A Prospective, Randomized Double-Armed Efficacy Evaluation of AposTherapy® for the Treatment of Knee Osteoarthritis

Regulatory Sponsor:	*NYU Langone Medical Center* *Department of Orthopaedic Surgery* *333 E. 38th Street* *New York, NY 10016*
Funding Sponsor:	*Apos US Management, Inc.* *708 3rd Avenue, 3rd Floor,* *New York, NY 10017*
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Study Device (Non-Interventional)	*AposTherapy® System*
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Protocol Number:	*S14-02127*
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Study Summary

Title	*A Prospective, Randomized Double-Armed Efficacy Evaluation of AposTherapy® for the Treatment of Knee Osteoarthritis*
Short Title	*Efficacy of AposTherapy® in Knee OA*
Protocol Number	*S14-02127*
Methodology	*A prospective, interventional, randomized, double-arm clinical evaluation study*
Study Duration	*12 Months*
Study Center(s)	*Single-center*
Purpose	*To examine the efficacy of AposTherapy® versus a control group, in the short-term at 6 months and in the long-term at 12 months post-treatment, with the primary efficacy assessment based on improvement in knee pain score and improvement in function in patients following diagnosis of knee osteoarthritis (OA).*
Number of Subjects	*120 subjects (60 patients in each group)*
Diagnosis and Main Inclusion Criteria	*Patients suffering from symptomatic unilateral or bilateral knee OA; males and females between the ages of 40-75; Having radiographically assessed OA of the knee; and, having VAS-Pain ≥ 3, on a scale between 0-10.*
Study Product and Planned Use	*AposTherapy® is a non-surgical, non-drug treatment for knee pain. This non-invasive biomechanical device is comprised of convex adjustable pods that are placed under the hind-foot and fore-foot regions of each foot.*
Reference therapy	*For the active group, every biomechanical device will be personally calibrated to suit the individual patient and their unique therapeutic needs. The comparator group will receive a non-calibrated sham device.*
Statistical Methodology	*The analysis of power is performed conservatively by assuming the largest variability in pain scores observed in the preliminary data (e.g., reduction of pain scores of 3.0 in active group and 0 of control group with a pooled standard deviation of 3.60 corresponds to an effect size of 0.8. After accounting for a 10% loss to follow-up we would expect to enroll 60 patients in each group for a total of 120 patients. With 120 samples (60 each), the two-sided t-test will have 80% power at the 0.05 significance level to detect differences of pain score of 0.8 SD units between control and case*

I. PURPOSE OF THE STUDY AND BACKGROUND

Purpose

The purpose of this study is to examine the efficacy of AposTherapy® versus a control group, in the short-term at 6 months and in the long-term at 12 months post-treatment, with the primary efficacy assessment based on improvement in knee pain score and improvement in function in patients following diagnosis of knee osteoarthritis (OA).

Background & Study Rationale

With the rising incidence of osteoarthritis (OA) in today's aging population, increased attention has been directed toward the management of this debilitating disease. OA ranks as the number one most expensive condition among Medicare patients over the age of 65 [Cutler, 2012]. For knee osteoarthritis, total knee arthroplasty remains an effective and successful treatment option, with well over 700,000 total knee arthroplasties (TKA's) performed annually in the United States [CDC 2010]. Despite the popularity of TKA, the progression of knee OA to end stage degenerative joint disease requiring surgery can take a considerable amount of time to manifest [Kalunian, 2014]. Before surgical options are considered, more conservative measures are initially prescribed in the management of patients with knee OA, with non-pharmacologic physical therapy and lifestyle modifications being the first line treatment.

A wide variety of physical therapies have been evaluated for knee OA, ranging anywhere from personalized exercised programs to gait kinematic analysis and correction [Abbott, 2013; Jones, 2013; Della Croce, 2013]. In particular, a biomechanical approach to reducing pain within a patient's knee can involve off-loading the diseased compartment, as well as promote focused muscle strengthening, thereby providing additional dynamic stability to the knee. For patients with mild varus deformities, some mixed success has been reported, such as the use of lateral wedged insoles. In these studies, the knee adduction moment was successfully reduced, demonstrating the biomechanical success of the insoles. However, the results regarding the correlation to pain reduction were mixed, though it has exhibited promise and prompted suggestion of modest improvement in pain and function [Jones, 2014; Skou, 2013].

AposTherapy is a non-invasive solution to restore normal knee kinematics during gait and activities of daily living. Through a personalized gait analysis, a patient's shoes are customized to adjust the ground reaction forces transmitted to the knee. This theory is in parallel with the biomechanical approach to lessen the moment arm responsible for loading on the patient's diseased and symptomatic knee compartment. In addition, the shift in external forces of the corrected gait pattern, induced by the biomechanical device, challenges neuromuscular control of the surrounding dynamic stabilizers of the knee and in turn can condition a more coordinated motor response [Bar-Ziv, 2010; Haim, 2011]. AposTherapy patients can also potentially experience more than biomechanical advantages. Having dedicated equipment for exercising can serve as a reminder, where AposTherapy patients can gain a psychological edge in the motivation of maintaining a physically active and healthy lifestyle.
With the proper application of this biomechanical device, this study aims to evaluate the effect of AposTherapy® on pain and function as compared to a control group who receive a non-calibrated biomechanical device. Successful use of the AposTherapy® device can potentially decrease pain and improve function in patients with established OA, while encouraging a more active and healthy lifestyle.

Study Design

The study will be divided into two phases:

Phase I - A prospective, interventional, randomized, double-arm clinical evaluation of patients who have been diagnosed with OA of the knee. The active treatment arm (personally calibrated biomechanical device) will be compared to a control arm (sham-placebo device) **(similar shoes without biomechanical elements).**

Phase II – Open-label, cross-over study design. After the completion of phase one patients will be un-blinded to their group allocation. Patients that were allocated to the sham-placebo control group will cross

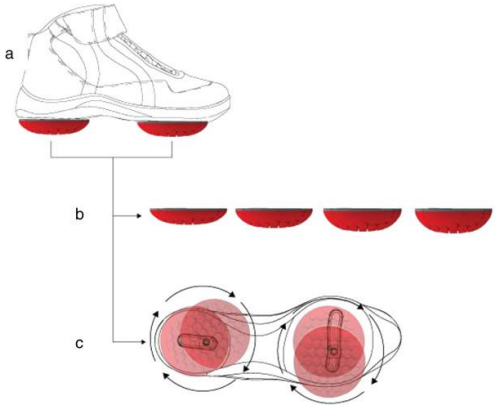
to the active group and will receive the AposTherapy treatment. Patients that were allocated to the active group will continue with treatment.

Study Device

AposTherapy® is a non-surgical, non-drug treatment for knee pain. This non-invasive biomechanical device is comprised of convex adjustable pods that are placed under the hind-foot and fore-foot regions of each foot. For the active group, every biomechanical device will be personally calibrated to suit the individual patient and their unique therapeutic needs. The comparator group will receive a non-calibrated sham device.

The Apos device utilized during the AposTherapy treatment is listed as class I medical device with the FDA. The device is not intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; It is not purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; It is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; It does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

Figure 1. The biomechanical device



The Apos Device. (a) *Biomechanical device comprising two individually calibrated elements and a foot-worn platform. The elements are attached to a platform under the hindfoot and forefoot regions.* ***(b)****The biomechanical elements are available in different degrees of convexity and resilience.* ***(c)*** *The specially designed sole of the platform includes two mounting rails and a positioning matrix to enable flexible positioning of each biomechanical element. [Elbaz, 2014].*

Figure 2. The sham device

Objectives and Hypothesis of Study

1. The primary objective is to evaluate the efficacy of AposTherapy® at 6 months, with the primary efficacy assessment based on improvement in knee pain score and improvement in function in patients with knee OA. The hypothesis is that patients fitted with the calibrated AposTherapy® device will demonstrate an improvement in knee pain intensity and improvement in function compared to patients who are fitted with a sham-placebo Apos device.

2. After completion of 6 months of therapy, patients will be un-blinded to their group allocation and the second phase of the study will commence, including the following aims:
   a. To evaluate the long-term (12 months) effect of AposTherapy® on the level of pain and the level of function of patients with knee OA. We hypothesize that patients will maintain the diminished levels of pain and improved function.
   b. To evaluate the changes in the level of pain and the level of function of patients that were originally allocated to the control group and will now cross-over and commence AposTherapy® treatment for 6 months. We hypothesize that patient will report an improvement in the level of pain and improvement in function following 6 months of treatment.

Primary Efficacy Endpoints

- Phase I:
  - Improvement in knee pain score and improvement in function, as measured by change from baseline Western Ontario and McMaster University (WOMAC) score to 6 months post treatment.

- Phase II:
  - Long-term effect (12 months) of AposTherapy on pain and function, as measures by WOMAC, of patients with knee OA
  - Improvement in knee pain and knee function, as measured by WOMAC, of patients with knee OA that were allocated to the sham control group and have crossed-over to the active group, receiving AposTherapy for 6 months.

Secondary Efficacy Endpoints

- Phase I:
  - Improvement in WOMAC scores between all study time points – pre-treatment and following 3 months and 6 months post-treatment;
  - Improvement in Visual Analog Score (VAS) score between all study time points;
  - Improvement in Short-Form 36 (SF-36) score between all study time points;
  - Reduction in usage of pain killers or NSAIDS

- Phase II:
  - Original Active group - Improvement in knee pain and knee function scores, as measured by change from baseline WOMAC score to 12 months post treatment;
  - Original Active group - Improvement in VAS score between baseline and 12 months post treatment;
  - Original Active group - Improvement in SF-36 score between baseline and 12 months post treatment;
  - Original Active group - Reduction in usage of pain killers or NSAIDS
  - Cross-over group - Improvement in WOMAC scores between all study time points – pre-treatment and following, 3 months and 6 months post-treatment;
  - Cross-over group - Improvement in Visual Analog Score (VAS) score between all study time points;
  - Cross-over group - Improvement in Short-Form 36 (SF-36) score between all study time points
  - Cross-over group - Reduction in usage of pain killers or NSAIDS

Outcome Measure Evaluation Criteria

Western Ontario and Mac Master University (WOMAC) – the WOMAC is a self-administered osteoarthritis outcomes instrument designed to assess lower extremity pain and function in osteoarthritis of the knee or hip. The minimal clinically important difference (MCID) proportion is a 16.0% reduction in WOMAC [Hmamouch, 2014].

Visual Analog Score (VAS) Scale - the VAS is a validated pain scale that asks subjects to rate the amount of pain they are currently experiencing on a line up to 100mm (no pain is equal to 0mm and the worst imaginable pain is equal to 100mm). An improvement of 20 points from the baseline score is considered a statistically significant improvement at that visit [Gallagher, 2001].

Short-Form (36) Health Survey – the SF-36 is a patient reported survey of health that is designed to measure health status. The survey consists of eight (8) sections, where the lower the score the more disability and the higher the score the less disability [Maruish, 2009].

At each follow-up visit, subjects will be asked on their use of any rescue medications or therapy for their knee pain. Rescue medications or therapy will include, but are not limited to, NSAIDs, physical therapy and surgical interventions. While participating in the study, subjects should refrain from taking corticosteroid and/or hyaluronic acid injections. Subjects will also be asked about their compliance with the device (ex. how long and how often the device was worn?). Research personnel will collect and record such data and note when the subject had the intervention.

Additionally, at each follow-up visit, subjects will be asked to report any changes in their knee symptoms. This change in symptoms can include, but are not limited to, pain, swelling, redness, or any overall changes in their health since the screening/baseline visit. Research personnel will collect and record such data and note when these changes occurred.

II. CHARACTERISTICS OF THE RESEARCH POPULATION

Number of Subjects
A total of one-hundred and twenty (120) patients will be enrolled in this study (60 patients assigned to each group).

Gender of Subjects
Men and women will be included in this study.

Age of Subjects
Subjects will be at least 45 years of age and no older than 75 years of age

Racial and Ethnic Origin
There are no enrollment restrictions based on race or ethnic origin.

Inclusion Criteria

- Males and females between the ages of 40-75;
- Patients suffering from symptomatic unilateral or bilateral knee OA at the medial compartment for at least six months;
- Fulfilling the ACR clinical criteria;
- Having radiographically assessed OA of the knee with a Kellgren-Lawrence grade more than or equal to grade 2; and,
- Having VAS-Pain ≥ 3, on a scale between 0-10.
- Patients who have a shoe size between US 4 and US 12

Exclusion Criteria

- Patients suffering from acute septic arthritis.
- Patients who received a corticosteroid injection within 3 months of the study.

- Patients who received hyaluronic acid (HA) injections within 6 months of the study
- Patients suffering from avascular necrosis of the knee.
- Patients with a history of knee buckling or recent knee injury.
- Patients who have had a joint replacement or other major surgery to the knee, hip or ankle (ipsilateral or contralateral side).
- Patients suffering from neuropathic arthropathy.
- Patients with an increased tendency to fall.
- Patients exhibiting a lack of physical or mental ability to perform or comply with the study procedure.
- Patients with a history of pathological osteoporotic fracture.
- Patients suffering from symptomatic degenerative arthritis in lower limb joints other than the knees.
- Patients with referred pain in the knees from primary back or hip joint pain.
- Patients with neurological deficits to the lower extremity (ex. foot drop)
- Patients whose shoe size is less than US 4 and greater than US 12
- Patients who have had arthroscopy within 6 months of the study
- Patients with inflammatory arthropathy
- Patients with any central nerve system disease/neurological problem (i.e. Parkinson's, post CVA (stroke), etc.).

Vulnerable Subjects
We do not intend to enroll vulnerable subjects.

Subject Withdrawal
Patients are free to withdraw at any time from the study. While participating in the study, patients should avoid any other treatment modality apart from rescue pain medication (Acetaminophen/Paracetamol) as long as it is possible. If patients require injection therapy or surgery on the study knee(s) during the course of the study, the patient will be withdrawn from further data collection.

III. METHODS AND PROCEDURES

Sample Size Analysis
Assuming normality on the data, we calculated the statistical power for various detectable effect sizes listed in Table X using PASS 2011 software (http://www.ncss.com/download_PASS11.html). The analysis of power is performed conservatively by assuming the largest variability in pain scores observed in the preliminary data (e.g., reduction of pain scores of 3.0 in active group and 0 of control group with a pooled standard deviation of 3.60 corresponds to an effect size of 0.8. After accounting for a 10% loss to follow-up we would expect to enroll 60 patients in each group for a total of 120 patients. With 120 samples (60 each), the two-sided t-test will have 80% power at the 0.05 significance level to detect differences of pain score of 0.8 SD units between control and case [Bar-Ziv, 2013].

Methods and Procedures

Phase I - A prospective, interventional, randomized, double-arm clinical evaluation study. Patients over the age of 45 years who come into the office with symptomatic knee pain, and a Kellgren-Lawrence grade more than or equal to grade 2, and have pain levels above 2\10 may be included in the study.
Patient progress will be monitored for a six (6) months period, consisting of information from office visits and scores obtained at each study visit. Patients will be asked to return to the physician's office at specific time points (3 months and 6 months after the initial visit). After signing consent patients will be randomized to one of two groups:

- **Group 1: AposTherapy® Active Arm**
- **Group 2: AposTherapy® Control Arm**

Randomization Process
Blocked randomization will be used to assign subjects to their respective treatment arms. The allocation ratio will be one to one and the random method of selection will be through a computerized random

number generator. The on-site coordinator will be responsible for entering and maintaining the subject randomization information. After randomization has been completed, research personnel will review and document the patient's demographics, medical, and surgical history on the study case report forms. The baseline patient-reported outcome questionnaires will then be completed (these include the WOMAC, VAS, SF-36). The physician and research team will then perform a clinical evaluation of the knee.

Active Arm Process
During the baseline visit, the research and Apostherapy® team will conduct a clinical evaluation in order to develop a personalized therapy program for the patient. Utilizing state-of-the-art technology, an in-depth analysis consisting of step length; load distribution on each leg; walking velocity; and gait symmetry, will be obtained. This will give the physician and research team a better understanding of what movement may be causing the patient's pain, and what the appropriate treatment method will be. Based on the evaluation, the patient will receive a personally-calibrated foot-worn biomechanical device to help relieve pressure from the symptomatic areas, and re-train the muscular system around the joints. During their daily routine, patients will be asked to wear their custom-worn device for approximately 2 hours per day, throughout the study duration, starting with less than an hour of walking around the house and gradually increasing wearing time to outdoor walking. Patients will be asked to come to follow-up visits at the treatment center (located at 708 3rd Avenue, 3rd Floor, New York, NY 10017) at the following time points: 3 -4 weeks, 7 weeks, 12 weeks, 18 weeks, 24 weeks, 27 weeks, 36 weeks, 42 weeks and 52 weeks. During these visits the biomechanical device will be adapted according to the clinical needs of the patient

AposTherapy® Control Arm Process
During the baseline visit, the Apostherapy® team will meet with the patient to set them up with their device. Utilizing state-of-the-art technology, an in-depth analysis consisting of step length; load distribution on each leg; walking velocity; and gait symmetry, will be obtained. A personally-calibrated device will not be used for patients randomized to this group. The patient will receive a sham-placebo foot-worn biomechanical device. During their daily routine, patients will be asked to wear their custom-worn device for approximately 2 hours per day, up until the 6 month follow-up visit, starting with less than an hour of walking around the house and gradually increasing wearing time to outdoor walking. Patients will be asked to come to follow-up visits at the treatment center (located at 708 3rd Avenue, 3rd Floor, New York, NY 10017) at the following time points: 3 -4 weeks, 7 weeks, 12 weeks, 18 weeks, 24 weeks, 27 weeks, 36 weeks, 42 weeks and 52 weeks. During these visits the biomechanical device will be adapted according to the clinical needs of the patient (this will have no actual effect on the biomechanical device, since there are no biomechanical element in the sham device).

Phase I Study Visits
Patients will be followed for 6 months after enrollment. Patients will be seen for a screening/baseline visit and will then return to NYULMC (the physician's office) for a follow-up visit at, 3 months and 6 months from initial visit.

VISIT 1/2 - Screening/Baseline visit (the screening/baseline assessments may be completed in more than one session):

The following procedures will be conducted at the physician's office located at NYULMC Center for Musculoskeletal Care, 333 E. 38th Street, New York, NY):

- Sign Informed Consent Document;
- Review Inclusion/Exclusion Criteria;
- Randomize patient to one of two study arms;
- Review and document demographics, medical/surgical/concomitant medication history (complete data collection form);
- Physical Knee Evaluation (will include the following, but not limited to):
    - Pain: Note location and activities that increase and decrease symptoms, joint line tenderness, etc.
    - Knee Effusion: Presence or absence

  - Ligament Stability: Anterior drawer test, posterior drawer test, lachman test, pivot shift, valgus/varus stress test.
  - Stability: McMurray test; Apley's Grind test, patellar tilt test, patellar grind test, patellar apprehension test
  - Strength: Muscle strength (quadriceps, hamstrings, Iliopsoas)
  - Range of Motion: Passive and active ROM.
  - Sensation: Reflexes, function, sensation, etc. (normal/abnormal)
  - Posture/alignment: leg length discrepancy, foot position, etc.
- Standard Radiographic Testing: AP and Lateral x-ray views of the knee (to determine K-L grade) These x-rays are part of the standard practice when examining patients who present with osteoarthritis of the knee;
- Complete Patient Reported Outcome Questionnaires:
  - Western Ontario and Mac Master University (WOMAC)
  - Visual Analogue Scale (VAS) pain tool
  - Short-Form 36 (SF-36)
  - Creation of a treatment plan for the patient (time of usage, instructions of use etc…)

The following standard of care procedures will be conducted at the treatment center located at 708 3rd Avenue, 3rd Floor, New York, NY 10017:

- AposTherapy® device calibration according to patient's allocation

VISIT 3 & 4 – Three and Seven Week Follow Up

The following standard of care procedures will be conducted at the treatment center located at 708 3rd Avenue, 3rd Floor, New York, NY 10017:

- AposTherapy® device adjustment

VISIT 5 – 12 Weeks (3 Month) Follow Up (between 76-104 days after baseline)

The following procedures will be conducted at the physician's office located at NYULMC Center for Musculoskeletal Care, 333 E. 38th Street, New York, NY):

- Physical Knee Evaluation (same as screening/baseline)
- Adverse/Reportable Event review
- Review concomitant medications
- Complete Patient Reported Outcome Questionnaires:
  - Western Ontario and Mac Master University (WOMAC)
  - Visual Analogue Scale (VAS) pain tool
  - Short-Form 36 (SF-36)
- Compliance Follow-Up

The following standard of care procedures will be conducted at the treatment center located at 708 3rd Avenue, 3rd Floor, New York, NY 10017:

- AposTherapy® device adjustment

VISIT 6 – 18 Weeks Follow Up

The following standard of care procedures will be conducted at the treatment center located at 708 3rd Avenue, 3rd Floor, New York, NY 10017:

- AposTherapy® device adjustment

VISIT 7 – 24 Weeks (6 Month) Follow Up (between 150-210 days after baseline)

The following procedures will be conducted at the physician's office located at NYULMC Center for Musculoskeletal Care, 333 E. 38th Street, New York, NY):

- Physical Knee Evaluation (same as screening/baseline)
- Adverse/Reportable Event review
- Review concomitant medications
- Un-blinding of patient allocation and beginning of Phase II of the study
- Complete Patient Reported Outcome Questionnaires:
    - Western Ontario and Mac Master University (WOMAC)
    - Visual Analogue Scale (VAS) pain tool
    - Short-Form 36 (SF-36)
    - Subject Satisfaction Questionnaire
- Compliance Follow-Up

The following standard of care procedures will be conducted at the treatment center located at 708 3rd Avenue, 3rd Floor, New York, NY 10017:

- AposTherapy® device adjustment
- Administer device (for patients who have crossed over from control to active)

VISIT 8 – 27 Weeks Follow Up (only for patients that crossed-over from the control to intervention group)

The following standard of care procedures will be conducted at the treatment center located at 708 3rd Avenue, 3rd Floor, New York, NY 10017:

- AposTherapy® device adjustment

VISIT 9 – 36 Weeks Follow Up

The following procedures will be conducted at the physician's office located at NYULMC Center for Musculoskeletal Care, 333 E. 38th Street, New York, NY): **(Cross-Over Patient's Only)**

- Physical Knee Evaluation (same as screening/baseline)
- Adverse/Reportable Event review
- Review concomitant medications
- Complete Patient Reported Outcome Questionnaires:
    - Western Ontario and Mac Master University (WOMAC)
    - Visual Analogue Scale (VAS) pain tool
    - Short-Form 36 (SF-36)
- Compliance Follow-Up

The following standard of care procedures will be conducted at the treatment center located at 708 3rd Avenue, 3rd Floor, New York, NY 10017:

- AposTherapy® device adjustment

VISIT 10 – 42 Weeks Follow Up

The following standard of care procedures will be conducted at the treatment center located at 708 3rd Avenue, 3rd Floor, New York, NY 10017:

- AposTherapy® device adjustment

VISIT 11 – 52 Weeks (1 year) Follow Up

The following procedures will be conducted at the physician's office located at NYULMC Center for Musculoskeletal Care, 333 E. 38th Street, New York, NY):

- Physical Knee Evaluation (same as screening/baseline)
- Adverse/Reportable Event review
- Review concomitant medications
- Complete Patient Reported Outcome Questionnaires:

  - Western Ontario and Mac Master University (WOMAC)
  - Visual Analogue Scale (VAS) pain tool
  - Short-Form 36 (SF-36)
- Compliance Follow-Up

The following standard of care procedures will be conducted at the treatment center located at 708 3rd Avenue, 3rd Floor, New York, NY 10017:

- AposTherapy® device adjustment

Phase II – An open-label, cross-over study design.

After completion of 6 months RCT, patients from both groups will be un-blinded to their group allocation. Patients that were allocated to the **active group**, receiving AposTherapy® treatment, will continue with the treatment plan. Patients from the active group will be followed for 6 months after commencing phase II of the study, completing a 12 months treatment program. Patients will return to NYULMC (the physician's office) for a follow-up visit at 6 months from commencement of phase II (12 months form initial visit of phase I). Patients will be asked to come to a follow-up visit at the treatment center (located at 708 3rd Avenue, 3rd Floor, New York, NY 10017) at the following time point: 52 weeks from original baseline. During this visit the biomechanical device will be adapted according to the clinical needs of the patient.

Patients that were allocated to the control group will receive the AposTherapy® device and treatment. The device, with calibrated elements, will be individually calibrated to the patients according to his\her clinical condition. During their daily routine, patients will be asked to wear their custom-worn device for approximately 2 hours per day, throughout the study duration, starting with less than an hour of walking around the house and gradually increasing wearing time to outdoor walking. Patients that crossed from the control group to the active group will be assessed after 3 months and 6 months from commencement of phase II. The results of the 6 months will serve as their new baseline results for phase II of the study. Patients will be asked to come to follow-up visits at the treatment center (located at 708 3rd Avenue, 3rd Floor, New York, NY 10017) at the following time points: 27 weeks from original baseline, 36 weeks from original baseline, 42 weeks from original baseline, and 52 weeks from original baseline. During these visits the biomechanical device will be adapted according to the clinical needs of the patient.

Study schedule:

Study Periods	***Screening***	***Treatment, Intervention Period***									
Visit	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***	***9***	***10***	***11***
Time (week)	*-2*	*0*	*3*	*7*	*12*	*18*	*24 – final assessment for phase I, un-blinding patients, cross-over design and commence of phase II*	*27– only for patients that crossed-over from the control group to the intervention group*	*36*	*42*	*52*
Patient Information and Informed Consent ***(at NYULMC)***	X										
Demographics ***(at NYULMC)***	X										
Medical History ***(at NYULMC)***	X										
In- /Exclusion Criteria ***(at NYULMC)***	X										
Full Research Assessment (Physician) ***(at NYULMC)***	X				X		X		X (Cross-over patients only)		X
Radiography ***(at NYULMC)***	X										
Randomization ***(at NYULMC)***	X										
Concomitant Therapy ***(at NYULMC)***	X				X		X		X Cross-over patients only)		X
Primary Variables **(at NYULMC)**	X				X		X		X		X
Secondary Variables **(at NYULMC)**	X				X		X		X		X
Adverse Events **(at NYULMC)**					X		X		X		X
Administer Medical Device ***(at Apos Center)***		X					X – for patients who crossed-over from control to active				
Adjustment Medical Device **(at Apos Center)**			X	X	X	X	X – active group	X	X	X	X

Data Analysis

Phase I:

- Primary outcome measures will include comparing scores at baseline and the following study time points (baseline, 3 months and 6 months) obtained from the WOMAC. The WOMAC is a validated outcomes assessment used to measure patients' opinion about their knee and associated problems.
- Secondary outcome measures will include comparisons of all measured variables between baseline and all time points including VAS score, SF-36 score, improvement and maintenance in knee function using physical examination findings (these include, but are not limited to: Pain, Knee Effusion, Ligament Stability, Stability, Strength, Range of Motion, Sensation, Posture/alignment); and monitoring usage of rescue medications or NSAIDs. All data will be obtained from the completed case report forms that are being utilized for this study.

Phase II:

- Original active group – evaluating the changes in pain, function, quality of life and usage of rescue medications or NSAIDs following 12 months of therapy.
- Cross-over group – comparing scores at baseline and the following study time points (baseline, 3 months and 6 months) obtained from the WOMAC, SF-36, knee function and usage of rescue medications or NSAIDs.

DATA SAFETY MONITORING PLAN (DSMP)

I. Study Monitoring

The principal investigator, Dennis Cardone, DO, will be the data safety monitor for this project. After a three (3) months follow-up period, Dr. Cardone will review the data for SAE's, protocol deviations and other issues. If it is determined that certain events occur above an expected rate (i.e. increased knee pain), then enrollment will be stopped.

II. Types of Data

Under this DSMP, the following data/events will be captured and documented:

- Duration of AposTherapy® use;
- Monitoring of patient falls;
- Patient Outcomes Assessments;
- Reportable and/or adverse events
- Protocol Deviations

III. Responsibilities and roles for gathering, evaluating and monitoring the data:

Principal Investigator

After a three (3) months follow-up period, the PI will meet with any co-investigators and the Research Coordinator to discuss the current findings and analysis. During these meetings, the PI will also be responsible for verifying data accuracy, and compliance with the study protocol.

Research Coordinator

The Research Coordinator will be responsible for providing data management support to the PI by collecting and documenting the required study data. This information will be documented in a secure Microsoft Excel spreadsheet with appropriate headings to distinguish the various types of data/events. The Research Coordinator will meet with the PI and any co-investigators to discuss the current findings/analysis, concerns/issues (unanticipated problems and adverse events), and the overall study in general.

IV. Reporting Adverse Events and Unanticipated Problems to the Monitoring Entity

All reportable events will be sent to the IRB in accordance with the timeframes specified by NYU SoM guidelines. The Principal Investigator will have the responsibility of completing and submitting a Reportable New Information (RNI) form to the IRB through Research Navigator.

V. Assessments

After a three (3) months follow-up period, and then at 6 months and 12 months after the study start, the Principal Investigator, Co-Investigator(s) and Research Coordinator will review and assess the data and/or events captured under the DSMP.

VI. Criteria for Action

Should there be an event or series of events that occur that increases the risks to the participants, the "following steps" will be taken:

1. An investigation into the event will be conducted;
2. If required, a Reportable New Information (RNI) form will be submitted to the IRB;
3. All primary study staff (PI, Co-I, Research Coordinator) will be notified;
4. After a review,
    a. The protocol may be modified;
    b. The study may be suspended; or
    c. A decision may be made to close out the study

VII. Procedures for Communicating – dissemination of safety information

Outcomes of monitoring reviews will be communicated to the IRB through a yearly summary that will include a narrative on all adverse and reportable events (previously reported or not, serious or not), as well as any proposed changes to the protocol and/or study analysis.

Data Storage and Confidentiality

All patient health information will be de-identified and assigned a code. Information linking participants' names, medical record numbers or other PHI will be stored in the office of the study coordinator at NYU Center for Musculoskeletal Care (333 E. 38th Street, 4th Fl., NY, NY) separate from the medical information. Access to the information linking the linkage codes with participant identifiers shall be documented. Participant medical information will be stored electronically within a password protected database available only to the principal investigator, co-investigators, and research staff as necessary for data analysis. The names, medical record numbers, and other PHI of the study participants will be deleted from their stored medical information and replaced with a linkage code. Access to participant medical information contained within this project will be restricted to approved study personnel.

IV. RISK/BENEFIT ASSESSMENT

The following are risks and discomforts that patients may experience during their participation in this research study.

AposTherapy®

The AposTherapy® device has minimal risks: no physical injury, psychological, social or economic harm, discomfort/inconvenience, or breach of confidentiality is foreseen. If any physical or psychological discomfort is experienced, or patients no longer want to participate in the study, they can withdraw at any point and it will not affect their ongoing care.

AposTherapy® has been monitoring falls and other adverse effects through patients' reporting. To date, we have collected an insignificant and negligible number of fall reports (that in most cases were not related to the device and resulted from environmental or personal factors). Furthermore, to date, all studies reported no serious adverse events, and no falls recorded.

Loss of confidentiality

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

Psychological Risks

When completing the questionnaires, patients may come across a question or answer choice that they find unpleasant, unsure on how to answer or otherwise objectionable. For instance, a few of the questions

may cause patients to think about negative emotional states. For the questionnaires we are evaluating, there is no right or wrong answer.

Protection against Risks
The Principal Investigator is responsible for the collection, management and retention of research data and all study related regulatory files. The Principal Investigator shall adopt an orderly system of data organization, which includes a complete regulatory binder that dates the records being retained. The PI will be responsible for communicating all study methods and systems to all research personnel, and for their compliance with the study protocol and all NYU and Federal regulations. Patient PHI, such as MRNs can only be used within NYULMC's administrative records, thus ensuring minimal research risks and protecting patient identity from public utilization. As the owner of the research data, the medical center will assert its rights with respect to research data in order to assure compliance with regulatory and contractual requirements.

Potential Benefits to the Subjects
While there are no guarantees, the use of AposTherapy® may demonstrate improvement in knee function, a reduction in pain intensity and higher patient satisfaction.

V. INVESTIGATOR'S QUALIFICATIONS AND EXPERIENCE

The CV, human subjects' tutorial completion report, and medical license (if applicable) are available for all investigators who are participating in this study. All research personnel have medical research experience and are qualified to participate in this quality study. Most importantly, staff have been properly educated and certified with CITI training to conduct research in a matter that will maintain full patient confidentiality.

VI. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT/ASSENT

Method of Subject Identification and Recruitment
Appropriate patients, who meet all of the inclusion criteria and none of the exclusion criteria, will be identified from the clinical office of the Principal Investigator. Study rationale will be explained and the patients will be recruited to participate in the trial for a 12 months duration.

Process of Consent
Written consent will be obtained from subjects who are eligible participants based upon their medical condition (as determined by their physician). The consent process will take place during an office visit at which time the investigator has determined subject's voluntary participation has been upheld. Subjects will be informed about the study and the intended purpose. They will be given the opportunity to ask questions and receive thorough explanations. They will be made aware of the possible risks and anticipated benefits. They will also be informed of alternative procedures. Subjects will then be given another opportunity to ask questions and agree or disagree to consent.

Subject Capacity
All subjects enrolled in this study will have capacity to provide informed consent.

Debriefing Procedures
No information will be withheld from the subject. Patients will be told if they received the calibrated or non-calibrated device after completing the study.

Consent Forms
Informed consent will be obtained from all subjects and documented with a signed, written consent form using the NYU SoM's English standard consent form.

Documentation of Consent
In addition to following the consent process, it is understood by the study staff that retrieving informed consent is an ongoing process that continues after the actual informed consent has been signed. There is

a “Documentation of Consent” checklist that will be used as additional documentation. This form will serve as secondary proof that the informed consent process has been executed.

Costs to the Subject

Subjects will not incur any additional financial costs as a participant in this study beyond those normally associated with this type of condition. All procedures (physical exam and radiographic imaging) performed in this study will be billed to the patient/patient’s insurance provider, hospital insurance or third party payer as per standard of care. The study device (AposTherapy®) and the study questionnaires are being provided by the sponsor free of charge.

Payment for Participation

No payments/reimbursements will be provided to subjects for their participation in this study.

VII. References

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