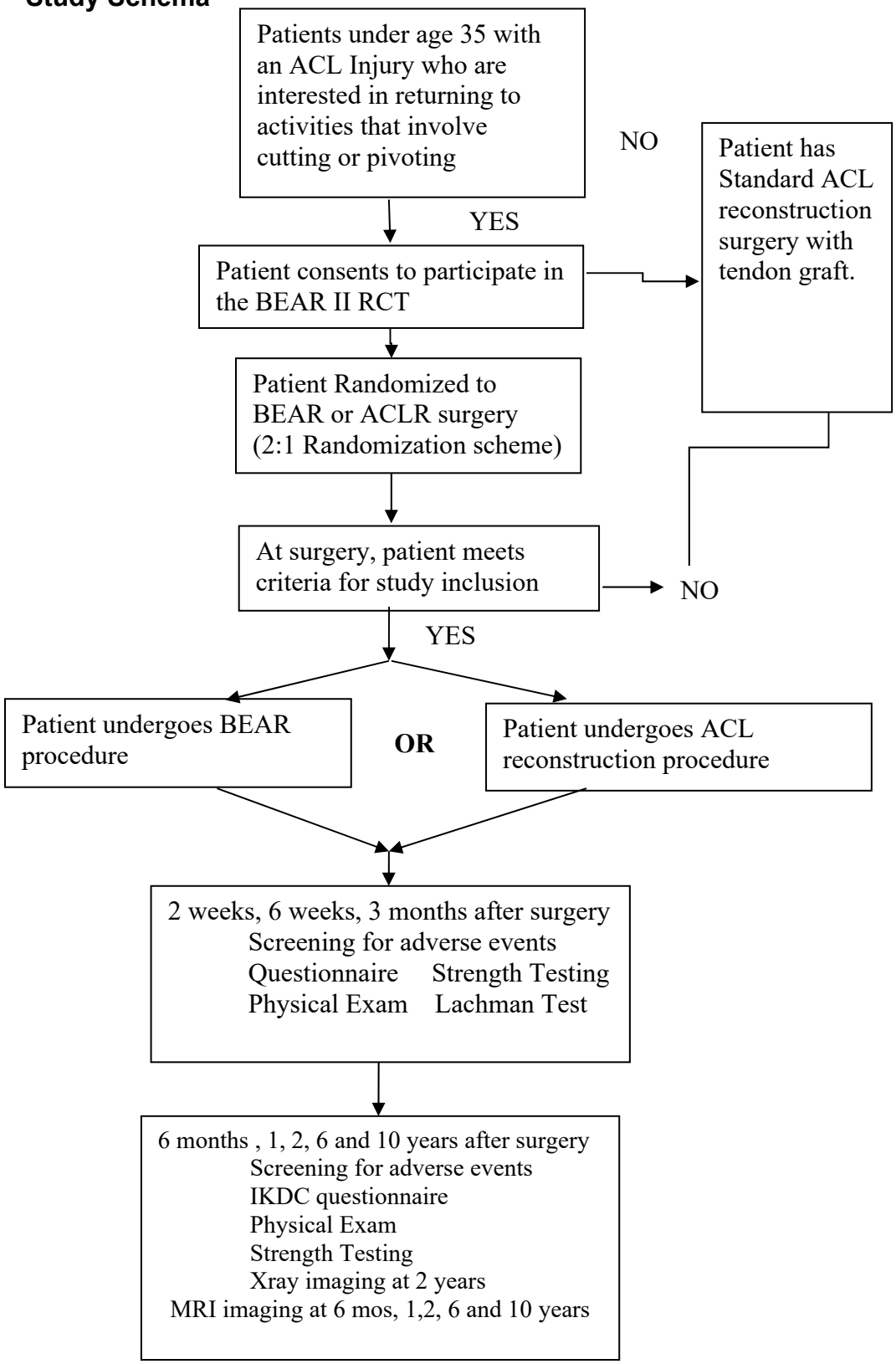
Study Sponsor:	**Miach Orthopaedics, Inc.**
Sponsor Contact:	[redacted]
Study Device:	**Extracellular Matrix Based Scaffold (BEAR® Implant)**
Protocol Short Title	***BEAR II Trial*** ***Bridge-Enhanced ACL Repair II***

Study Device	Anterior Cruciate Ligament Repair Scaffold/BEAR® Implant
IDE number:	G150268

1.1 List of Abbreviations

ACL	Anterior Cruciate Ligament
AOSSM	The American Orthopaedic Society for Sports Medicine
BCH	Boston Children's Hospital
BEAR	Bridge-Enhanced ACL Repair Implant
CRF	Case report forms
EQuIP	Education and Quality Improvement Program at Boston Children's Hospital
IKDC	International Knee Documentation Committee (validated patient questionnaire for assessing knee function)
LCL	Lateral Collateral Ligament
MCL	Medial Collateral Ligament
MOON	Multicenter Orthopaedic Outcomes Network (previously established prospective cohort of over 3000 patients who have had ACL reconstruction)
MOP	Manual of Operating Procedures
MRI	Magnetic Resonance Imaging
PCL	Posterior Cruciate Ligament
REDCap	Research Electronic Data Capture data management system
ROM	Range of Motion
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Event
VAS	Visual Analog Score for Pain

1.2 **Study Schema**



1.3 Study Summary

Title	**B**ridge-**E**nhanced **A**CL **R**epair II Trial
Short Title	BEAR II Trial
Protocol Number	CP-02-001
Phase	Pivotal Trial
Methodology	Single center, 2-arm, randomized, controlled clinical trial. 2:1 Randomization Scheme.
Study Duration	14 years
Study Center(s)	Single-center, Boston Children's Hospital.
Objectives	To determine the efficacy of the BEAR® implant and demonstrate its non-inferiority to the standard of ACL reconstruction in terms of knee stability and patient reported outcomes, as well as its superiority in terms of regaining muscle strength at 3, 6, and 12 months after surgery. Additional objectives are to determine if safety outcomes including infection, graft rejection, and need for further surgical procedures are different between patients undergoing the BEAR procedure and those undergoing ACL reconstruction, as well as if markers of early osteoarthritis are clinically different in the two groups at the two year time point. Subjects will be followed up at 6 and 10 years post-surgery to evaluate long-term outcomes and osteoarthritis.
Number of Subjects	Up to 100 (up to 67 with bridge-enhanced ACL repair, and up to 33 with autograft ACL reconstruction)
Diagnosis and Main Inclusion Criteria	Anterior cruciate ligament injury, within 45 days of injury
Study Product(s), Dose, Route, Regimen	BEAR® Implant
Duration of administration	Single administration at surgery; implant resorbed over approximately 8 weeks
Reference therapy	ACL reconstruction with autograft tendon
Statistical Methodology	Noninferiority testing for the Bridge-Enhanced ACL Repair procedure vs. the ACL Reconstruction procedure will be performed with the primary outcome measures of IKDC patient reported outcome and AP knee laxity. Noninferiority analysis will be based on comparing the 95% confidence interval for each primary outcome to pre-specified noninferiority margins.

1.4 Background and Significance

1.4.1 *Disease Background*

The annual incidence of anterior cruciate ligament (ACL) injury in the US is estimated at 1 per 1,000 people [46]. ACL injuries have immediate and long-term effects on the quality of life, and are known risk factors for post-traumatic osteoarthritis [47]. In the past, surgeons tried to repair the ACL; however, it failed to heal in over 90% of patients [48]. The reason for this was unknown. Thus, the current gold standard of treatment, ACL reconstruction, which involves removal and replacement of the ligament with a tendon graft, has become popular (**Figure 1**). However, patients treated with ACL reconstruction continue to exhibit progressive articular cartilage and joint damage in the injured knee. A recent prospective cohort study suggests that 62% of ACL reconstructed patients with an isolated ACL injury presented with radiographic evidence of posttraumatic osteoarthritis 10–15 years post-surgery [49]. Considering that many patients sustain ACL injuries before the age of 16, these injuries may place young patients at risk for premature post-traumatic osteoarthritis before age 30 even with our current best treatment methods.

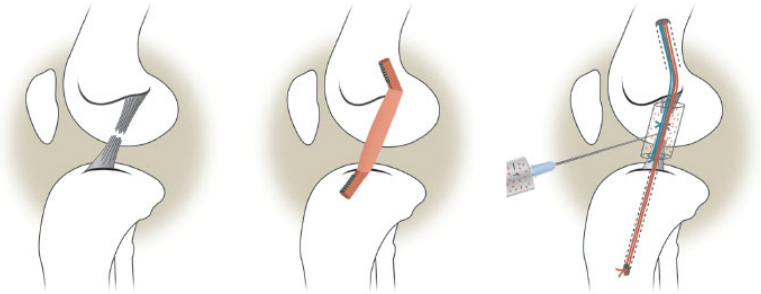


Figure 1: Schematic demonstrating an ACL tear (left panel), our current method of treatment with removal of the ACL and replacement with a tendon graft (ACL reconstruction, middle panel) and the novel treatment of repair and regeneration we have developed from this injury ("Bridge-enhanced ACL repair," right panel).

1.4.2 *Study Device Background and Associated Known Toxicities*

1.4.2.1 Device Description

The BEAR® device is a bovine collagen based implant (**Figure 2**). The bovine tissue is sourced from New Zealand (which is a country free of bovine spongiform encephalopathy) and is further treated to remove bovine cell fragments and DNA. The manufacturing process is completed using aseptic conditions and no serum or cells are introduced in the process. The resulting implant is terminally sterilized using electron beam irradiation. Lot testing of the implant has confirmed sterility of the implant after sterilization and has also confirmed the absence of bovine viruses.

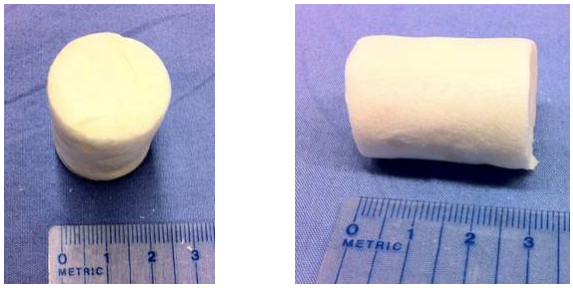


Figure 2: The collagen device prior to implantation (Scale = centimeters).

1.4.2.2 The principle of operation of the device

The primary device reported above will be implanted at the time of surgical stabilization of the ACL with sutures as previously reported. In brief, surgical stabilization is accomplished as previously performed for non-enhanced ACL repair with devices previously approved by the FDA for soft tissue repair (sutures and cortical buttons). This repair will be accomplished using sutures and two cortical buttons (Endobutton from Smith and Nephew or equivalent device as deemed by the FDA). The sutures to stabilize the knee will be made of Ethibond. Two #2 Ethibond sutures will be used to reconnect the femur and tibia, and a #2 Vicryl suture used to pull the tibial ACL remnant toward the femoral attachment site. Once implanted, the patient's own blood is added to the implant and saturates it. The blood clots within the implant and the implant stabilizes the clot in the gap between the torn ligament ends. The implant is replaced within 2 to 3 weeks with ACL cells and native collagen and blood vessels consistent with fibrovascular repair tissue.

1.4.2.3 Device implantation

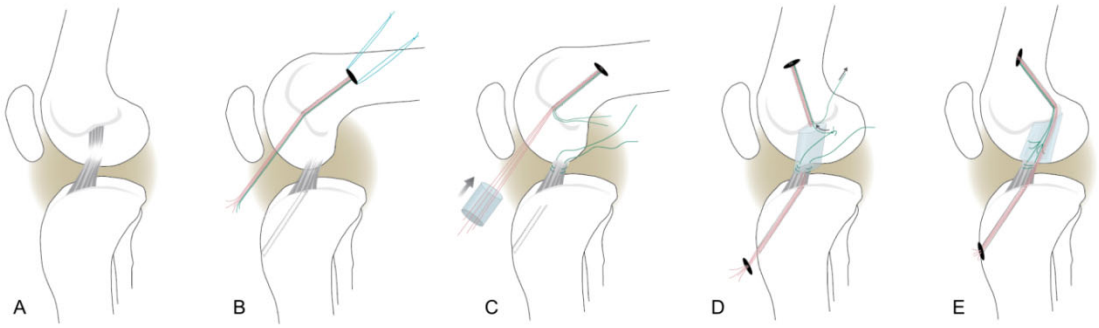


Figure 3: Stepwise demonstration of the "bridge-enhanced ACL repair" technique using the collagen device (seen first in C where it is threaded onto sutures). In this technique, the torn ACL tissue is preserved (A). Small tunnels (4 mm) are drilled in the femur and tibia and an extracortical button with sutures attached to it is passed through the femoral tunnel and engaged on the proximal femoral cortex. One set of sutures from this extracortical button is threaded through the collagen implant, tibial tunnel and secured in place with a second extracortical button (red sutures). A second set of sutures (green) from the Endobutton were tied to the Kessler suture placed in the tibial stump of the ACL

(green sutures). The collagen device is then saturated with 5 cc of the patient's blood. The collagen device is not load bearing, the initial strength of the repair is dependent on the suture repair of the ACL. The ends of the torn ACL then grow into the collagen implant and the ligament reunites.

The implant device works by immobilizing the blood in between the two torn ends of the ligament. It is not load bearing. The suture repair of the ACL is the load bearing structure for the repair, as it has been in past studies of ACL repair.

1.4.2.4 Device Mechanism

The device is porous and can absorb blood. The device immobilizes the autologous blood in the ligament wound site and as the blood naturally forms a clot, or provisional implant, the device is able to protect the clot and maintain it within the wound site. The blood clot goes on to release the wound healing growth factors and proteins [8, 15] which are effective in healing ligaments that are outside the joint (medial collateral ligament) and in preclinical models, are able to stimulate the ingrowth of surrounding cells into the implant [28, 58, 60]. This scar has been shown to have strength similar to that of an ACL tendon graft in the porcine model at 3, 6 and 12 months after surgery [36, 40]. The only function of the device is to keep the blood in the wound site and protect it from being prematurely washed away by the synovial fluid in the joint.

1.4.2.5 Other Agents/Devices

The implant described above is designed to be implanted at the time of surgical stabilization of the ACL with sutures as previously reported. In brief, surgical stabilization is accomplished as previously performed for non-enhanced ACL repair with devices previously approved by the FDA for soft tissue repair (sutures and cortical buttons). This repair will be accomplished using sutures and two cortical buttons (Endobutton from Smith and Nephew or equivalent device as deemed by the FDA. The sutures to stabilize the knee will be made of Ethibond. Two #2 Ethibond sutures will be used to reconnect the femur and tibia, and a #2 Vicryl suture used to pull the tibial ACL remnant toward the femoral attachment site.

Once implanted, the patient's own blood is added to the implant and saturates it. The blood clots within the scaffold implant and the implant stabilizes the clot in the gap between the torn ligament ends. The implant is replaced within 2 to 3 weeks with ACL cells and native collagen and blood vessels consistent with fibrovascular repair tissue.

1.4.3 *Summary of non-clinical in vitro/in vivo studies*

1.4.3.1 Efficacy in Preclinical Models

Recent ACL bridge-enhanced repair studies in three large animal models have demonstrated that placement of the extracellular matrix device in the injury site of the ACL can stimulate biological and mechanical healing of the ligament [2, 22, 23, 28, 30, 31, 58, 59, 94]. With the current treatment model, the mechanical properties of the ACL bridge-enhanced repair are equivalent to those of an ACL reconstruction at 3, 6 and 12 months after surgery (**Figure 4**).

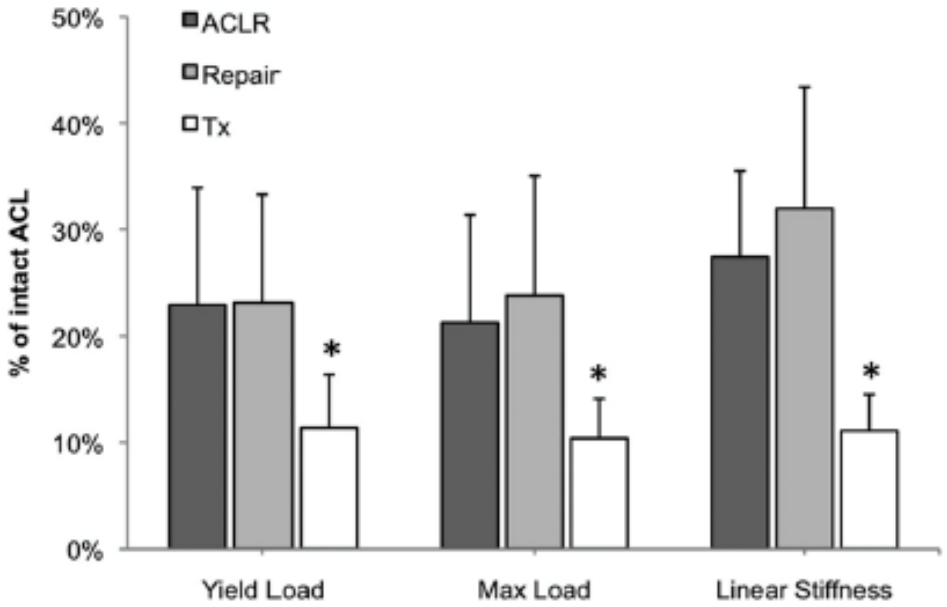


Figure 4: Tensile structural properties of the bridge-enhanced stress-protected ACL repair (labeled as Repair) were identical to those of ACL reconstruction (labeled as ACLR) with a graft in a randomized large animal study (n = 8/group; $p > 0.60$ for all parameters). Both treatment groups had a more functional repair than that of the untreated ACL transection.

In addition, it has also been recently reported that the stimulation of ligament repair and regeneration using the "bridge-enhanced ACL repair" (BEAR) technique prevents the development of post-traumatic osteoarthritis after an ACL injury [40]. In the most recent study, 80% of the knees that had a conventional ACL reconstruction developed post-traumatic osteoarthritis while the knees in the bridge-enhanced ACL repair group (BEAR) did not 1 year after surgery (**Figure 5**).

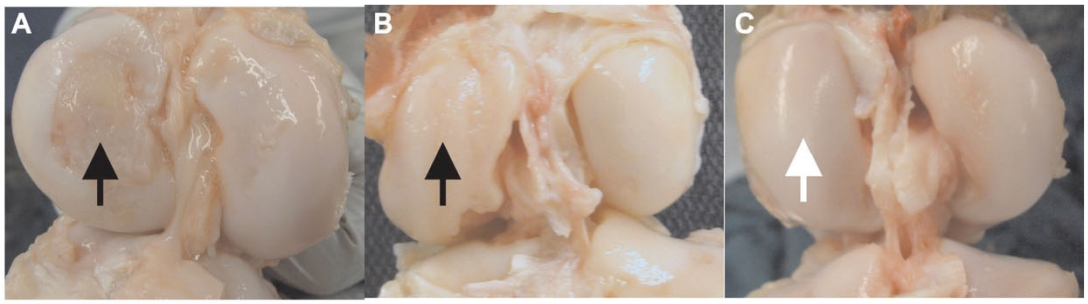


Figure 5: The distal femur cartilage 1-year after (A) an untreated ACL rupture, (B) after conventional ACL reconstruction, and (C) after bridge-enhanced ACL repair. Note the damage to the medial femoral condyle in the untreated and ACL reconstructed knees (black arrows) and the lack of damage in the medial femoral condyle in the bridge-enhanced ACL repaired knee (white arrow).

1.4.3.2 Safety in Preclinical Models

1.4.3.2.1 Sterility Testing

Sterility testing was performed for each lot prior to release. A Sterility Testing Qualification study was performed by Microtest, Inc, for the implant and the BEAR® implant was successfully validated for USP<71>/EP 2.6.1 Sterility testing. Subsequent lots (071301A/B, 081301B/C, 081302A/B/C) were each tested for sterility according to specification USP 36<71>/EP 2.6.1 and no growth was found, thus the implants passed the lot sterility testing.

1.4.3.2.2 Viral testing

A literature review of our processing methods and the ability of similar methods to eliminate the four classes of virus (RNA, DNA, enveloped, non-enveloped) was conducted. The three steps of acidic pH, detergent and 15 kGy electron beam terminal sterilization are all used in our processing. In previously published literature, the use of an acidic environment results in a reduction in viral load by 10^3 to 10^8. The use of Triton X as a detergent results in a reduction in viral load by 10^5 to 10^7. The use of electron beam at 13 to 18 kGy for allograft tissue results in a reported reduction by 10^6. The BEAR™ manufacturing process incorporates all of these steps. For our investigational device exemption studies, we will continue to perform lot testing for the presence of virus for the four classes of virus (DNA+, DNA-, RNA+ and RNA-(Charles Rivers Laboratories ,Wilmington, MA; STM-V-615.3, *In Vitro* Test for Bovine Adventitious Agents (9 CFR) in Products Other than Bovine Serum).

Prior testing for the presence of bovine virus has been conducted on all lots of implants designated for clinical/human use. In brief, testing was performed at Charles River Laboratories under GLP conditions. Samples of our implant were hydrated and portions of the resulting solution inoculated in duplicate into cell cultures that are generally susceptible to bovine viruses. The inoculated cultures were maintained for 21 days, with subcultures taken at 7 and 14 days post-inoculation. Spot slides were prepared for the detection of the following bovine viruses (Bovine Adenovirus Type 3, Bovine Parvovirus, Rabies Virus ERA Strain, Reovirus Type 3, Bovine Viral Diarrhea Virus, Blue Tongue Virus Type 10, Bovine Respiratory Syncytial Virus) and fluorescent antibody staining used to identify the presence of virus. Hemadsorption testing of parainfluenza virus-inoculated positive controls was also performed on Day 21 samples as an additional test. There was no evidence of bovine virus in the implant material.

1.4.3.2.3 Biocompatibility

Biocompatibility testing was performed at NAMSA according to the requirements of the International Organization for Standardization 10993-1, Biological evaluation of medical devices, Fourth Edition 2009-10-15. The following tests were performed under GLP conditions:

- Cytotoxicity Study Using the ISO Elution Method (V0014)
- ISO Maximization Sensitization Study - Extract (T261)
- ISO Intracutaneous Study with Sponsor Provided Control - Extract (T251)
- ISO Systemic Toxicity Study - Extract (T0625)

- Genotoxicity, Bacterial Reverse Mutation Study (V0023)
- Genotoxicity, in vitro Chromosomal Aberration Study in Mammalian Cells - Extract (V002)
- Genotoxicity, Mouse Peripheral Blood Micronucleus Study (T0566)
- ISO Muscle Implantation Study - 2 week (T250)
- 6 week Systemic Toxicity Study in Rats Following Subcutaneous Implant (T0118)

The results of the studies are summarized below.

1.4.3.2.3.1 Cytotoxicity Study: 10993-Part 5

A single preparation of the test article was extracted in single strength Minimum Essential Medium (IX MEM) at 37°C for 24 hours. The negative control, reagent control, and positive control were similarly prepared. Triplicate monolayers of L-929 mouse fibroblast cells were dosed with each extract and incubated at 37°C in the presence of 5% C02 for 48 hours. Following incubation, the monolayers were examined microscopically for abnormal cell morphology and cellular degeneration.

- The test article extract showed evidence of causing slight cell lysis or toxicity.
- The test article extract met the requirements of the test since the grade was less than a grade 2 (mild reactivity).

1.4.3.2.3.2 Maximization Sensitization Study - Extract (T261; 10993-10).

The test article, the BEAR™ implant, was evaluated for the potential to cause delayed dermal contact sensitization in a guinea pig maximization test. This study was conducted based on the requirements of ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. The test article was extracted in 0.9% sodium chloride USP. The extract was intradermally injected and occlusively patched to ten test guinea pigs. The extraction vehicle was similarly injected and occlusively patched to five control guinea pigs. Following a recovery period, the test and control animals received a challenge patch of the appropriate test article extract and the vehicle control. All sites were scored for dermal reactions at 24 and 48 hours after patch removal.

- The test article extract showed no evidence of causing delayed dermal contact sensitization in the guinea pig.
- The test article was not considered a sensitizer in the guinea pig maximization test

1.4.3.2.3.3 Intracutaneous Study with Sponsor Provided Control - Extract (T251; 10993-10)

The test article, the BEAR™ ACL implant, was evaluated for the potential to cause irritation following intracutaneous injection in rabbits. This study was conducted based on ISO 10993-10, Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization. The test article was extracted in 0.9% sodium chloride USP solution (SC). A 0.2 mL dose of the test article extract was injected intracutaneously into five separate sites on the right side of the back of each of three animals. Similarly, the extract vehicle alone (negative control) and the sponsor provided control article extract was injected on the left side of the back of each animal. The injection sites were observed immediately after injection. Observations for erythema and edema were conducted at 24

hours after injection and continuing daily for 7 days after the injection. The test was performed on both our implant as well as a control of SURGIFOAM, another collagen-based implant which has been FDA approved for clinical use (P990004/S002).

- Both the test article and SURGIFOAM had an increase over the negative control values as would be expected for a collagen-based implant.
- There was no significant difference between the test article and SURGIFOAM in this study.

1.4.3.2.3.4 Systemic Toxicity Study - Extract (T0625; 10993-11).

The test article, the BEAR™ implant, was evaluated for acute systemic toxicity in mice based on ISO 10993-11, Biological evaluation of medical devices - Part 11: Tests for systemic toxicity. The test article was extracted in 0.9% sodium chloride USP solution. A single dose of the test article extract was injected into a group of five animals. Similarly, a separate group of five animals was dosed with the extraction vehicle alone (vehicle control). The animals were observed for signs of systemic toxicity immediately after injection and at 4, 24, 48 and 72 hours after injection. Body weights were recorded prior to dosing and on days 1, 2 and 3. A gross necropsy was performed after the last observation to asses any abnormalities in the viscera.

- There was no mortality or evidence of systemic toxicity from the extract injected into mice. The test article extract met the requirements of the study. There were no abnormalities noted at gross necropsy in the viscera.

1.4.3.2.3.5 Genotoxicity, Bacterial Reverse Mutation Study (V0023, 10993-3).

A bacterial reverse mutation assay was conducted to evaluate whether a dimethyl sulfoxide (DMSO) extract and a saline extract of the BEAR® implant would induce reverse mutations at the histidine locus of the Salmonella typhimurium tester strains TA98, TA100, TA1535, and TA1537 or at the tryptophan locus of Escherichia coli tester strain WP2uvrA. The assay was conducted in the presence and absence of metabolic activation. Tubes containing molten top agar were inoculated with culture from one of the five tester strains, along with the DMSO or saline extract. An aliquot of sterile water for injection or rat liver S9 homogenate, providing metabolic activation, was added. The mixture was poured across triplicate plates. Parallel testing was conducted with negative controls (extraction vehicle alone) and positive controls. The mean number of revertants for the test extract plates was compared to the mean number of revertants of the negative control plates for each of the five tester strains.

- The DMSO and saline test article extracts were considered to be nonmutagenic to S. typhimurium tester strains TA98, TA100, TA1535, and TA1537, and to E. coli tester strain WP2uvrA.

1.4.3.2.3.6 Genotoxicity, in vitro Chromosomal Aberration Study in Mammalian Cells - Extract (V002, OECD Test No. 473).

The test article, the BEAR™ implant, was extracted in serum free McCoy's medium and dimethylsulfoxide (DMSO). A chromosomal aberration study was conducted to determine whether the extract would cause genotoxicity in Chinese hamster ovary (CHO-WBL) cells in the presence and absence of S9 metabolic activation. The serum free McCoy’s medium extract was supplemented to 10% with fetal bovine serum prior to

dosing the cells. The DMSO test article extract was diluted 1:100 with McCoy's 5A complete medium prior to dosing the cells. A monolayer of CHO-WBL cells was exposed to the test article extracts in duplicate and in the presence and absence of S9 metabolic activation. Parallel testing was also conducted with a corresponding negative and positive control. The extraction vehicle without the test article served as the negative control. Cells were exposed for 4 hours with and without metabolic activation, and for 20 hours without metabolic activation.

- The serum free McCoy's medium test article extract did not produce a statistically significant increase in chromosome aberrations as compared to the negative control in the presence or absence of S9 metabolic activation.
- The DMSO test article extract did not produce a statistically significant increase in chromosome aberrations as compared to the negative control in the presence or absence of S9 metabolic activation.

1.4.3.2.3.7 Genotoxicity, Mouse Peripheral Blood Micronucleus Study (T0566; OECD Test No. 474).

The test article, the BEAR™ implant, was evaluated for the potential to produce cytogenetic damage, resulting in micronuclei formation in the mouse peripheral blood micronucleus model. The test article was extracted in 0.9% sodium chloride USP solution. For three consecutive days, twelve mice (six per sex) were injected intraperitoneally with the test article extract. Similarly, six animals per sex were dosed with either the vehicle as the negative control or methyl methanesulfonate as a positive control. All animals were observed immediately following dosing and daily for assessment of general health. On day 4, blood was collected from the tail veins and reticulocytes were evaluated for the presence of micronuclei by flow cytometry.

- The test article extract did not induce micronuclei in mice.

1.4.3.2.3.8 Muscle Implantation Study - 2 week (T250; 10993-6).

Sterile implant test articles were aseptically prepared. Negative control articles were sterilized by steam. The test article and negative control were intramuscularly implanted and animals were euthanized 2 weeks later. Muscle tissues were excised and the implant sites examined macroscopically. A microscopic evaluation of representative implant sites from each animal was conducted to further define any tissue response.

- The macroscopic reaction was slight as compared to the negative control article.
- Microscopically, the test article was classified as a moderate irritant as compared to the negative control article.

The muscle implantation study in rabbits results demonstrated the BEAR™ implant had a slight macroscopic reaction as compared to the negative control (High density Polyethelene or HDPE). Microscopically, the BEAR® implant was classified as a moderate irritant as compared to the HDPE. This was due to two things:

- The presence of some necrotic fibers around the implant
- A greater concentration of inflammatory cells, including macrophages, lymphocytes and plasma cells around the BEAR® implant than around the HDPE implant.

As the BEAR® implant is designed to stimulate wound healing, and the influx of inflammatory cells is a critical part of wound healing in the first two weeks after implantation, the influx of inflammatory cells was expected. The necrosis of the muscle fibers was thought to be due to the implantation of the implant in muscle, rather than in the fluid environment of the joint where it is designed to be used. The implant is also designed to be hydrated with blood or platelet rich plasma prior to implantation, which was not done in this biocompatibility study. Pathologists from NAMSA and from Charter both thought the small amount of muscle necrosis visualized on the slides was likely due to the fact there was minimal fluid around to hydrate the material, which resulted in drying or dessication of the cells adjacent to the material (see emails from Dr Carraway(NAMSA) 12-3-2013 and Dr Kramer (Charter) 12-5-2013). Dr Kramer went back and evaluated the pathologic slides from VIV-001 and VIV-003 and while he did see inflammation around the BEAR® implant when implanted in the fluid environment of the knee joint, he did not see any necrosis in those studies.

- The consensus opinion was that the scoring as a moderate irritant was due to the implantation in the muscle, rather than the fluid environment of the joint, where the implant is designed to be used.
- The signs of irritation were not seen in the pathologic analyses in the porcine model when the scaffold was implanted in the joint.

1.4.3.2.3.9 6 week Systemic Toxicity Study in Rats Following Subcutaneous Implant (T0118; 10993-6, 10993-11).

The test article, the BEAR® implant, was surgically implanted in the subcutaneous tissue of the rat to evaluate potential systemic toxicity and local tissue response at the implantation site. A separate group of animals was similarly implanted with high density polyethylene (HDPE) to serve as the control group. Twelve male and 12 female rats were randomly assigned to either the test or control group (6/sex/group). Animals were observed daily for overt signs of toxicity. Detailed clinical examinations were conducted weekly. Animals were weighed prior to implantation, at weekly intervals, and on the day of euthanasia. At 6 weeks, blood samples were collected for hematology and clinical chemistry analysis, and the animals were euthanized. A necropsy was conducted, selected organs were collected and weighed, and implantation sites were excised and examined macroscopically. A microscopic evaluation of the implantation sites and collected organs was conducted.

- Clinical observations, body weights, necropsy results, organ weights, organ/body weight ratios and organ/brain weight ratios were not adversely affected by implantation of the test or control articles.
- There were no changes in hematology or clinical chemistry values considered related to implantation with the test article.
- Necropsy observations and microscopic evaluation of collected organs revealed no evidence of a test article related response.
- Microscopic evaluation of the implantation sites indicated no significant difference in the local tissue response between the control and test articles.
- There was no evidence of systemic toxicity from the test article following subcutaneous implantation in the rat.

- Microscopically, the test article was classified as a nonirritant in males and a slight irritant in females.
- Overall, microscopically the test article was considered as a nonirritant as compared to the control.

1.4.3.3 Clinical Data

With the preclinical data in a large animal model showing similar ACL strength with the bridge-enhanced repair and the ACL graft, we next obtained FDA and IRB approval for a first-in-human study to begin to determine if this device is safe in humans as well. A 2-arm, single center study was designed to determine if any adverse events occur at a higher rate with bridge-enhanced ACL repair than with the gold standard of care, ACL reconstruction. At this time, ten patients have undergone bridge-enhanced ACL repair, with no severe adverse events of deep joint infection, inflammation, or implant failure. All patients are at least three months out from surgery, and as in vivo resorption time in the porcine knee was 6 to 8 weeks, we anticipate much, if not all, of the implant has also been resorbed in these patients.

1.4.3.3.1 Safety Outcomes/Adverse Events

Under IDE G140151, we have started a first-in-human study of the BEAR implant. This controlled cohort study consisted of twenty patients undergoing surgery for an ACL injury. Ten of the patients received the BEAR implant repair technique (BEAR) and ten had ACL reconstruction with an autograft hamstring tendon (ACLR). We have currently completed enrollment, and all patients who had the BEAR procedure are between two and eight months postoperative. We currently have data at three months (N=8 BEAR, N=5 ACLR) and six months (N=7 BEAR and N=4 ACLR) postoperatively.

1.4.3.1 Safety Outcomes/Adverse Events

The adverse events reported (see **Table 1** for a complete listing) were similar in both the intervention and control groups. Each safety outcome criteria is detailed below and all adverse event data can be found in **Table 1**. In addition to the adverse events we evaluated specifically for the study, one patient in the intervention group had one day of a urticarial reaction 5 weeks after surgery, which resolved without intervention. Upon further questioning, this patient had a pre-operative history of urticaria with stress, which would flare for a few hours and then resolve. In addition, one patient in the intervention group was diagnosed with mild frostbite (listed on the AE sheet as a burn) over the knee after use of the cooling device. Protection of the area from cold over the next week resulted in complete resolution of the erythema. Lastly, one of the patients in the control group sustained a deep venous thrombosis post-operatively.

Table 1: All listed adverse events for the patients in the initial safety study. Of note, eight patients have undergone the intervention while only four have undergone the control procedure. The only severe adverse event noted was a deep venous thrombosis, which occurred in a patient in the control group.

Study ID	Adverse Event CTCAE 4.03	Grade (1-5)	Attribution to study device	Expected	Outcome
Control	Dizziness	1	0 - Not related	0 (No)	1 - Resolved, no sequelae
Control	Fever	1	0 - Not related	0 (No)	1 - Resolved, no sequelae
Control	Joint effusion	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Control	Joint effusion	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Control	Joint effusion	1	0 - Not related	1 (Yes)	
Control	Joint effusion	1	0 - Not related	1 (Yes)	
Control	Joint effusion	1	0 - Not related	1 (Yes)	
Control	Joint effusion	1	0 - Not related	1 (Yes)	
Control	Joint effusion	1	0 - Not related	1 (Yes)	
Control	Joint effusion	1	0 - Not related	1 (Yes)	
Control	Joint Range of Motion Decreased	1	0 - Not related	1 (Yes)	
Control	Muscle weakness lower limb	1	0 - Not related	0 (No)	1 - Resolved, no sequelae
Control	Muscle weakness lower limb	1	0 - Not related	0 (No)	
Control	Nausea	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Control	Nausea	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Control	Pain	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Control	Pain	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Control	Pain	1	0 - Not related	1 (Yes)	
Control	Pain	1	0 - Not related	1 (Yes)	
Control	Pain	1	0 - Not related	1 (Yes)	
Control	Pain	2	0 - Not related	1 (Yes)	
Control	Pain	2	0 - Not related	1 (Yes)	
Control	Pain	2	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Control	Pain	2	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Control	Pain	2	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Control	Pain	2	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Control	Pain	2	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Control	Pain	2	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Control	Pain	2	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Control	Pain	2	0 - Not related	1 (Yes)	
Control	Paresthesia	1	0 - Not related	1 (Yes)	
Control	Thromboembolic event	2	0 - Not related	1 (Yes)	1 - Resolved, no sequelae

Study ID	Adverse Event CTCAE 4.03	Grade (1-5)	Attribution to study device	Expected	Outcome
Intervention	Burn	1	0 - Not related	0 (No)	1 - Resolved, no sequelae
Intervention	Fall	2	0 - Not related	0 (No)	1 - Resolved, no sequelae
Intervention	Joint effusion	1	0 - Not related	0 (No)	
Intervention	Joint effusion	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Joint effusion	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Joint effusion	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Joint effusion	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Joint effusion	1	0 - Not related	1 (Yes)	2 - Resolved, with sequelae
Intervention	Joint effusion	1	0 - Not related	1 (Yes)	
Intervention	Joint effusion	1	0 - Not related	1 (Yes)	
Intervention	Joint effusion	1	0 - Not related	1 (Yes)	
Intervention	Joint effusion	1	0 - Not related	1 (Yes)	
Intervention	Muscle weakness	2	1 - Possibly related	0 (No)	1 - Resolved, no sequelae
Intervention	Muscle weakness	2	1 - Possibly related	0 (No)	1 - Resolved, no sequelae
Intervention	Baker Cyst	2	0 - Not related	0 (No)	1 - Resolved, no sequelae
Intervention	Nausea	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Nausea	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Nausea	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Nausea	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Nausea	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Nausea	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Neutrophil count decreased	1	0 - Not related	0 (No)	
Intervention	Neutrophil count decreased	1	0 - Not related	0 (No)	
Intervention	Pain	1	0 - Not related	0 (No)	
Intervention	Pain	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Pain	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Pain	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Pain	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Pain	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Pain	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Pain	1	0 - Not related	1 (Yes)	
Intervention	Pain	2	0 - Not related	1 (Yes)	
Intervention	Pain	2	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Pain	2	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Pain	2	0 - Not related	1 (Yes)	1 - Resolved, no sequelae

Intervention	Pain	2	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Pain	2	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Pain	2	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Pain	2	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Pain	3	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Pain	3	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Pain	3	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Pain	3	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Paresthesia	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	Urticaria	2	0 - Not related	0 (No)	1 - Resolved, no sequelae
Intervention	Vomiting	1	0 - Not related	1 (Yes)	1 - Resolved, no sequelae
Intervention	White Blood Cell decreased	1	0 - Not related	0 (No)	
Intervention	White Blood Cell decreased	1	0 - Not related	0 (No)	
Intervention	White Blood Cell decreased	2	0 - Not related	0 (No)	1 - Resolved, no sequelae

1.4.3.1.1 Adverse Events: Infection

No patients in either group were diagnosed with a deep joint infection.

1.4.3.1.2 Adverse Events: Inflammation

No patients had signs or symptoms, which would necessitate an arthrocentesis for diagnosis of inflammation or infection. Patients in both groups have had an effusion after surgery, consistent with what would be expected after knee surgery (see **Table 1** for a complete listing). The majority of the effusions in both groups had resolved by the three month time point (**Figure 6**) and were in the range of what would be considered as expected by our medical monitors.

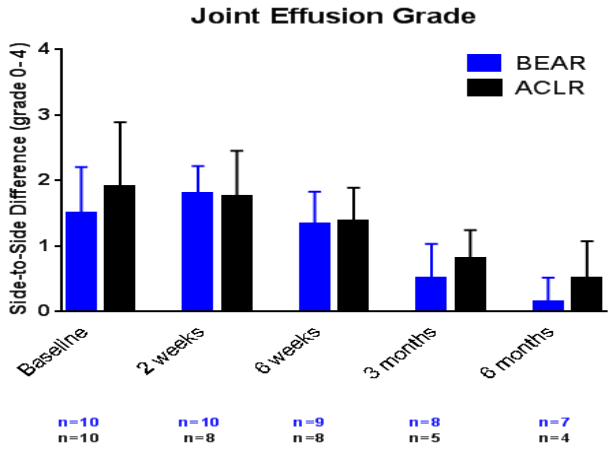


Figure 6: Effusion scores at baseline, two weeks, six weeks, three months and six months after both bridge-enhanced ACL repair (intervention group) and the group undergoing ACL reconstruction (control group). The effusion score reports the amount of effusion measured in the patient at that clinical visit. No statistically significant difference was seen between groups.

1.4.3.1.3 Adverse Events: Muscle Atrophy

Our pre-established criteria for muscle atrophy was that if at the six week follow-up visit, the patient cannot ambulate independently and continues to require crutches for ambulation, the patient will be classified as having muscle atrophy and treated accordingly. For 2 patients in the 10 intervention patients who have been evaluated at the six week time point, and 2 patient in the 8 control patients that have been evaluated at the six week time point, one crutch or a cane was still being used at the six week time point. All patients were able to discontinue use of any ambulatory aid by eight weeks post-operatively.

1.4.3.1.4 Adverse Events: Pain

No patients in either group required re-hospitalization for pain after their surgery. The pain scores for the patients in the two groups have been similar and the averages illustrated in **Figure 7**. These pain scores were in the range of what would be considered as expected by our medical monitors.

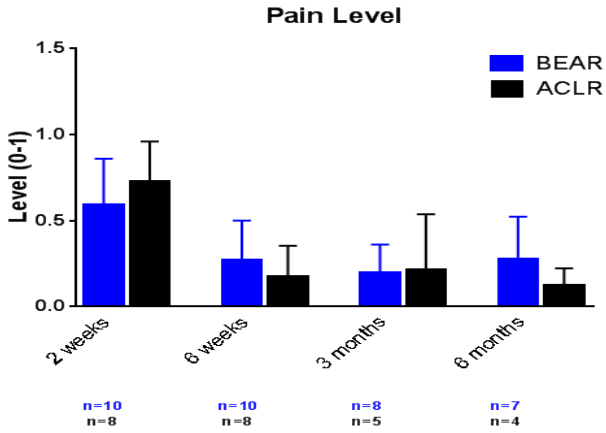


Figure 7: Self-reported pain scores at baseline, two weeks, six weeks, three months and six months after both bridge-enhanced ACL Repair (intervention group) and the group undergoing ACL Reconstruction (ACLR group). The pain score reports the highest level of pain the patient experienced since the last clinical visit. No statistically significant difference was seen between groups.

1.4.3.1.5 Adverse Events: Implant Failure

No patient in either group has had a Lachman exam that demonstrated 6mm or greater AP knee laxity than the unoperated knee.

1.4.3.2 Efficacy Outcomes

Efficacy outcomes, including IKDC (International Knee Documentation Committee) scores, Lachman Testing, MRI imaging, knee range of motion and muscle strength have also been collected for these patients are the details are outlined below. These data are presented as of 11-3-2015.

1.4.3.2.1 IKDC scores

The preoperative IKDC scores were 33+/- 11 points for the BEAR patients and 40 +/- 10 for the ACL reconstruction patients. IKDC scores improved in both groups at three months and again at six months (**Figure 8**). No statistically significant differences were found between the scores in the two groups at in this small number of patients.

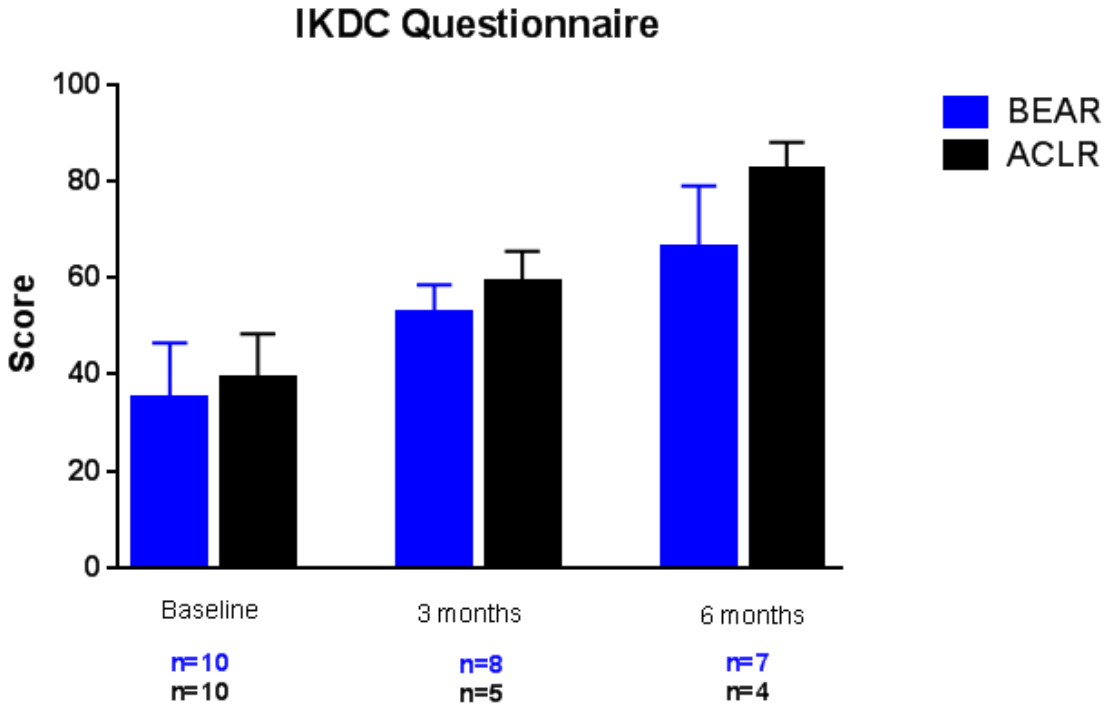


Figure 8: IKDC scores pre-operatively and post-operatively at 3 and 6 months for the patients in the study as of 11-3-2015.

1.4.3.2.2 Knee Laxity

The average side-to-side difference in knee laxity at three months post-operatively as measured by manual Lachman testing was 1.0 +/- 1.5 for the BEAR group and 0.4 +/- 1.2 for the ACL reconstructed group. At six months, the values were 1.5 +/- 1.2 in the BEAR group and 0.3 +/- 0.5 in the ACL reconstruction group. There was no clinically or statistically significant difference between the groups in this small number of patients. No patient in either group had a Lachman on the operative side which was more than 4 mm greater than the contralateral knee. KT-2000 instrumented testing for anteroposterior laxity at six months revealed the average side-to-side difference in knee laxity at six months was 2.0 +/- 2.0 for the BEAR group and 1.5 +/- 1.8 for the ACL reconstructed group.

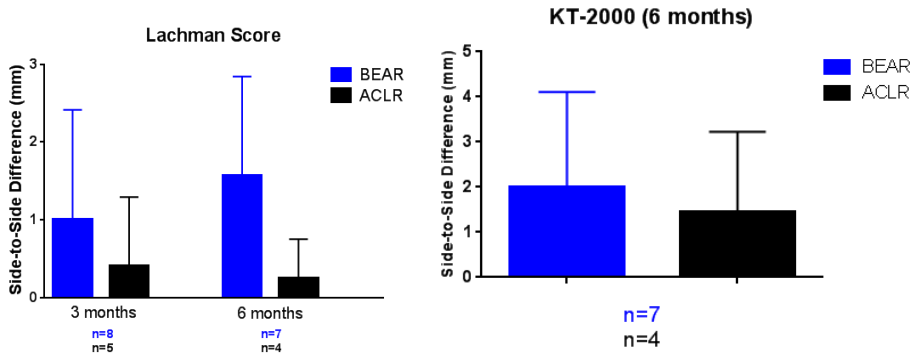


Figure 9: Anteroposterior knee laxity in the two groups as measured by Lachman (manual) testing and KT-2000 (instrumented) testing post-operatively. No significant difference was noted between groups.

1.4.3.2.3 MRI Imaging

All patients in the bridge-enhanced repair group had the presence of tissue in the region of the healing ACL (**Figure 10**).Using the algorithm from the porcine model for MR prediction of the maximum load of the ACL, the average predicted maximum load at three months after surgery for the BEAR patients was 730+/- 184N, while that for the ACL reconstructed patients was 970 +/- 290N. There was no significant difference between the groups in this small number of patients. Note this analysis was only on n=8 of the repair patients and n=5 of the ACL reconstruction patients , all of the patients who have had their three month MRI completed as of November 3, 2015.

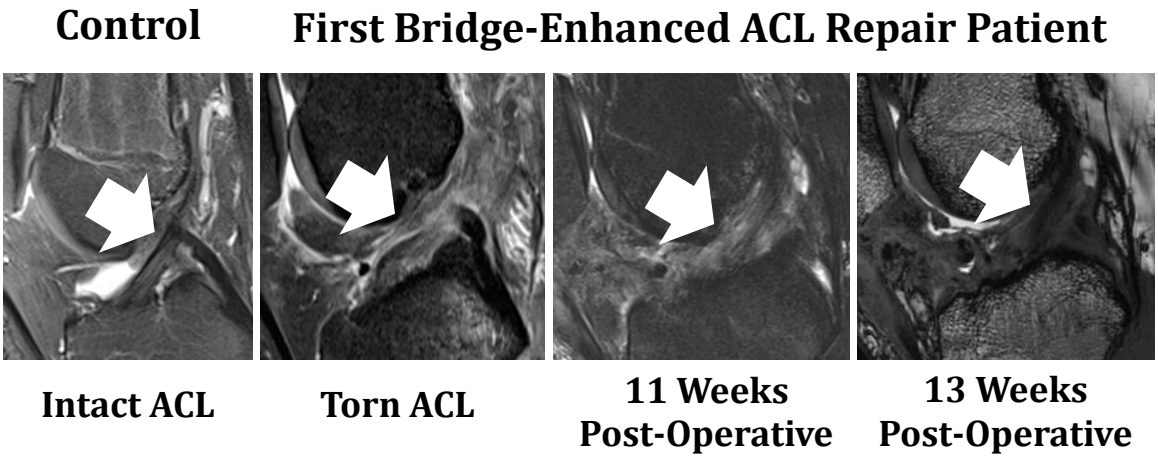


Figure 10: MRI appearance in the sagittal plane of an intact ACL (left hand panel) and the first bridge-enhanced repair patient. The second panel is the torn ACL, the third panel shows the MR appearance at 11 weeks and the last panel shows the appearance at 13 weeks post-operatively on the CISS sequence.

1.4.3.2.4 Knee Range of Motion

The range of motion was restricted both at baseline and at two and six weeks when compared to the contralateral side in both groups of patients. The range of motion was

within 5 degrees of the contralateral side in extension by three months in all patients and within 25 degrees of full flexion in the BEAR groups, both of which were considered in the expected range (**Figure 11**). Range of motion in both flexion and extension had returned to within 3 degrees of normal in all patients by six months post-operatively.

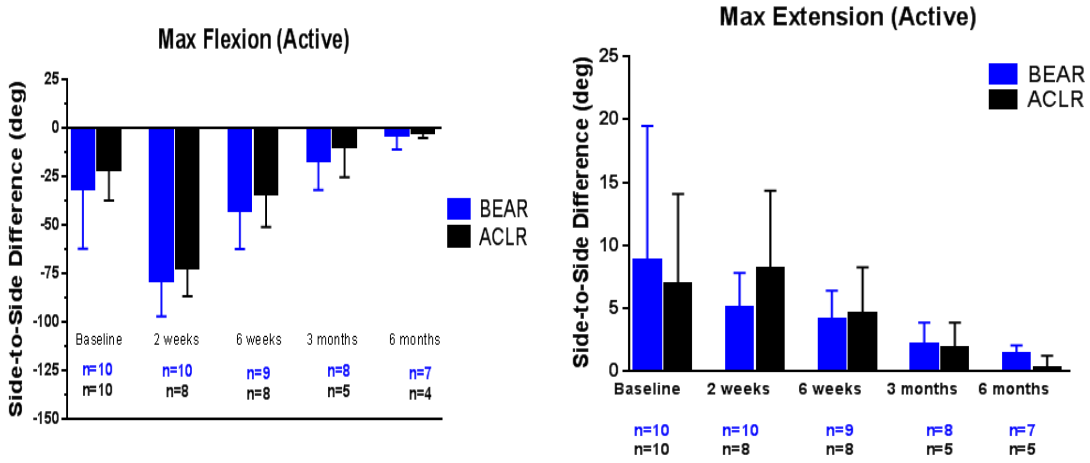


Figure 11: Active Range of Motion in the bridge-enhanced repair (BEAR) group and the ACL reconstruction (ACLR) group at baseline, 2 weeks, 6 weeks, three months and six months after surgery. No significant differences in range of motion in the two groups were detected in this early analysis.

1.4.3.2.5 Muscle Strength

At three months after surgery, for patient data available as of 11/2/2015, the average recovery in hamstring strength at three months after surgery (calculated as (operative/contralateral) x 100) was 77 +/- 16 percent in the intervention group and 52 +/- 6 percent in the ACL reconstructed group (means +/- SD). At six months after surgery, it was 87 +/- 12 in the intervention group and 68 +/- 19 percent in the ACL reconstruction group (**Figure 12**). Using a mixed measures ANOVA, the effect of treatment was significant (P< 0.01), with the BEAR patients having improved hamstring recovery when compared to the ACL reconstructed patients.

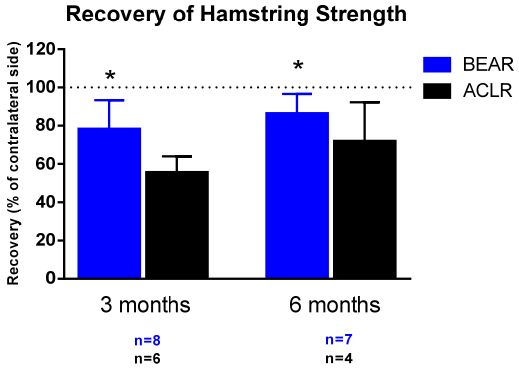


Figure 12: Recovery of hamstring strength after the bridge-enhanced ACL repair (BEAR) and ACL reconstruction (ACLR). The BEAR patients had significantly improved hamstring strength recovery at these early time points (three and six months, 0 < 0.01.)

1.4.4 *Rationale*

With the preclinical data in a large animal model showing similar ACL strength with the bridge-enhanced repair and the ACL graft, and the feasibility study showing no significant adverse events in the intervention group, the next step is to determine if this device results in an outcome after ACL surgery that is not inferior to the result obtained with autograft ACL reconstruction, the current gold standard of treatment for patients thought to benefit from surgical treatment for their ACL injury. The benefits of the bridge-enhanced procedure are that patients do not have to have the extra trauma of an autologous graft harvest. Use of allograft tendon for the ACL graft also avoids the trauma of autologous graft harvest; however, use of allograft is no longer recommended in patients under 25 years of age due to the relatively high failure rate of allografts (20 to 30%) and risk of additional surgery on the operative knee (30%) in this age group. If we can show use of the implant leads to similar results as the autograft ACL reconstruction procedure, patients will benefit from not having a second area of their leg compromised to treat the ACL injury. This 2-arm, single center study is designed to determine if patient reported outcomes after a bridge-enhanced ACL repair are non-inferior to patient reported outcomes after the gold standard of care, ACL reconstruction in terms of knee laxity and patient reported outcomes at two years and to determine if there is superiority for the BEAR procedure in terms of early return of muscle strength.

1.5 Study Objectives

1.5.1 *Primary Objective*

The overall objective of this study is to determine the non-inferiority of the efficacy of the BEAR® Implant when compared with an ACL reconstruction with an autograft reconstruction (current gold standard). The outcomes for evaluating the primary objective will include a patient reported score on the International Knee Documentation Committee (IKDC) validated outcome measure at two years after surgery and a measure of AP knee laxity at two years after surgery.

1.5.2 *Secondary Objective(s)*

Our secondary objectives are:

1) to determine if patients having ACL surgery with the BEAR Implant recover their hamstring or quadriceps strength more quickly than patients undergoing ACL reconstruction. To assess this, we will measure the hamstring and quadriceps strength at 3 and 6, 12 and 24 months after surgery. We hypothesize that at 3 and 6 months, patients who received BEAR surgery will have superior hamstring strength than those who received hamstring autograft.

2) to determine if markers of early osteoarthritic change are less prevalent in the BEAR patients than in patients undergoing ACL reconstruction at two years out from surgery. We will collect imaging data, as well as patient reported outcome data using the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire, during the course of this study. While we think it is unlikely either group will have clinically significant changes in the 2 year time frame for this protocol, we will collect this data during the two year primary outcome assessment period and again at six and ten years post-surgery.

3) to determine if there are any increased safety risks associated with use of the BEAR Implant. These potential safety risks include loss of range of motion of the knee, development of bovine Type I collagen antibodies, infection (superficial or deep surgical site infection), graft or repair failure, development or graft/device rejection as evidenced clinically or serologically, need for further surgeries, development of prion disease or other viral diseases, or occurrence of deep venous thrombosis. We will also record any other adverse events which occur during the course of the trial.

4) to determine if patients undergoing the BEAR procedure are able to get back to work and sports at the same rate as patients undergoing ACL reconstruction, and to determine if there is a difference in the rate of meeting the return-to-sport criteria for patients in the BEAR and ACL reconstruction groups.

5) to determine whether the patient reported outcomes or graft failure rates can be predicted by the surrogate prediction of maximum load and stiffness of the healing ACL using a novel MRI technique [38, 41, 95]. This technique provides a non-invasive way to assess the healing ACL or ACL graft and will be another imaging modality to assess the relative volume, tissue quality and orientation of the ACL after the BEAR procedure and autograft ACL reconstruction at 6 months, and 2 years after surgery.

6) to determine whether the volume and orientation of the ACL after the BEAR procedure is different from the volume and orientation of the ACL graft after ACL reconstruction. This will also be measured using the MRIs obtained at 6 months and 2 years after surgery.

Measures of efficacy will be evaluated using physical exam, laxity testing, strength testing and imaging. Specific tests will be performed as noted in

Table 3 at time points up to (and including) two years out from surgery.

Table 2: Primary and Secondary Study Objectives.

Primary Study Endpoints	Secondary Study Endpoints
• Patient Reported Outcomes (IKDC) • Knee Anteroposterior Laxity as measured by KT instrumented laxity testing	• Quadriceps and Hamstring Strength • KOOS patient reported outcome score • Imaging findings associated with early osteoarthritis • Knee range of motion • Bovine Type I collagen antibody presence • Deep joint infection • Incision and drainage of a deep surgical site infection • Evidence of Graft Rejection • Graft or repair failure • Return to work/sports • Additional surgeries on the operative knee • MRI imaging of the ACL • All adverse events

1.5.3 *Endpoints*

The endpoints for the primary and secondary objectives will be measured as follows:

1.5.3.1 PRIMARY ENDPOINTS

The primary outcomes for this trial will be the score on the IKDC questionnaire at one and two years after surgery and the AP laxity of the knee as measured by KT testing at one and two years after surgery.

1.5.3.1.1 IKDC Outcome

The IKDC patient-reported outcome measure instrument will be administered to all patients at six months, 1, 2, 6, and 10 years after surgery. For the IKDC outcomes, a difference of 11.5 points between control and BEAR groups will be considered clinically significant, at the primary analysis at two years, as previously published [34].

1.5.3.1.2 Anteroposterior (AP) Laxity

The anteroposterior (AP) knee laxity will be determined using a KT arthrometer at the 30lb (130N) setting on both knees of the subject at six months and 1, 2, 6 and 10 years after surgery (see Appendix C). Both sides will be covered with a sleeve so the licensed examiner cannot tell which is the operated knee or which procedure the patient had. Values for both knees will be recorded. For knee laxity, a difference of 2.0 mm in the side-to-side difference measurements at 2 years after surgery, the primary analysis, for the patients in the bridge-enhanced repair group vs. the ACL reconstruction group will be considered clinically significant.

1.5.3.2 SECONDARY ENDPOINTS

1.5.3.2.1 Hamstring and Quadriceps Strength

The strength of the quadriceps, hamstring and hip abductor musculature will be determined at three, six, twelve and twenty-four months after surgery. Both sides will be covered with a sleeve so the licensed examiner cannot tell which is the operated knee or which procedure the patient had. The quadriceps testing will be performed in a seated position with the knee flexed 90 degrees so as not to stress the repair or healing graft. Values for both knees will be recorded. In addition, Biodex testing will be performed at the six, twelve and twenty four month follow-up. Hop testing will also be performed at six, twelve and twenty four months if the patients have progressed to hopping as part of their rehabilitation with their physical therapist and if the patient feels comfortable doing the test. Lastly, static and dynamic balance testing will be performed at six, twelve and twenty-four months after surgery.

1.5.3.2.2 KOOS Score

The Knee Injury and Osteoarthritis Outcome Score (KOOS) score is another validated patient outcome measure with three domains: Pain, Knee Related Quality of Life and Sports. We will collect data for all three domains at twenty four months after surgery. A 10 point difference between groups will be considered statistically significant based on prior studies validating the KOOS score [96].

1.5.3.2.3 Xray Imaging

A semiflexed weight bearing MTP view, as well as a lateral projection, will be obtained at baseline and at two years after surgery to assess joint space narrowing and the presence of osteophytes suggestive of early OA. The signs to be identified include peaking of the intercondylar tubercles and buttressing osteophytosis [97]. Joint space width changes will be measured as previously reported by Jones et al for a large cohort of patients undergoing ACL reconstruction at two years post-operatively [98] where joint space widening was noted in the ACL reconstruction cohort. This joint space widening at this time point has been reported by others as associated with early osteoarthritis [99] which is why it will be measured here. The Kellgren and Lawrence system will be used to classify the severity of knee osteoarthritis using five grades:

- **Grade 0**: no radiographic features of OA are present
- **Grade 1**: doubtful joint space narrowing (JSN) and possible osteophytic lipping
- **Grade 2**: definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph
- **Grade 3**: multiple osteophytes, definite JSN, sclerosis, possible bony deformity
- **Grade 4**: large osteophytes, marked JSN, severe sclerosis and definite bony deformity

At the 2 year time point, we do not anticipate seeing any clinically significant change on the K-L scale for either group, but we will plan to collect the data at baseline and 2 years in preparation for a longer term follow up of this cohort.

1.5.3.2.1 Range of Motion

Active and passive range of motion will be measured using a goniometer at three months, six months and one and two years after surgery. Both sides will be covered with a sleeve so the licensed examiner cannot tell which is the operated knee or which procedure the patient had. Values for both knees will be recorded. In addition, a standing active flexion angle will be recorded for both knees.

1.5.3.2.2 Bovine Type I Collagen Antibodies

As prior studies of bovine collagen products have reported a 2-3% rate of patients having elevated levels of bovine type I collagen antibodies[79], likely from dietary exposure [80, 81], we will plan to screen patients pre-operatively for the presence of these using a test for levels of IgE antibodies to bovine gelatin (hydrolyzed collagen).Patients with a positive test (low, moderate, high, or very high level) for these antibodies will be excluded from the study. Preoperative levels of IgG antibodies to type I collagen will also be measured, but will not be used to screen for hypersensitive individuals as levels of IgG are not thought to correlate with adverse events or hypersensitivity (NIAID Consensus statement 2010).

In addition, as 10% or greater of patients receiving other bovine collagen implants can develop bovine type I collagen antibodies[84], with the peak antibody detection at approximately four to six months, we will test all patients post-operatively at the six month time point for the presence of both IgE and IgG antibodies.

1.5.3.2.3 Deep Joint Infection/Incision and Drainage of Deep Surgical Site Infection

We will also monitor patients for any signs of a post-operative infection. If there is clinical suspicion for a possible deep joint infection (fever greater than 101 degrees Fahrenheit, increasing pain in the knee, presence of an effusion, drainage from the knee), a knee arthrocentesis will be performed and if organisms are cultured from the joint fluid, the patient will be classified as having a deep joint infection (according to CDC/NHSN Surveillance Definitions for Specific Types of Infections) and treated accordingly. Any patient diagnosed with a deep joint infection or who undergoes incision and drainage of a

deep surgical site infection will have the event recorded as an adverse event. These adverse event data will be evaluated as a secondary outcome of the study.

1.5.3.2.4 Evidence of Graft Rejection

If a patient presents with a swollen, warm knee and there is clinical suspicion of marked inflammation versus septic joint, an arthrocentesis will be performed. If the synovial fluid culture is negative for organisms, the patient will be classified as having a marked inflammatory reaction and treated accordingly. Bovine Type I collagen antibodies, ANA, CBC with differential, CRP and ESR lab tests will be performed as well for all symptomatic subjects. In addition, a urinalysis will be performed and in subjects having protein in the urinalysis, a protein electrophoresis will also be performed. Evidence of graft rejection, clinically or by serology, will be recorded as a secondary outcome measure, as well graft removal for any reason.

1.5.3.2.5 Graft or repair failure

A patient shall be noted to have had a graft or repair failure when one or more of the following criteria are met: positive pivot shift exam, Lachman exam with greater than 6 mm side to side difference, absence of tissue in the expected ACL location on MRI imaging, MR evidence of graft or repair loss of continuity or symptomatic instability requiring revision of the ACL surgery.

1.5.3.2.6 Other adverse reactions

Any adverse reactions, including (but not limited to) deep venous thrombosis, loss of function, need for prolonged parenteral pain medication, development of neurologic symptoms or additional trauma will also be recorded for all patients in the study.

In addition, if any evidence of prion disease is noted, a workup will be initiated. Evidence of prion disease could include: any rapidly developing dementia, neurologic symptoms of difficulty walking and changes in gait (other than those expected after knee surgery), hallucinations, confusion or difficulty speaking. If the patient or clinician are concerned prion disease may be developing, the patient will be referred for a neurologic consultation and workup may include MRI of the brain, electroencephalogram (EEG), blood tests and a complete neurologic and ophthalmologic exam. These would be conducted at the discretion of the examining neurologist.

In addition, prior reports of injectable collagens have reported embolic complications including pulmonary embolism[90] and blindness[91] and other complications[92] [93]. While implantation of a large implant into a joint cavity may have a significantly lower risk profile for embolism than an injectable material placed in the vicinity of blood vessels, collagen can activate platelets. The study team will monitor for signs and symptoms of a possible deep venous thrombosis in all study patients and patients presenting with calf pain, ankle swelling, a positive Homan's sign, shortness of breath or clinician concern for possible deep venous thrombosis will be referred for ultrasound

screening for a DVT, and if positive, a referral to hematology for treatment with anticoagulation as indicated.

Any additional surgical procedures that the subject requires on the operative knee, as well as any surgical procedures required on the contralateral knee, will also be recorded and reported as an additional secondary outcome measure. These include (but are not limited to) additional surgery to address meniscal or cartilage pathology, scar tissue, arthrofibrosis, removal of symptomatic hardware or graft removal for any reason.

1.5.3.2.7 Return to work/sports

Time for patients to return to full time work or school, as well as sports, will be recorded for all patients in the study. Failure to return to work or sports will be recorded as a secondary outcome, and if the failure is due to the operative knee, that will also be recorded. In addition, the length of time for patients to meet return to sport criteria, including 90% strength on the operative side for quadriceps and hamstring strength and achievement of a hamstring to quadriceps ratio of 0.60, will also be recorded for all patients. All strength testing will be performed with a sleeve over both knees so the examiner is blinded to both operative side and the procedure performed.

1.5.3.2.8 MRI

MRI will be used at six months, 1, 2, 6 and 10 years with the same specific sequence previously validated in the porcine model to predict the yield and maximum load of the repaired ACL or ACL graft (see Appendix B). In addition, MR imaging will be used to measure the volume and orientation of both the ACL repaired using the BEAR technique and the ACL reconstruction as well as that of the contralateral knee. During the course of this study, we will determine if the values for maximum load, yield load, stiffness, volume or orientation of the healing ACL or graft, as well as the relative value of these parameters compared with the contralateral side, are predictive of patient outcomes, including patient reported outcomes on the IKDC or KOOS testing, graft or ACL re-rupture, rate of return to sport/work and muscle strength.

1.6 Patient Selection

Participants in both groups will be screened and recruited during their visit to the Boston Children's Hospital Orthopaedic Surgery or Sports Medicine Clinics, with referral to Dr Lyle Micheli, Dr Yi-Meng Yen or Dr Dennis Kramer in the event the patient is willing to participate in the clinical trial and are thought to be a candidate for ACL reconstruction with autograft tendon. Patients will be thought to be a candidate for surgery if they are under 35 and active. The most recent AAOS Clinical Practice Guideline states: "Moderate evidence supports surgical reconstruction in active young adult (aged 18 to 35 years) patients with an ACL tear." A recent systematic review also concluded that surgical stabilization should be considered the preferred method of treatment for skeletally immature individuals with complete ACL tears (Vavken and Murray, Arthroscopy, 2011 May; 27(5):704-16). Non-operative treatment is also considered reasonable by some surgeons for active adult patients who participate exclusively in non-cutting athletics (e.g swimming, bicycling, skiing), or non-athletic young adults. For this

reason, in this proposed trial, we will only enroll patients where there is moderate evidence that surgical reconstruction has benefit (i.e. active young patients younger than 35 years of age).

The eligibility criteria (see below) will be the same for both groups. On average, 20 ACL reconstructions are performed on patients aged 14 to 35 years, each month, by these surgeons in the sports medicine group. This number should be sufficient to consent and enroll up to 100 patients over a 14 month period. Patients found to be eligible will be offered participation. The treating surgeon and research coordinator will explain the study to the patient and answer all questions. The research coordinator will review the consent document, obtain required signatures and provide the patient with a photocopy of the consent form for his/her records.

1.6.1 *Inclusion Criteria*

1.6.1.1 At Preoperative Exam

To be eligible for this trial the subjects must meet all of the following criteria:

- **Age**: All patients must be at least 14 years of age and have closed femoral and tibial physes. The upper age limit will be 35 years of age.
- **Sex**: Both male and female
- **ACL**: Complete tear, confirmed by MRI
- **Time from injury to screening**: ≤45 days
- **MRI**: ACL tissue present on pre-operative MRI - at least 50% of the ACL length must still be attached to the tibial plateau
- **Prior surgery on affected knee**: None
- **History of prior infection in knee**: None
- **Regular use of tobacco or nicotine in any form**: None
- **Use of corticosteroid within last 6 months:** None
- **Underwent chemotherapy treatment**: Never
- **History of sickle cell disease**: None
- **History of anaphylaxis**: None
- **Any condition that could affect healing or infection risk (Diabetes, inflammatory arthritis, etc**): None
- **Medial collateral ligament injuries**: Grade I or II may be included
- **Bovine Type I collagen antibodies**: Patient must not have clinically significant levels of IgE antibodies to bovine gelatin on pre-operative screening or a known history of allergy to beef or bovine derived products.
- Patients who have selected surgical treatment of their ACL injury and have been thought to be surgical candidates by the treating physician
- Patients along with their surgeon must be willing to undergo either hamstring autograft or bone patellar tendon bone autograft, if randomized to the control group

1.6.1.2 Inclusion Criteria at Surgery

- **ACL abnormal on arthroscopic inspection**: Yes

- **Time from injury to surgery**: ≤45 days
- **Meniscus**: No displaced bucket handle injuries requiring repair
- **ACL tissue present**: More than 50 percent of the length of the ACL remains attached to the tibial insertion site
- **Synovectomy/plica**: All may be included
- **Chondral injury**: Chondral injury on either condyle that is not full-thickness may be included.

1.6.2 *Exclusion Criteria*

1.6.2.1 At Pre-operative Exam

To be eligible for this trial the subjects must meet none of the following criteria:

- Prior surgery on affected knee
- History of prior infection on affected knee
- Regular use of tobacco or nicotine in any form
- Use of corticosteroid within last 3 months
- Ever underwent chemotherapy treatment
- History of sickle cell disease
- History of anaphylaxis
- Any condition that could affect healing or infection risk (Diabetes, inflammatory arthritis, etc)
- Diagnosis of posterolateral corner injury (LCL complete tear, Biceps femoris tendon avulsion, tear of the arcuate ligament, tear of the popliteus ligament)
- Diagnosis of Grade III medial collateral ligament injury
- Bovine Type I collagen antibody level deemed clinically significant or a known allergy to beef or bovine derived products. Diagnosis of complete patellar dislocation
- Preference for conventional ACL reconstruction other than hamstring autograft or bone patellar tendon bone autograft (e.g., allograft, other autografts).

1.6.2.2 Exclusion Criteria at Surgery

- ACL deemed normal on arthroscopic inspection
- Time from injury to surgery is >45 days
- Length of remaining ACL attached to the tibial insertion site less than 50 percent
- Displaced bucket handle meniscal injury requiring repair
- Diagnosis of full-thickness chondral injury on either condyle
- Grade III medial collateral ligament injury

1.6.3 *Early Withdrawal of Patients*

Patients will be withdrawn from the study, if for any reason their surgery cannot be scheduled within 45 days of their injury. Physical examination and imaging will be used to assess patient eligibility for the trial; however, the extent of soft tissue damage may not be fully appreciated until the time of surgery. Some patients will be deemed eligible, consented, and then later, during surgery, found to meet exclusion criteria and will be withdrawn from the trial if they do not want to be part of the ACL reconstruction group. Patients will be withdrawn from the trial if initial arthroscopic inspection of the knee reveals that the ACL tissue has resorbed so that less than 50% of the length of the ACL remains at the tibial insertion site. Patients will also be withdrawn if the surgeon discovers during surgery that the meniscus has a displaced bucket handle tear that requires repair and/or there is a full-thickness chondral injury on either condyle. Under these circumstances, the surgeon will repair all soft tissue damage and perform an ACL reconstruction using the technique that s/he believes will be most efficacious for the patient. Patients also may choose to withdraw from the study at any time and for any reason.

Any patient who has bovine type I collagen antibodies at a level greater than 2 standard deviations above that of normal human sera will be excluded from participation in the study.

The reason for withdrawal and the circumstances of withdrawal will be documented for all patients withdrawn from the study. Even though patients may be disqualified prematurely from the study on one basis (i.e. missing a post-operative evaluation point), every effort will be made to obtain permission to continue to follow subjects with a protocol deviation to obtain primary outcome data at the final, twelve-month time point. These data are critical for the accurate assessment of the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study procedure or device.

1.7 **Treatment Plan**

1.7.1 *General Study Design*

The protocol will be approved by the Investigational Review Board (IRB) of Boston Children's Hospital and by the Food and Drug Administration prior to the start of the investigation.

This study is to be conducted in the USA according to ISO 14155:2011 (Clinical investigation of medical devices for human subjects – Good clinical practice); United States Code of Federal Regulations Title 21 Part 50 (Protection of Human Subjects) and Part 56 (Institutional Review Boards); 21 CRF Part 812 (Investigational Device Exemptions); and other applicable government regulations and institutional research policies and procedures. This is an efficacy study of the BEAR® ACL implant and will be carried out in the form of a randomized controlled trial of approximately 100 patients. We will recruit patients in two strata: those who, along with their surgeon, would prefer hamstring autograft if randomized to conventional ACL reconstruction, and those who

would prefer bone patellar tendon bone (BPTB) autograft. Our goal is to recruit 87 patients in the hamstring-preference stratum. We expect an additional 10-15 in the BPTB stratum for a total of approximately 100. Randomization will be in 2:1 ratio so there will be approximately 67 BEAR and 33 Control patients in total.

After consenting but before randomization, all patients will complete additional testing and evaluation including questionnaires, laboratory studies of blood and urine, physical exam and imaging. If a patient has positive antibodies to bovine Type I collagen at a level greater than 2 standard deviations from normal, they will not be eligible for the trial. Second, if a patient is found to have less than 50% of the length of the ACL remaining at the time of surgery, they will be discontinued from the study.

All patients in the trial will have preauthorization for their surgical procedure obtained using the diagnosis code for an ACL tear and the procedure code 29888 - Arthroscopically assisted ACL repair or reconstruction. This is an established code and the modifier Q1 will be added to the procedure code to notify the insurance carriers that the patient is participating in a clinical trial. Patients will be informed that the billing for their surgery will be handled in the same way it would be if they were having ACL surgery outside of the trial. If the patient's insurance refuses to give preauthorization for the costs of the surgery because of the patient's participation in the trial, the patient will have the option to leave the study at any time.

The length of study participation for each patient will be 24 months from the time of surgery, with 6 post-operative visits taking place at 1-2 weeks, 6 weeks, and 3, 6, 12 and 24 months. The primary endpoints to be monitored are a patient reported outcome (IKDC score) and a knee AP laxity measure. The secondary endpoints evaluated for efficacy will include muscle strength, KOOS patient reported outcome scores, imaging outcomes, knee range of motion, bovine type I collagen antibody presence, incidence of deep joint infection or inflammatory/immune reaction, graft or repair failure, time to return to work/sports, rates of additional surgery and ACL strength, volume and orientation as predicted by MRI (**Table 3**).

1.7.2 ***Surgical Procedures***

Participants in the intervention and control groups will be screened and consented by a licensed professional during a visit to the Boston Children's Hospital Orthopaedic or Sports Medicine Clinics. After consenting to participate in the trial, patients will be randomized to either the BEAR (Intervention) procedure or ACL reconstruction (Control), as the current gold standard treatment of ACL injuries. Both treatments are based on well-established surgical techniques, long used in suture repair or reconstruction of ruptured ACL. The main safety and efficacy related outcomes of ACL surgery will be closely monitored over a 24 month period following established protocols and guidelines in order to assess the safety and efficacy of the Bridge-Enhanced ACL repair compared to the ACL reconstruction.

1.7.2.1 Control Group; ACL Reconstruction with Hamstring or Bone-Patellar Tendon-Bone (BPTB) Autograft

These patients will undergo a standard arthroscopic ACL reconstruction, with surgeon/patient preference dictating what type of graft will be used to stabilize the knee. As autologous hamstring tendon and bone-patellar tendon-bone grafts have not been found to be statistically different in clinical or biomechanical outcome studies involving the primary outcome measures [100-103], both hamstring and bone-patellar tendon-bone graft will be used in this study. Tunnel position will be considered acceptable if the intra-articular exit of both femoral and tibial tunnels are within the footprint of the original ACL. The general schematic of the procedure is presented in **Figure 13** below and a detailed description of the surgical procedure is outlined in *Appendix A: Surgical Procedures*.

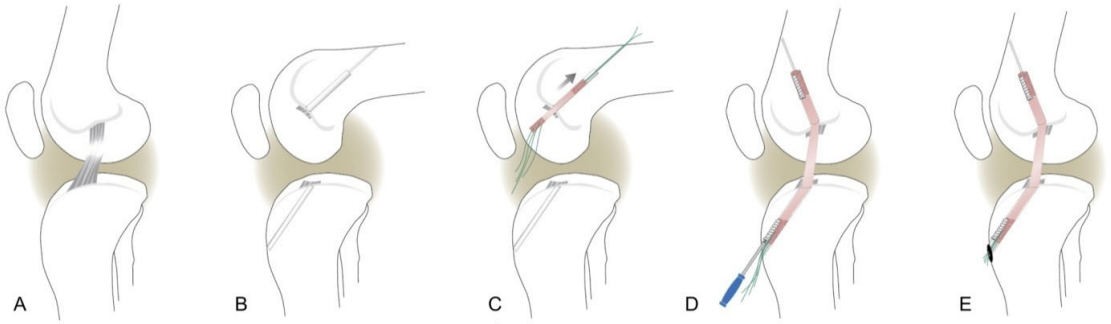


Figure 13: Standard ACL reconstruction procedure. In this procedure, the torn ACL is removed from the knee (B) and then large tunnels (10mm) are drilled in the femur and tibia. A graft is taken from the back of the patient's thigh, passed through the tunnels (C and D) and fixed in place with interference screws. This figure illustrates replacing the anterior cruciate ligament with a bone-patellar tendon-bone graft using an interference screw. In this study, the preferred femoral fixation technique will be suspensory fixation with a cortical button (Endobutton or similar) construct.

1.7.2.2 Intervention Group; Bridge-Enhanced ACL Repair with BEAR® Implant

Patients will receive anesthesia and undergo surgery under the same conditions as the ACL reconstruction group, with two exceptions: 1) the surgical approach utilized to perform the repair will be a mini-arthrotomy instead of arthroscopy; and 2) repair of the knee joint will be achieved by inserting the extracellular matrix sponge (BEAR™ scaffold) and suture construct and allowing the ACL to regenerate and repair on its own, rather than replacing it with hamstring graft. A suture stent will be placed across the knee for initial stabilization as shown in panel B below. The tunnel positions for the suture stent will be considered acceptable if the intra-articular exit of both femoral and tibial tunnels are within 2 mm of the footprint of the original ACL. The general schematic of the procedure is presented in **Figure 14** below and a description of the surgical procedure is outlined in detail in *Appendix A: Surgical Procedures*.

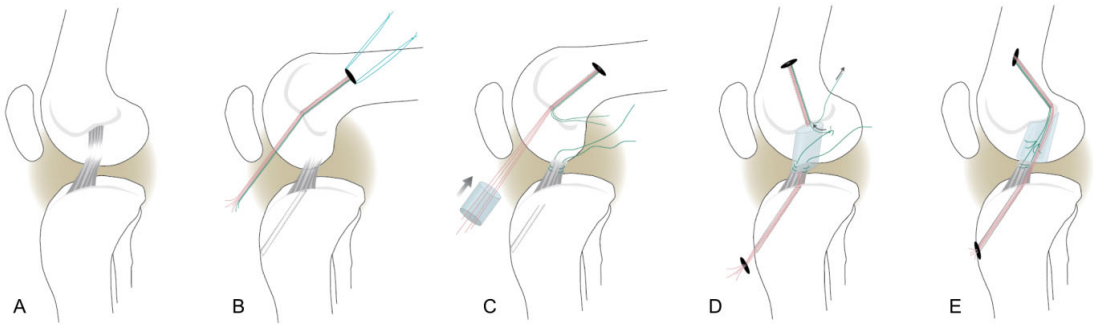


Figure 14: Stepwise demonstration of the "Bridge-Enhanced ACL repair" technique using the collagen device (seen first in C where it is threaded onto sutures). In this technique, the torn ACL tissue is preserved (A). Small tunnels (4 mm) are drilled in the femur and tibia and an cortical button (Endobutton or similar) with sutures attached to it is passed through the femoral tunnel and engaged on the proximal femoral cortex. One set of sutures from the button is threaded through the collagen implant, tibial tunnel and secured in place with an extracortical button (red sutures). A second set of sutures (green) from the Endobutton were tied to the Kessler suture placed in the tibial stump of the ACL (green sutures). The collagen device is then saturated with 5 mL of the patient's blood. The collagen device is not load-bearing; the initial strength of the repair is dependent on the sutures. The ends of the torn ACL then grow into the collagen implant and the ligament reunites.

1.7.2.3 Major differences in the control and interventional procedures

- The intervention group will need to have 20 ml of blood drawn during surgery (for a CBC test and to deliver 10 cc of blood to the implant), while the control group will only need 10 ml (for the CBC only).
- The intervention group will need a 2-inch incision at the joint to expose the ACL and allow for delivery of the implant. This mini-arthrotomy carries the theoretical additional risks of infection and arthrofibrosis; however, a recent study has demonstrated no difference in outcomes for ACL surgery performed arthroscopically versus with an arthrotomy [104].
- The control group includes a 2 inch incision over the hamstring insertion site to allow for harvesting of the hamstring tendons for a graft, or a 3 inch incision over the front of the knee if a bone-patellar tendon-bone graft is used. The BEAR group requires a 1 cm incision for tunnel creation. The larger incision carries a potentially greater risk of bleeding, infection and superficial nerve injury.
- The control group requires harvesting of two of the medial hamstring tendons or a piece of bone from the patella and tibia with the middle third of the patellar tendon, the investigational group does not. This may lower the risk of hamstring or patellar graft harvest pain and post-operative hamstring or quadriceps weakness for the intervention group.

1.8 Study Procedures

Participants in the intervention and control groups will be screened and consented by a licensed professional during their initial visit to the Boston Children's Hospital Orthopaedic or Sports Medicine Clinics. **Table 3** below is an outline of the visit schedule that all patients will follow and the measures performed at each visit.

Table 3: Visit Schedule and Measures for Intervention (BEAR) and Control (ACLR) Patients.

	Pre-Op	Intra-Op	Post-Op					
Measure	**Baseline**	**Surgery**	**1-2 wks (5-15 days)**	**6 wks (±1 wk)**	**3 mos (±2 wks)**	**6 mos (±1 mo)**	**1 and 2 years (±2 mos)**	**6 and 10 years** (-6 mos/+1 yr)
Screening & Eligibility	X							
Informed Consent	X							
History (fever, pain, stiffness, VAS score)	X		X	X	X	X	X	X
Clinical Exam (wound, thigh circ, swelling)	X		X	X	X	X	X	X
Knee X-ray (semiflexed MTP view)	X						X (2 yrs only)	X
MRI	X[1]					X[2]	X[2]	X[2]
Biomechanical Testing (6 and 10 years only) optional								X
Knee Range of Motion	X	X	X	X	X	X	X	X
Knee Laxity (Lachman)	X	X			X	X	X	X
Pivot Shift		X				X	X	X
Knee Laxity (KT-1000)						X	X	X
Strength Testing			X	X	X	X	X	X
IKDC	X				X	X	X	X
KOOS Questionnaire	X					X	X	X
MOON questionnaire	X						X (2 yrs only)	X
ACL-Return to Sports survey						X	X	X
Bovine Type I collagen Ab	X					X		
CBC and Chemistries	X	X						
Urinalysis	X							
ANA, CRP, ESR	X							
Protein C and S	X							
Research labs (blood and urine)							X	X
Adverse Events		X	X	Xx	X	X	X	X

[1]Standard MRI
[2]Research MRI

1.8.1 *Study Visits*

1.8.1.1 Baseline/Preoperative Assessment:

Patients will be screened by a licensed professional at the Baseline visit to determine eligibility for the study. If deemed eligible to participate, the patient will be asked if they would like to participate in the randomized controlled study. If informed consent is granted for participation, the research coordinator will complete a screening form (FORM 1), and a pre-operative questionnaire. The licensed examiner will complete a physical exam on both knees (including goniometer range-of-motion for flexion and extension and thigh circumference measurements at mid patella and 5 and 10 cm above the joint line) and record. Pre-operative imaging results will also be recorded. The research coordinator will also document the patient has signed the informed consent.

The patient will also complete a pre-operative questionnaire. The questionnaire contains the three KOOS subscales, Marx activity score and SF-36 elements. This questionnaire will also be administered at two years post-operatively.

Patient will also have a standardized knee x-ray series (the semiflexed postero-anterior metatarsophalangeal and lateral knee x-ray) performed at that visit.

Patients will also have blood and urine testing performed at this visit. These tests will include: Bovine Type I collagen antibodies, ANA, CBC with differential, protein C and S, CRP and ESR. In addition, a urinalysis will be performed and in subjects having protein in the urinalysis, a protein elect**r**ophoresis will also be performed.

1.8.1.2 Randomization Procedures

Patients will be randomized in 2:1 (BEAR:ACL Reconstruction) ratio using a stratified random permuted-block allocation procedure, with two strata representing surgeon/patient autograft preference:

1. Hamstring Preference: randomize to BEAR or Hamstring autograft.
2. Bone Patellar-Tendon Bone (BPTB) preference: randomize to BEAR or BPTB autograft.

Allocation concealment will be accomplished by using sequentially numbered sealed envelopes, separate sets for each stratum. The study statistician will generate the allocation sequence using random block sizes that will not be revealed to study staff involved in recruitment or randomization.

After graft preference stratum is determined, the next sequential unopened envelope for that stratum will be opened. If the treatment allocation is to ACL Reconstruction, the patient will receive either Hamstring or BPTB autograft according to which stratum they are in. We anticipate that the vast majority (~90%) of patients will be in the Hamstring-preference stratum.

1.8.1.3 Randomization, Blinding and Unblinding Criteria

After patients have been enrolled in the study, they will be randomized by the statistician. The surgeon and surgical schedulers will be notified of the group assignment; however, the patients will not be notified as to which procedure they will have. We will plan to reveal the group assignment to the patients at the two-year post-op time point. The surgeon, research coordinator, research study nurses, medical monitoring committee members and statistician will be unblinded as to patient assignment and the interim data reports to the medical monitors and statistician will contain information on the patient assignments. All post-operative physical examinations will be performed by an examiner who is blinded as to study group, and both knees will be covered with sleeves prior to the examiner entering the room to conceal which is the operative knee and which procedure was performed. The physical therapists will not be informed which surgery the patient received, just that they had ACL surgery, and patients in both groups will follow an identical PT protocol. Unblinding of the patient will occur in the event of any of the following: persistent knee inflammation/effusion requiring removal of implant, deep joint infection, graft or repair failure or any evidence of prion disease symptoms. A patient shall be noted to have had a graft or repair failure when one or more of the following criteria are met: positive pivot shift exam, Lachman exam with greater than 10 mm side to side difference, absence of tissue in the expected ACL location on MRI imaging, MR evidence of graft or repair loss of continuity or symptomatic instability requiring revision of the ACL surgery. Evidence of prion disease could include: any rapidly developing dementia, neurologic symptoms of difficulty walking and changes in gait (other than those expected after knee surgery), hallucinations, confusion or difficulty speaking. If the patient or clinician are concerned prion disease may be developing, the patient will be referred for a neurologic consultation and workup may include MRI of the brain, electroencephalogram (EEG), blood tests and a complete neurologic and ophthalmologic exam. These would be conducted at the discretion of the examining neurologist. In addition, unblinding of the patient will be performed in the event of any Grade 4 or 5 serious adverse event.

1.8.1.4 Intra-operative Assessment

Before the day of surgery, the research coordinator will prepare the CRF with the patient name, identification number, date of surgery and study arm. The research coordinator will bring the form to the operating room and complete the remaining questions during the surgery with the assistance of the surgeon. A preoperative exam will be performed under anesthesia and the results recorded. During surgery, arthroscopic examination of the menisci, chondral surfaces and ACL will be performed and the results recorded. Specifically, it will be recorded whether the ACL is abnormal on arthroscopic inspection.

For the menisci, it will be recorded whether the meniscus is normal, it is injured but does not require repair or has a displaced bucket handle tear that requires repair. For the ACL, the length of the ACL remaining (recorded as a percentage of the distance between the femoral and tibial insertion sites of the native ACL) will be recorded. The presence of any chondral injury, as well as the area of the injury and the grade of injury, will also be recorded. In addition, the CRF will be completed by the research coordinator in the operating room to document additional findings at surgery.

A patient will be excluded from the study if the ACL is noted to be normal on arthroscopic exam, if they have a displaced bucket handle meniscal injury requiring repair or if a full thickness chondral injury is present. Patients will be withdrawn from the trial if initial arthroscopic inspection of the knee reveals that the ACL tissue has resorbed so that less than 50% of the length of the ACL remains at the tibial insertion site. The finding of less than 50% of the ACL length being present will be noted on the case report form.

The research coordinator will also bring the following documents to be given to the study patient and family regarding post-operative care:

1. Subject Document: Post-operative Instructions
2. Subject Document: Post-operative Physical Therapy Prescription and Protocol

1.8.1.5 Scheduled Post-operative Follow-up:

The timing of follow-up visits for this study is identical to the clinical schedule (with the exception of 6 and 10 year follow up visits) and is identical for both groups (BEAR and ACLR). Patients will return to see the surgeon at approximately 1-2 weeks (5-15 days), 6 weeks (±1 week,) 3 months (±2 weeks,) 6 months (±1 month) 12 and 24 months (±2 month) and 6 and 10 Year (-6 mos/+1 yr) post procedure.

At the 1-2 week time point, the research coordinator will complete the CRFs with the pertinent history and patient questionnaire. A pertinent physical exam will be performed by a licensed professional on both knees (including goniometer range-of-motion for flexion and extension and thigh circumference measurements at the superior pole of the patella and 5 and 10 cm above the joint line, as well as temperature, wound check and standard post-operative knee joint examination – see **Table 3**) and the results recorded on the CRF.

At the 6 week time point, the research coordinator will complete the CRFs with the pertinent history and patient questionnaire. A pertinent physical exam will be performed by a licensed professional on both knees (including goniometer range-of-motion for flexion and extension and thigh circumference measurements at the superior pole of the patella and 5 and 10 cm above the joint line, as well as temperature, wound check and standard post-operative knee joint examination – see **Table 3**) and the results recorded on the CRFs.

At the 3 month time point, the research coordinator will complete the CRFs with the pertinent history and patient questionnaire. A pertinent physical exam will be performed by a licensed professional on both knees (including goniometer range-of-motion for flexion and extension and thigh circumference measurements at the superior pole of the patella and 5 and 10 cm above the joint line, as well as a standard post-operative knee joint examination – see **Table 3**) and the results recorded on the CRFs. The patient will then complete an IKDC questionnaire. Strength testing will also be performed for quadriceps, hamstring and hip adductor testing and the results recorded.

At the 6 month time point, the research coordinator will complete the CRFs, with the pertinent history and patient questionnaires. A pertinent physical exam will be performed by a licensed examiner on both knees (including goniometer range-of-motion for flexion and extension and thigh circumference measurements at the superior pole of the patella and 5 and 10 cm above the joint line, standard post-operative knee joint examination - see **Table 3**) and the results recorded on the CRF. Strength testing will also be performed, as well as KT testing and hop testing at this visit and the results recorded. The patient will then complete an IKDC questionnaire. The patient will also undergo an MRI using the CISS sequence to evaluate the repair and the contralateral ACL.

At the 12 month time point, the research coordinator will complete the CRFs with the pertinent history and patient questionnaires. A pertinent physical exam on both knees (including goniometer range-of-motion for flexion and extension and thigh circumference measurements at mid patella and 5 and 10 cm above the joint line, as well as temperature, wound check and standard post-operative knee joint examination - see **Table 3**) will be performed by a licensed examiner and the results recorded. Strength testing will also be performed as well as KT-1000 testing and hop testing at this visit and the results recorded. The patient will then complete an IKDC questionnaire. The patient will also undergo an MRI using the CISS sequence to evaluate the repair and the contralateral ACL.

At the 24 month, 6 and 10 year time points, the research coordinator will complete the CRFs with the pertinent history and patient questionnaires. A pertinent physical exam on both knees (including goniometer range-of-motion for flexion and extension and thigh circumference measurements at mid patella and 5 and 10 cm above the joint line, as well as temperature, wound check and standard post-operative knee joint examination - see **Table 3**) will be performed by a licensed examiner and the results recorded. Strength testing will also be performed as well as KT-1000 testing and hop testing at this visit and the results recorded. The patient will then complete an IKDC questionnaire and KOOS/MARX/SF-36 questionnaire. The patient will also have a repeat of the x-ray taken at the pre-operative visit, namely a semiflexed MTP x-ray and will have blood and urine collected for laboratory testing. The patient will also undergo an MRI using the CISS sequence to evaluate the repair and the contralateral ACL.

Biomechanical Testing to be completed at the 6 and 10 Year Visit (optional):

To assess the long-term effect of BEAR vs ACLR in knee function during daily activity (i.e. walking) and balance. There is solid evidence on gait changes after ACL surgery leading to knee pain and OA. This would be a great addition to current imaging studies to evaluate risk of PTOA in BEAR vs ACLR. The primary outcomes are asymmetry in knee rotation and loading during walking.

The surgeon will ask about adverse events at each visit, including screening for neurologic symptoms, and document any responses. If any adverse events have occurred or are potentially occurring, the research coordinator will complete the CRF and follow the procedures detailed in Section 9.

1.8.1.6 Unscheduled Visits:

Patients may return to the clinic at a time point that is not a protocol specified follow-up visit. If the Investigator determines that a clinic visit is required in order to evaluate an adverse event or patient reported complaint, an "Unscheduled Visit" case report form should be completed. The evaluation at an unscheduled visit requires an updated patient history since the time of the last patient contact, documentation of complaints/symptoms and medications, and description of treatment provided and any changes to post-operative care schedule.

1.8.2 *Outcome Measures*

Training: All licensed examiners will be trained in the protocol procedures before using these in the study.

Patient Reported Function (IKDC): This scale was specifically developed to be sensitive and responsive to highly active patients with knee injuries [105, 106]. The American Orthopaedic Society for Sports Medicine (AOSSM) developed the IKDC and recommends it as a primary outcome measure. This scale has been widely used in multiple ACL injury related cohorts such as the MOON cohort [107-112] as one of the most commonly utilized validated patient-reported outcome assessment in sports medicine [105].

Instrumented Laxity (KT): Testing will be performed by experienced, certified athletic trainers or physician assistants trained using standardized equipment according to the MOON protocol, Manual of Operating Procedures (MOP) and instructions by MEDmetric (KT device manufacturer). This testing will be performed at 6, 12 and 24 months and 6 and 10 years after surgery. The anterior displacement at 130N (30lbs) will be used to obtain a side-to-side difference in millimeters. **Patients will wear a sleeve over both knees at the time of examination to minimize potential bias**.

Muscle Strength: The strength of the quadriceps, hamstring and hip abductor musculature will be determined at three, six, twelve and twenty-four months and 6 and 10 years after surgery. **Patients will wear a sleeve over both knees at the time of examination to minimize potential bias**. The quadriceps testing will be performed in a

seated position with the knee flexed 90 degrees so as not to stress the repair or healing graft. Values for both knees will be recorded. In addition, Biodex testing will be performed at the six, twelve and twenty four month follow-up. Hop testing will also be performed at six, twelve and twenty four months and 6 and 10 years if the patients have progressed to hopping as part of their rehabilitation with their physical therapist and if the patient feels comfortable doing the test. Lastly, static and dynamic balance testing will be performed at six, twelve and twenty-four months and 6 and 10 years after surgery.

***KOOS Score*:** The KOOS score is another validated patient outcome measure with three domains: Pain, Knee Related Quality of Life and Sports. We will collect data for all three domains at 3, 6, 12 and twenty four months and 6 and 10 years after surgery. A 10 point difference between groups will be considered statistically significant based on prior studies validating the KOOS score [96].

***Xray Imaging*:** A semiflexed weight bearing MTP view, as well as a lateral projection, will be obtained at baseline and at two, six and 10 years after surgery to assess joint space narrowing and the presence of osteophytes suggestive of early OA.

***Range of Motion*:** Active and passive range of motion will be measured using a goniometer pre-operatively, intra-operatively and at 2 weeks, six weeks, three months, six months and one, two, six and 10 years after surgery. **Both sides will be covered with a sleeve so the licensed examiner cannot tell which the operated knee is or which procedure the patient had**. Values for both knees will be recorded. In addition, a standing active flexion angle will be recorded for both knees.

***Functional testing*:** Hop testing, as well as static and dynamic balance testing and Biodex testing for flexion and extension strength will be evaluated at six, twelve and twenty four months for all study subjects. These data will be used to determine the percentage of patients meeting return to sport criteria at each time point. At the 1-2 week, 6 week and 3 month post-operative visits, we will assess whether the patient is able to perform a straight leg raise without an extensor lag. At three, six, 12 and 24 months and six and ten years after surgery, for both groups, we will measure quadriceps strength, hamstring strength and hip abductor strength using a hand-held dynamometer on both the involved and contralateral knees. Biodex testing for flexion and extension strength will be measured at six, 12 and 24 months and six and ten years after surgery. The ratio of the measurement from the surgical leg to the contralateral uninjured knee will be calculated and compared between treatment groups. **Patients will wear a sleeve over both knees at the time of examination to minimize potential bias**.

Knee Examination: An independent examiner (not the operating surgeon) will perform the physical exam based on the MOON (Multicenter Orthopaedic Outcomes Network) protocol. **Patients will wear a sleeve over both knees at the time of examination to minimize potential bias**. The exam will include range of motion, presence or absence of effusion and crepitus, and a series of tests including the Lachman (at baseline, 3, 6, 12 and 24 months and 6 and 10 years), anterior drawer, posterior tibial sag, medial and lateral joint opening, pivot-shift, and internal and external rotation tests at the designated time points.

Evaluation of the BEAR or ACL Reconstruction Using MRI: The experimental MRI protocol will be used to estimate the biomechanical properties of the healing ligament or graft, as well as these properties in comparison to the contralateral ACL, in the clinical trial [113]. In a previous study, we found that using a combination of volume and signal intensity could accurately predict the structural properties of a healing ACL at both 15 and 52 weeks of healing using our minipig model of ACL surgery (yield load, failure load, linear stiffness; $R2 > 0.68$) [113, 114]. MR imaging with the CISS sequence will be used to measure the volume and orientation of both the ACL repaired using the BEAR technique or the ACL reconstruction and the contralateral knee. MRI will be performed at 6 months, 2, 6 and 10 years after surgery to help us gain additional information about the status of the healing ACL or graft using this new MRI sequence.

Biomechanical evaluation of knee function and lading after ACL Surgery

Rationale: 3D biomechanical evaluation of gait and balance have been widely used to asses knee function after ACL surgery.2,8 These studies have direct implications in treatment assessment and evaluation of knee osteoarthritis (OA) risk.2,3,9 A poor balance, measured as shorter single-leg standing or larger sway, is indicative of inferior knee function, higher risk of re-injury and posttraumatic OA. 1,7,8 A higher degree of asymmetry in knee motion and loading in sagittal and frontal planes have also been consistently linked to higher risk of posttraumatic OA after ACL surgery.2,3,9 Evaluation of single-leg standing balance and gait biomechanics will shed light on relative efficacy of BEAR to restore normal knee function and biomechanics after surgery. The following tests will be conducted at each follow up visit:

Static Balance Test: Subjects will complete an instrumented balance error scoring system test. This test has been used to measure static postural stability in those with ankle1,7 and knee8 related impairments. Subjects were asked to maintain balance on a single leg with closed eyes for as long as they could for up to 20 seconds. Each subject will complete 3 trials per leg. This test is a way to measure the somatosensory and/or visual information processing ability of an individual, which may be affected following a lower extremity orthopedic injury. Participants will stand on a pressure-sensing device (Equilibrate, Balance Engineering Inc., Henrietta, NY), which will provide objective information related to the control of posture in each stance. Tests

Outcomes Measures (measured for each trial)

1. Balance time
2. Body sway.

Joint kinematic Test: Subjects will be fitted with reflective markers in a validated, reliable marker set for motion analysis4,6. Three-dimensional motion capture will be performed with a 10 camera (Motion Analysis Corporation, Santa Rosa, CA) Motion Analysis system. Neutral tibiofemoral alignment will be defined using the methodology outlined by Kvist et al5. Subjects will be instructed to walk for 10 meters at a self-selected speed following a pre-defined straight walking path marked on the floor.

Outcome Measures (measured for each knee)

1. Knee flexion angle
2. External knee flexion moment
3. External knee adduction moment

6 Years Visits (<1 hr prep and testing):

1. 3D Motion Capture (joint rotations) + Force Plate (joint loads) data during level walking
    a. Outcomes: lower extremity kinetics and kinematics

2. Single-legged Standing balance on force plate
    a. Outcomes: balance time, COP trajectory

1.8.3 *Post-operative Physical Therapy*

Prior to hospital discharge from their ACL surgery, Intervention and Control patients will be given a prescription for physical therapy. They will also be given a copy of the trial's standardized Physical Therapy Protocol *(Appendix D)* to give to the physical therapist they choose to see for treatment. (Because BCH is a large referral center and patients come from all over New England, we will not mandate that all subjects receive physical therapy at the same location.) The goal of providing a standardized protocol is to reduce the variation in post-operative physical therapy, thus minimizing the likelihood that it is responsible for any observed differences in physical function or other outcomes between the two groups. If a patient does not attend at least four physical therapy sessions in the first three months after surgery, this will be recorded on the case report form; however, they will be kept in the study.

1.8.4 *Study Timeline*

We anticipate completing the twenty four-month follow-up for this study in 3.5 years. Each patient will be enrolled and followed for efficacy measures until 24 months. We anticipate requiring 14 months for subject recruitment, an additional two years to complete the 2 year follow-up for the efficacy measures and then two months to analyze and report the results. We anticipate to complete the long term follow up of 6 and 10 years within 14 years of study start to account for patient visit windows and to perform the study analyses.

1.9 Adverse Event Criteria and Reporting Procedures

1.9.1 *Adverse Event Monitoring*

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who

will enroll in future studies using similar devices. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study device, will be monitored until:

1. The adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
2. Any abnormal laboratory values have returned to baseline;
3. There is a satisfactory explanation other than the study device for the changes; or, observed
4. Death

1.9.2 *Definitions*

1.9.2.1 Adverse Event Definitions

An adverse event is any untoward medical occurrence experienced by a subject that occurs in temporal association with the use of an administered investigational intervention, whether considered intervention-related or not. An event can be any sign, symptom, laboratory abnormality, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

1.9.2.2 Severity of Adverse Events

The severity of an AE is graded as follows:

- **Mild (grade 1):** the event causes discomfort without disruption of normal daily activities.
- **Moderate (grade 2):** the event causes discomfort that affects normal daily activities.
- **Severe (grade 3):** the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- **Life-threatening (grade 4):** the patient was at risk of death at the time of the event.
- **Fatal (grade 5):** the event caused death.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree

of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Associated with the Investigational Device: There is a reasonable possibility that the adverse effect may have been caused by the investigational device.

Life-Threatening Adverse Effect: Any adverse effect that places the subject, in the view of either the investigator or the sponsor, at immediate risk of death from the effect as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious Adverse Effect (SAE): An adverse effect is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

1. Results in death.
2. Is life-threatening.
3. Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4. Results in persistent or significant disability or incapacity.
5. Is an important medical event which may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes.

Unanticipated Adverse Effect: Any adverse effect, the nature, specificity, severity, or frequency of which is not consistent with the risk information in the clinical study protocol or elsewhere in the current IDE application.

1.9.3 *Eliciting Adverse Effect Information*

Study subjects in both groups will be routinely questioned about adverse effects at study visits. They will also be instructed about signs and symptoms associated with potential adverse effects and will be encouraged to call and report them in between study visits.

1.9.4 *Abnormal Test Findings*

An abnormal test finding will be classified as an adverse effect if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug or other therapy (Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse effect.)
- The test finding leads to a change in study dosing or exposure or discontinuation of subject participation in the clinical study
- The test finding is considered an adverse effect by the investigator

1.9.5 *Causality and Severity Assessment*

The investigator will promptly review documented adverse effects and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse effect; 2) if there is a reasonable possibility that the adverse effect was caused by the investigational device or other study treatments; and 3) if the adverse effect meets the criteria for a serious adverse effect. If the investigator's final determination of causality is "unknown and of questionable relationship to the investigational device or other study treatments," the adverse effect will be classified as associated with the use of the investigational device or other study treatments for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the investigational device or other study treatments," this determination and the rationale for the determination will be documented in the respective subject's case history. The sponsor will ultimately review all events that have been reported by the sites and determine if they meet criteria for UADE reporting to the FDA.

The relationship between the treatment type and any adverse event will be determined by the investigator, medical monitor, and Data Monitoring Committee using the following criteria:

- **Not Related:** The event is clearly related to other factors, such as the subject's clinical state, therapeutic interventions or drugs administered to the subject.
- **Possibly Related:** The event follows a compatible temporal sequence from the time of the ACL procedure, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions or drugs administered to the subject.
- **Probably Related:** The event follows a reasonable temporal sequence from the time of the ACL procedure, and cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions or drugs administered to the subject.

1.9.6 *Recording and Assessment of Adverse Effects*

All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of treatment group, if applicable, or suspected causal relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s) will be recorded in the subjects' case histories. Events will be recorded according to the date and time of first presenting symptom, severity, and their duration, as well as any treatment prescribed. After the ACL procedure, all new adverse events that were not present at enrollment will be recorded. Any medical condition or abnormal laboratory value present at enrollment that remains unchanged or improves, will not be recorded as an adverse event. However, worsening of a medical condition that was present at enrollment will be considered a new adverse event and reported. Abnormal laboratory values, if felt by the investigator to be clinically significant, will also be recorded on the Adverse Event Form and assessed in terms of severity and relationship to the treatment. For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a serious adverse effect) and; 2) an assessment of the casual relationship between the adverse effect and the investigational device or, if applicable,

the other study treatment or diagnostic product(s). Adverse effects or abnormal test findings felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

Serious adverse events will be reviewed by the Data Monitoring Committee who will be unblinded as to patient group assignment. Differences of opinion as to the causality, classification, or expectedness of events will be adjudicated by the Data Monitoring Committee. All unresolved adverse events will be followed by the investigators until the events are resolved or the adverse event is otherwise explained or has stabilized.

1.9.7 *Post-Surgery Procedures for Adverse Events*

At each contact with the patient, the Investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedure results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse events that occur after the study period should also be recorded, reported promptly and followed.

1.9.8 *Reporting Adverse Events*

Reports of all serious adverse events will be submitted to the local IRB, and the local institutional Biosafety Committee by the site investigator in the shortest time possible after the notification of the event and per site institutional guidelines. The sponsor will report the serious device related adverse events to the Data Monitoring Committee as soon as possible and no later than 10 calendar days after the event. For any adverse event determined to be an Unanticipated Adverse Device Effect (UADE), the sponsor- will submit a safety report to the site to report to their IRB as soon as possible and, in no event, later than 10 working days after the sponsor-investigator first receives notice of the adverse effect. UADEs will also be reported to the Data Monitoring Committee in the same timeframe. Follow-up information to reported adverse effects will be submitted to the IRB as soon as the relevant information is available. The safety report will consist of:

- A completed Form FDA 3500A: http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM387002.pdf
- A cover letter analyzing the significance of the event

Similarly, UADEs will be reported by the sponsor to the FDA by submitting an expedited safety report to the FDA's Center for Devices and Radiological Health as a report to the IDE. A copy of this safety report will be provided to all participating study investigators.

The completed Form FDA 3500A and cover letter will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the sponsor first receives notice of the adverse effect. If, following receipt and investigation of follow-up information regarding an adverse effect that was previously determined not to be a UADE, the sponsor determines that the event does meet the requirements for expedited reporting, the sponsor will submit a completed Form FDA 3500A and cover letter as soon as possible, but in no event later than 10 working days, after the determination is made. Subsequent to the initial submission of a completed FDA Form 3500A, the sponsor will submit additional information concerning the reported adverse effect as requested by the FDA.

1.9.9 *Risk Mitigation Strategy*

Risks to the patients who have agreed to participate in the study will be minimized to the greatest extent possible. This study is incorporating the following measures:

1. All research staff working on this trial will have completed the required human subject protection education/training.
2. The surgeons who participate in this clinical study will be trained to select the qualified patients and perform the proper technique for use of the collagen device. The surgeons, Dr. Lyle Micheli, Dr. Yi-Meng Yen and Dr. Dennis Kramer will be trained by the PI on proper surgical technique and will practice this technique prior to performing the surgery on any study patients. They each have over 15 years of surgical experience.
3. Patient selection is of paramount importance. Patients will be thoroughly screened and only those that meet the eligibility criteria will be offered participation in the study. The inclusion and exclusion criteria have been carefully chosen to describe the best patient for the surgical implant procedure. Patients will have all of their questions answered by the licensed professional during the informed consent process and it will be made clear that participation is voluntary. The recruitment process will be documented by a consent form, which will be signed by the patient and/or legal guardian. Patients will be given a signed, original copy of the consent form for their records.
4. Patients will be placed on a post-operative management plan commensurate with their medical history and operative recovery protocol.
5. The patient will be closely monitored for complications and adverse events using case report forms and patient records. Any complaint of symptoms will be recorded if it results in an unscheduled visit when a patient presents with new or worsening pain, neurological, and/or functional symptoms as compared to a previous visit and or when surgical intervention is required to resolve the event.
6. The PI and research team will review adverse events on an ongoing basis at every planned and unplanned clinical visit and report them to the sponsor and other appropriate parties, as required, in a timely manner. Investigators will be instructed to call in any unexpected or potentially serious adverse events as per federal regulation.

7. If an unreasonable risk occurs, the PI will terminate the clinical investigation within a timely fashion from the date the risk was determined to be unreasonable, with consideration given to the risk.
8. Additional details about risk mitigation are available in the Failure Mode Effect Analysis (FMEA) and hazard identification documentation found in section 1.9.11 Stopping rules**Error! Reference source not found.**

1.9.10 *Justification for the Investigation*

The annual incidence of ACL injury in the US is estimated at 1 per 1,000 people [46]. ACL injuries have immediate and long-term effects on the quality of life, and are known risk factors for post-traumatic osteoarthritis [47]. In the past, surgeons tried to repair the ACL; however, it failed to heal in over 90% of patients [48]. The reason for this was unknown. Thus, the current gold standard of treatment, ACL reconstruction, which involves removal and replacement of the ligament with a tendon graft, has become popular. However, patients treated with ACL reconstruction continue to exhibit progressive articular cartilage and joint damage in the injured knee. A recent prospective cohort study suggests that 62% of ACL reconstructed patients with an isolated ACL injury presented with radiographic evidence of posttraumatic osteoarthritis 10–15 years post-surgery [49]. Considering that many patients sustain ACL injuries before the age of 16, these injuries may place young patients at risk for premature post-traumatic osteoarthritis before age 30 even with our current best treatment methods.

In our preclinical studies, we have found that use of a bridge-enhanced ACL repair technique, using the BEAR® Implant, results in improved healing of the ACL, avoidance of the need to harvest a graft and a significant decrease in the incidence of post-traumatic osteoarthritis. Biocompatibility and sterilization studies suggest the device is biocompatible and sterile. Thus, this new technique could represent a less invasive method of ACL surgery with equivalent mechanical results to the current technique and the potential future benefit of cartilage protection. A clinical study of a small number of patients revealed no serious adverse effects with use of this technique in human patients. Now a non-inferiority trial of efficacy to show this less invasive technique gives similar outcomes to the standard procedure of ACL graft reconstruction is proposed.

The potential benefits of Bridge-Enhanced ACL repair are expected to outweigh the potential risks. If the Bridge-Enhanced extracellular matrix sponge (BEAR® Implant) allows the ACL to regenerate with outcomes that are non-inferior to that of a reconstructed ACL, patients can avoid the more invasive reconstruction that requires harvest of a graft from the hamstring tendons to replace the ruptured ACL. While the use of allograft tendon (cadaver graft) also avoids the need for harvesting hamstring or patellar tendon for an autologous graft, the use of allograft is not recommended in patients under 25 years of age, due to a relatively high failure rate of allograft (reported rates of 20 to 30%) and risk of needing additional surgery on the knee within two years of surgery (30%). Therefore, autograft is almost exclusively used in this patient demographic. Furthermore, unlike standard reconstruction where any remaining ACL tissue is removed, this new technique preserves the anatomic and physiologic characteristics of the ligament. The surgery requires less instrumentation (and thus, less potential for contamination), and results in less bone loss for the patient. Finally,

although patients in this study will not be followed long enough to assess development of arthritis, earlier work in our pre-clinical large animal models showed a lower rate of post-traumatic arthritis in bridge-enhanced repairs as compared to standard reconstructions [115].

1.9.11 *Stopping Rules*

Early stopping of the trial for safety related reasons will be considered by the Data Monitoring Committee consisting of two orthopedists and an immunologist. The committee will be notified after any joint infection and the committee will meet/conference call as soon as possible after two such infections have occurred. They will use the following rule as a guideline in consideration of early stopping and the committee may deviate from the rule based on clinical expertise, judgment, and a global review of trial methodology. Early stopping will be considered if, in the Intervention Group, two or more of the first 20 subjects or if three or more of all Intervention subjects, develop a deep joint infection, or experience a serious adverse event of any type thought to be related to the BEAR® Implant. **Table 4** shows the probability of triggering this rule, as a function of the true underlying (but unknown) event rate assuming a total of 60 BEAR patients. (The calculations are relatively insensitive to this total sample size.)

Table 4: Stopping rule probabilities as a function of true event rate.

True event rate	0.01	0.05	0.10	0.20	0.30
Probability [≥2 events of first 20]	1.7%	26.4%	60.8%	93.1%	99.2%
Probability [≥3 events of 60]	3.3%	60.7%	95.1%	>99.9%	>99.9%

For example, with a true background event rate of .01, there is a very small chance (1.7%) of triggering the stopping rule within the first 20 patients or overall (3.3%), but if the true rate is .20, the rule would be triggered with high probability (93.1% within the first 20 patients, >99.9% overall). This rule is to be considered a guideline and the committee may deviate from the rule based on clinical expertise, judgment, and a global review of trial methodology and conduct.

1.10 Device Information

1.10.1 *BEAR® Implant*

- Other names for the drug(s)/device: In our prior IDE application, the device was called the BEAR™ Scaffold.

- Classification – type of agent/device: Experimental Device, Category A, Class III

- Mode of action: Absorbs autologous blood and holds it in the wound site of the ACL, allowing the cells in the blood (platelets, white blood cells) to stimulate healing of the ligament.

- Storage and stability: Can be stored at room temperature for twenty-four months.

- Preparation: The implant is removed from its double peel pack at the time of surgery and sutured into place during surgery.

- Route of administration for this study: Surgical, via a mini-arthrotomy.

- Incompatibilities: Unknown.

- Availability: Provided by study sponsor. Manufactured using GLP conditions with design control at Boston Children's Hospital.

- Side effects: Unknown, but may include insufficient healing of the ligament, infection, inflammation, knee stiffness.

- Nursing implications: The outer peel pack is not sterile on its outer surface. The inner surface of the outer peel pack and entire inner peel pack are sterile, as is the device.

1.10.2 *Return and Retention of Study Device*

Please return any unused study devices to the MIACH™ Laboratories in the Orthopaedic Research Laboratories on Enders 2. Complete address below:

MIACH™ Laboratories
Enders 216.3
Boston Children's Hospital
300 Longwood Ave
Boston, MA 02115

1.11 Data Management Methods

1.11.1 *Data Management and Record Keeping*

Information that is typically collected as part of routine care will be stored in the patient's medical record. Data obtained exclusively for research purposes will be stored in a separate research folder, unless it is deemed clinically relevant, in which case it will also be placed in the medical record.

1.11.2 *Source 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 a variety of original documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, patients' 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, patient files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

1.11.3 *Case Report Forms*

The study case report form (CRF) is the primary data collection instrument for the study and will be developed by the research team. 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 recording error has been made, to correct such an error, draw a single straight line through the incorrect entry and record the correct data above it ("DO NOT ERASE OR WHITE OUT ERRORS".) All such changes must be initialed and dated. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. The case report forms can be found in the study Manual of Operations.

Case Report Forms have been created for screening for patients who would meet the inclusion criteria, a baseline history and physical examination form, imaging, surgery, the history and physical exam at each follow-up appointment, adverse event reporting and the conclusion of a patient's participation in this trial. The detailed case report forms can be found after this section.

1.11.4 *Confidentiality and Security*

Information about study patients will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Data will be entered by the clinical sites onto electronic CRFs in a 21 CFR Part 11 compliant Electronic Data Capture System (EDC). The database will be maintained by a data management group contracted with the Sponsor. In order to maintain confidentiality, each subject will be assigned a unique study identification (ID) number which will be recorded on all study documents and used to enter data into the system.

All study data will be recorded in source documents and transferred to the official electronic case report forms The source documents will be maintained at each site.. Identifiable data, such as patient name, contact information and medical record numbers will only be stored at the clinical study site. All study-related documents will be archived for the required length of time after completion of the study. Database backup routines are automated and executed daily to ensure data safety and reliability.

1.11.5 *Records Retention*

Records will be retained for the maximum length of time necessary, as dictated by the sponsor and FDA policies.

1.12 Quality Control Method

Data monitoring will be ongoing and focus on study performance with respect to patient recruitment, retention and follow-up, completion and flow of data forms, safety reporting, protocol adherence and quality of data. Monitoring will also include the ongoing review and assessment regarding the incidence, frequency, and severity of adverse events. It is the primary responsibility of the sponsor to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as adherence to the individual reporting requirements described within the protocol and per individual reporting requirements set forth by the IRB.

1.12.1 *Data Monitoring*

Study monitoring functions will be performed by Miach clinical (contract) monitors and/or clinical monitors from a qualified independent clinical research organization (CRO) in compliance with recognized applicable U.S. regulations (21 CFR Part 812 [Investigational Device Exemptions], 21 CFR Part 50 [Protection of Human Subjects] and 21 CFR Part 56 [Institutional Review Boards]), Good Clinical Practice, and recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964. The monitors will oversee progress of the investigation at each investigational site and work with site research coordinators to ensure adherence to the study protocol and informed patient consent obligations, as well as the aforementioned regulations and standards.
The frequency of monitoring will be adequate to assure the integrity of the study and will be defined in the monitoring plan. For example, initially, data will be reviewed after approximately two patients are enrolled and then again after two controls are enrolled. Every CRF completed to date and consent form will be reviewed for these subjects. The

same procedure will be followed after approximately the fifth patient and fifth control are enrolled. At this visit, the monitor will review any additional CRFs collected for the two patients and controls reviewed initially, as well as the consent forms and adverse event forms for every subject enrolled to date. The final monitoring visit will take place after the last patient and last control have completed the trial. The remaining CRFs for all subjects previously reviewed, will be examined, such that their whole research record will have been 100% monitored. The remaining consent documents and AE forms for all subjects will also be inspected. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, detailed medical records, diagnostic laboratory, etc.), and has adequate space and time to conduct the monitoring visits. Monitoring reports will be completed for all visits. Reports will include the date of the visit, a list of study site personnel, and a summary of the findings, problems, and actions taken to correct any deficiencies. The Data Monitor may recommend additional record review at any time, if she feels this is necessary.

1.12.2 *Data Monitoring Committee*

There will be a Data Monitoring Committee (DMC)made up of three physicians, two orthopedists and one immunologist, who will provide safety oversight and give consideration to early stopping of the trial. In the safety monitoring role, the DMC will establish a charter including a mission statement, operating procedure and proposed monitoring criteria for the study, including any required interim analysis time points for assessing safety and proposed study stopping rules. The rule is outlined in Table 4. The specific stopping rules shall remain confidential to the sites. Written minutes of all meetings shall be developed after each DMC meeting and major conclusions (i.e. the assessment for study continuation vs. stopping) shall be documented. Meeting summaries shall be included in reports to the IRB as appropriate. DMC will include a regular assessment of the number and type of adverse device events occurring for each patient as well as an aggregate review of the accumulated safety data. For every UADE reported to the FDA, the report will also be supplied to the DMC as soon as possible and, in no event, later than 10 working days after the sponsor first receives notice and determines a UADE has occurred. Any additional clinical information or laboratory results requested by the DMC will be provided in a timely manner.

1.12.3 *Safety Monitoring Plan*

A medical monitor will be assigned to review all events and event rates in the trial. A safety plan will be written to document the process for review and reporting of any events that meet regulatory reporting requirements.

1.12.4 *Auditing and Inspecting*

The sponsor and investigators will permit study-related monitoring, audits, and inspections by the sponsor, the independent data monitor and government regulatory bodies, 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.

1.12.5 *Changes and Amendments to the Protocol*

No changes will be made to this protocol unless specifically approved by Miach Orthopaedics, Inc. and the changes documented in an addendum to the protocol.

1.12.6 *Ethical and Legal Considerations*

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator must comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

1.13 **Data Analysis Plan**

Baseline characteristics and safety and efficacy outcomes will be summarized descriptively within each group using means, standard deviations, percentiles (e.g., minimum, median, maximum) for continuous variables and with counts and percentages for categorical variables. Patterns of change over time will be summarized using graphical methods and summary statistics.

The difference in means between groups, (BEAR minus control) will be calculated for continuous efficacy endpoints as a measure of relative treatment efficacy. Assuming higher scores are better, a positive difference in means will indicate that BEAR is better than control and a negative difference that BEAR is worse. (If lower scores are better, this interpretation is reversed.) 95% confidence intervals for the difference in means will be used to show a plausible range of relative treatment efficacy. Analyses of anteroposterior knee laxity, range of motion and muscle strength measures that are performed on both knees will be based on within-patient side-to-side differences (involved minus contralateral knee) or percent deficit (side-to-side difference as a percent of the contralateral knee). The intervention groups will then be compared with respect to these side-to-side differences.

For the patient-reported functional primary endpoint, IKDC score at 24 months, non-inferiority for BEAR will be demonstrated if the entire 95% CI lies to the right of the non-inferiority margin of -11.5. For the biomechanical primary endpoint, knee laxity at 24 months, a lower side-to-side difference (involved minus contralateral knee) is desirable so non-inferiority will be demonstrated if the 95% CI for the treatment group difference lies to the left of the non-inferiority margin of +2.0 mm. Choice of these non-inferiority margins is discussed further in Section 14. Similar analyses will be conducted at each visit during which the measurements are made although these will be considered secondary analyses.

Overall, demonstration of non-inferiority requires that both primary endpoints meet the CI criteria described above. Although the 95% CIs are two-sided intervals, only one side is relevant for demonstrating non-inferiority so the Type I error rate for each endpoint is α =0.025 and the combined statistical procedure is protected at an overall Type I error rate of $\alpha \leq 0.05$.

In addition to conducting the non-inferiority analyses for all patients, the hamstring-preference stratum is a subgroup of special interest and we will conduct the analyses within that group as a pre-specified subgroup analysis. If non-inferiority is demonstrated in the hamstring-preference subgroup, then we will test for superiority for the hamstring strength endpoint at 3 and 6 months in that subgroup. We hypothesize superiority of BEAR over hamstring graft at these early time points.

Treatment comparisons will be conducted both on an intention-to-treat (ITT) basis, with patients included in the treatment group they were randomized to, and on a per-protocol (PP) basis, with patients included in the surgical group according to which type of surgery they received. Whereas in a superiority trial an ITT analysis generally underestimates the treatment difference and is therefore conservative, in a non-inferiority trial the ITT analysis generally favors the conclusion of non-inferiority so demonstrating consistent conclusions with both ITT and PP approaches lends credibility to the conclusions.

In addition, we will use multiple imputation to investigate how robust the results are to outcome data that are missing due to attrition or other reasons. These analyses will include a “tipping point” strategy, in which missing data are imputed under a range of assumed biases until the p-value changes from significant to non-significant or vice versa. This sensitivity analysis identifies how non-representative the missing data would have to be to alter conclusions.

Outcomes measured longitudinally will be compared between treatment groups at each time point. Generally, the intervention groups will be compared using t-tests, Mann-Whitney tests and Fisher’s exact tests as appropriate and these tests will be interpreted carefully taking into account limitations of the design and statistical methods.

1.14 **Statistical Power and Sample Size Considerations**

Generally, non-inferiority will be tested by constructing a 95% confidence interval for the difference between the intervention group means and observing whether or not the confidence interval overlaps a pre-specified non-inferiority margin for that endpoint.

Of the two primary outcomes, the knee laxity endpoint requires the larger sample size. For AP laxity, we used an estimated SD=2.7mm from Fleming et al[116] based on the pooled standard deviations of the within-patient side-to-side difference scores for both the low tension and high tension groups (personal communication). Based on the Arneja and Leith[117] recommendation of a 2 to 3 mm threshold as the basis for a diagnostic test, we selected a clinically important difference to be 2.0 mm. Under this assumption, and assuming a 2:1 randomization, a sample size of N=69 (46 BEAR, 23 Control) will provide 80% power to test non-inferiority as described above. Inflating the sample size to account for an anticipated 20% attrition brings the sample size goal to N=87.

Because of our special interest in the hamstring graft subgroup, we will recruit until we have met the target N=87 subjects in the hamstring-preference stratum. Based on historical data at our institution, we expect ~85% of all randomized patients to be in the hamstring-preference subgroup so we project a total sample size, including subjects in the BPTB-preference stratum, to be about N=100. The remainder of the power calculations will be based on the smaller number of N=87 and therefore power is slightly underestimated.

Our second primary endpoint is the IKDC score at 24 months post-surgery. Irrgang[118] concluded that a change in the IKDC of 11.5 points was an optimal threshold with high sensitivity for distinguishing those who were or were not improved. Therefore, we used 11.5 as the non-inferiority margin. In a cohort of 69 subjects reported by Reinke[119], the SD of IKDC scores at two years was 10.5. In a systematic literature review of reconstruction and non-surgical cohorts with mean 13.9 years follow-up, Chalmers[120] reported a mean difference in IKDC scores of 5.8 and an effect size of .73, which implies a SD of 7.26. We used the most conservative of these SD estimates, 10.5. With that SD and the clinically important difference of 11.5 as recommended by Irrgang [118], our sample size of 87 patients (minus 20% projected attrition) gives us 99% power to detect non-inferiority between the groups for this primary outcome measure.

To project statistical power for some additional secondary endpoints, we considered the KOOS scores as a second patient-reported outcome measure. Roos et al [96] reported SDs for the Sports and Knee Related Quality of Life (krQOL) subscales at 6 months post ACL reconstruction of 15.8 and 10.1, respectively, and Roos and Lohmander [121] concluded that 10 points represented a clinically significant effect for the KOOS. Under these assumptions, our sample size of 87 patients will provide 69% and 97% power to test non-inferiority for the Sports and krQOL subscales of the KOOS, assuming 20% dropout at the two year time point.

For hamstring strength deficits after ACL surgery, Landes et al[122] reported a mean hamstring strength side-to-side difference of 17 Nm (a 23% deficit relative to the contralateral knee), with a SD of 14 Nm, 2 years after ACL reconstruction with hamstring tendon. Data obtained at Boston Children's Hospital for 235 patients undergoing

autologous hamstring grafts showed a mean 29% deficit (SD = ±23%) of hamstring strength at six months post-operatively. From the initial BEAR study, the patients undergoing ACL reconstruction had an average 33% deficit of hamstring strength at the six month time point, while the BEAR patients had only a 13% deficit, an estimated 20-point difference. At 3 months there was a larger treatment effect observed, 25 points. Assuming a SD of ±23%, our sample size of 87 patients (minus 20% projected attrition) will have 91% power to detect a 20-point difference in percent hamstring strength deficit at 3 or 6 months.

For imaging outcomes, we don't anticipate any significant changes in joint space on plain radiography at two years, so while we will collect these images at time zero and year two, this will be simply for baseline recording in the event the results of this proposed study warrant longer term study of these patients at time points when we might anticipate seeing joint space narrowing, such as at 6 or 10 years after injury as has been done for prior ACL reconstruction cohort studies.

Finally, with the 2:1 randomization, our sample size of N=87 will yield 58 BEAR patients, 46 after 20% attrition, for observing rare safety events such as graft removal due to an immune response. Forty-six evaluable patients will provide a 90% chance of observing at least one event if the true event rate is .049. However, such events are likely to occur early in follow-up, before potential dropout, so the number of evaluable patients could be as high as 58. In addition, if we consider the 10 BEAR patients in the pilot study, we could have a maximum potential of 68 evaluable patients in which to observe rare safety events. Therefore, we will plan to consider the safety outcomes for the patients in the initial BEAR I trial (IDE G140151) in addition to those in this current IDE study to improve our power to detect any differences between the ACL reconstruction and BEAR groups for these relatively rare safety events. With 58 or 68 evaluable patients, we will have a 90% chance of observing at least one event even for events that are more rare (event rates .039 or .033, respectively).

1.15 **Study Organization**

This will be a single clinical site prospective controlled trial conducted in the Department of Orthopaedic Surgery at Boston Children's Hospital. Miach Orthopaedics, Inc., will serve as the IDE Sponsor. Patients will be recruited from the practices of and operated on by Dr. Lyle Micheli, MD, Director of the Division of Sports Medicine, Dr. Yi-Meng Yen, and Dr. Dennis Kramer. All surgeons are already proficient with ACL reconstruction with hamstring tendon and will be trained on the bridge-enhanced repair technique prior to performing this operation. Six-month, 2 year, 6 year and 10 year study MRIs and x-rays will be read clinically at Boston Children's Hospital, and de-identified copies will be sent to Braden Fleming, PhD, a bioengineer at Brown University/Rhode Island Hospital, who developed and validated the MRI protocol that will be used to predict ACL strength for this study. Dr Fleming, or one of his team members, will be one of the readers of the MRIs for the experimental analyses of correlates of MR images with patient outcomes, as well as the analysis of the x-rays for radiographic changes consistent with osteoarthritis. Dr Martha Murray's lab will store the research samples (blood

serum/plasma and urine) for future use, to be determined later by Investigators. There will be a Data Monitoring Committee made up of three physicians, two orthopedists and one internal medicine physician. The committee's role is to review adverse events as they occur, to ensure individual patient safety and safety of the overall trial. Study monitoring functions will be performed by independent contract clinical monitors and/or clinical monitors from a qualified independent clinical research organization (CRO) as designated by the Sponsor.