Study Title: To Determine the Economic and Functional Impact of Peri-Operative Extension Assist Pneumatic Bracing for Primary Total Knee Arthroplasty (TKA) Non-Inferiority Trial

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Regulatory Sponsor:
This study is an investigator initiated research trial. The study site will be considered its own regulatory sponsor and is responsible for internal data monitoring and any study reporting required by ClinicalTrials.gov.

Background and Significance

Knee osteoarthritis (OA) is increasing in the United States rapidly due to increased lifespan and obesity. The use of unloader bracing has been proposed as an adjunct to current treatments. While the use of an unloader brace has not been shown to be beneficial for patients with Kellgren-Lawrence grade 1 and 2 osteoarthritis [1], unloader braces have shown benefits in patients with end-stage osteoarthritis, Kellegren-Lawrence grade 3 and 4. These benefits include increased time to total knee arthroplasty (TKA) and lower number of injections [2]. Indeed, pneumatic unloader knee bracing has also been shown to increase strength and function of these patients with end-stage knee OA [3]. Typically, the next step for end-stage knee OA is a TKA where OA accounts for 94-97% of TKAs [4,5].

While bracing has been shown to be beneficial for patients with OA in terms of function and strength, whether these unloader braces are also similarly beneficial after surgery needs to be examined. Therefore we questioned whether wearing a brace that has previously been shown to increase strength and function in OA patients can also increase strength and function in patients after TKA.

The primary objective of this study is to determine the efficacy of bracing in improving function and rehabilitation prior to and after TKA.

Additional goal of the study is to assess time taken to normalized function after TKA and its impact on cost. Secondary objectives are to quantify and observe pain medication use, swelling, muscle strength and girth, and gait efficiency.

Study Design

Methods

This a randomized, standard of care controlled study.

Sample

Potential subjects will be recruited from a pool of TKA patients presenting to Cleveland Clinic orthopedic providers at main campus that may benefit from using a knee brace.. This study aims to complete follow-up with 40 patients. 20 out of 40 patients will receive adjunct therapy using the OCSI brace. Patients will be allocated to one of these two groups via computer randomization. The PI (Dr. Higuera) will be blinded to patient compliance and evaluation during data acquisition and statistical analysis. All study patients will receive standard of care therapy (pain medications, and other modalities as needed). At home physical therapy will occur at standard of care scheduled intervals. Once physical therapy begins at Cleveland Clinic, patients in both the control and brace group will receive outpatient Physical Therapy 2 times a week for two weeks, then the number of physical therapy visits will be at the discretion of the clinician.

Patient selection:

- Age: 50 or older

- Radiographic: Varus or valgus knee deformity less than 10 degrees
- BMI of 40 or less

Research Procedures

Visit 0: Potential patients will be consented during their office visit with Dr. Mont. Once consented, patients will be computer randomized into either the knee brace group or the control group. For the knee brace group, measurements will be taken during the clinic visit, an order will be written for the brace and sent to Hanger Clinic where they will be in contact with the study participant to schedule the brace fitting. The subject can start wearing the brace at this time until surgery.

Visit 1 (6 weeks prior to surgery): Participant will meet with study coordinator and complete both questionnaires and physical tests.

Visit 2 (1 week prior to surgery): Participant will meet with study coordinator and complete both questionnaires and physical tests.

Visit 3 (1 week after surgery): Participant will meet with study coordinator and complete both questionnaires and physical tests. The brace will NOT be worn until after staple removal (10 to 14 days after surgery).

Visit 4 (6 weeks after surgery): Participant will meet with study coordinator and complete both questionnaires and physical tests.

Visit 5 (12 weeks after surgery): Patient will meet with study coordinator and complete both questionnaires and physical tests. At this point, the study time points are complete and the brace no longer needs to be worn for the study.

Chart review: At 9 months, the study team will review participant's chart for pain medication utilization and number of physical therapy visits during the study.

	Visit 0 **Office visit (scheduling surgery)**	**Visit 1** **6 weeks prior to surgery** **(±4 weeks)**	**Visit 2** **1 week prior to surgery** **(±1 week)**	**Visit 2** **1 week after surgery** **(±1 week)**	**Visit 3** **6 weeks after surgery** **(±2 weeks)**	**Visit 4** **12 weeks after surgery** **(±2 weeks)**	**9 months** **After surgery** **(chart review)**
Informed Consent	**X**						
Randomization	**X**						

Timed up and go (TUG) test		**X**	**X**	**X**	**X**	**X**	
Timed stair-climb test		**X**	**X**	**X**	**X**	**X**	
Single-limb stance time (bilateral)		**X**	**X**	**X**	**X**	**X**	
6 minute walk test		**X**	**X**	**X**	**X**	**X**	
AROM, PROM		**X**	**X**	**X**	**X**	**X**	
Knee Society objective score		**X**	**X**	**X**	**X**	**X**	
Knee Society functional Score		**X**	**X**	**X**	**X**	**X**	
KOOS (Jr)		**X**	**X**	**X**	**X**	**X**	
HSS scale		**X**	**X**	**X**	**X**	**X**	
Pain score on visual analog scale (rest)		**X**	**X**	**X**	**X**	**X**	
Pain score on visual analog scale (activity)		**X**	**X**	**X**	**X**	**X**	
Pain medications utilization		**X**	**X**	**X**	**X**	**X**	**X**
Number of therapy visits							**X**

- For this research study, we will ask you to fill out some additional physical tests will be performed. These tests include:
    - Timed up and go (TUG) test: standing up from seated position and walking to a designated line, walking back, and returning to seated position
    - Timed stair-climb test: walking up and down stairs
    - Single-limb stance time (bilateral): standing on one leg unassisted

    - 6 minute walk test: distance walked in 6 minutes
- Patient reported outcomes will also be assessed using multiple validated questionnaires
    - Knee Society Score (KSS)
    - Knee Injury and Osteoarthritis Outcome Score (KOOS Jr)
    - HSS scale
    - Visual Analog Scale (Pain score)

Participant Compliance

Study participants will be given a pedometer and notebook supplied by the sponsor to record daily steps. This will be used to monitor compliance with physical therapy and the use of the brace as it is expected there should be increased activity over time.

Data Analysis

Descriptive statistics (mean, standard deviation, and coefficient of variation) will be used to compare the demographics between the two cohorts. Functional metrics will be compared pre- and post-surgery at 0- and 3- months. Unless otherwise indicated, all testing of statistical significance will be two-sided, and a difference resulting in a p-value of less than or equal to 0.05 will be considered statistically significant. Also, after each analysis, General Linear Models (GLM) will be used to control for possible confounders, including BMI, gender, age, and ethnicity.

Adverse Events and Data Monitoring Committee

Procedural safety will be documented in this study through patient and surgeon reported adverse events. ARs will be documented for all ceases in this study.

An unanticipated problem involving risks to participants or others is any event that (1) is unforeseen, (2) caused harm or placed a person at increased risk of harm, and (3) is related to the research procedures.

An Adverse Event (AE) is any untoward or unfavorable medical occurrence, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptoms, or disease. Adverse events can encompass both physical and psychological harms.

An Internal Adverse Event (AE) is an untoward medical occurrence, which occurs to participants in research conducted by Cleveland Clinic and/or Cleveland Clinic is the IRB of record.

External Adverse Event (AE) is an untoward medical occurrence experienced by subjects enrolled at other institutions for the same study approved at Cleveland Clinic or a different study using the same study drug/device.

A Serious Adverse Event (SAE) is any adverse experience that results in any of the following outcomes:

- Death

- A life-threatening experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An Unexpected Adverse Event means any AE not previously known or included in the consent form or other risk information.

Related/Possibly Related means there must be reasonable evidence to suggest the event was caused by the device or investigational intervention.

1) Internal Serious Adverse Events (events that occur to participants enrolled in research being conducted by Cleveland Clinic and when Cleveland Clinic is the IRB of record) must be promptly reported to the IRB using the IRB AE report form within 10 working days from discovery/awareness which meet any of the following criteria as assessed by the PI/Co-I:
    a. Serious, unexpected, and related/possibly related
    b. AEs determined to be occurring at a significantly higher frequency or severity other than expected
    c. Other unexpected AE's, regardless of severity, that changes the risk benefit ration of the study and results in changes to the Research protocol or Informed Consent process/document
    d. All internal SAEs are also reported at continuing review using the AE Summary Log
2) External Serious Adverse Events (events experienced by subjects enrolled at other institutions for the same study approved at Cleveland Clinic or a different study using the same study device/drug) are reportable to the IRB using the IRB AE Report Form within 10 working days from discovery/awareness when:
    a. The External SAE report includes reasonable evidence as assessed by a central monitoring entity [Coordinating or Statistical Center, or a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC)] that the event is Serious, Unexpected, and Related/Possibly Related AND places the subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. This will require a change in the protocol and/or consent document.
    b. External SAE reports provided by the Sponsor to the investigator indicating the event is Serious, Unexpected and Related/Possibly related but without reasonable evidence or DSMB/DMC determination of greater risk are not reportable to the IRB within the 10 day window. Without Sponsor evidence or assessment the implications of the event cannot be determined by the research team and therefore

need not be reviewed. These SAE' shall be placed on the AE Summary log to be submitted at the annual continuing renewal.

3) DEATHS are to be reported to the IRB using the IRB AE Report Form according to the following guidelines:
    a. Internal Death
        i. Related/possibly related whether expected or unexpected– within 5 working days from discovery/awareness
        ii. not related and expected – at time of continuing review
        iii. Not related and unexpected – at time of continuing review except cancer studies
    b. External Death

    Related/possibly related and unexpected – within 5 working days from discovery/awareness not related whether expected or unexpected – at time of continuing review related/possibly related and expected – at time of continuing review
    c. ALL Deaths are also reported at time of continuing review using the AE summary log.
4) Non-serious Adverse events (Internal and External) that are both Related/Possibly related and unexpected are reported on the AE Summary Log at time of continuing review to assess trends.
5) An IRB staff (a qualified, licensed practitioner assigned to this function by the IRB chair and IRB Executive Director) reviews Adverse Event Reports to determine whether they represent Unanticipated Problem Involving Risks to Participants or Others. Events that are assessed, by either the IRB Staff or Investigator, to place subjects or others at a greater risk of harm than was previously known or recognized, or changes the risk/benefit ratio of the study, or requires a change in the protocol and/or consent document are referred to Full Board for review under Policy #70.
6) Events that do not involve risk to Participants or Others or changes to the informed consent or protocol do not require further review. Investigators are informed of the determination and the IRB file is updated.
7) The AE Summary Log is reviewed by the IRB at the time of continuing review to identify trends in frequency and severity which may impact subject safety.

This study is an Investigator Initiated research trial. Each study site will be considered its own regulatory sponsor and is responsible for internal data monitoring and any study reporting required by ClinicalTrials.gov.

References:

1) Mont MA, Cherian JJ, Bhave A, Starr R, Elmallah RK, Beaver WB Jr, Harwin SF. "Unloader Bracing for Knee Osteoarthritis: A Pilot Study of Gait and Function." *Surg Technol Int* 2015; 27:287-93.
2) Chughtai M, Bhave A, Khan SZ, Khlopas A, Ali O, Harwin SF, Mont MA. "Clinical Outcomes of a Pneumatic Unloader Brace for Kellgren-Lawrence Grades 3 to 4 Osteoarthritis: A Minimum 1-Year Follow-Up Study." *J Knee Surg*; 29(8):634-638.
3) Cherian JJ, Bhave A, Kapadia BH, Starr R, McElroy MJ, Mont MA. "Strength and Functional Improvement Using Pneumatic Bracing with Extension Assist for End-Stage Knee Osteoarthrtitis: A Prospective, Randomized trial. *J Arthroplasty* 2015. 30(5):747-753.
4) Lawson EH, Gibbons MM, Ingraham AM, Shekelle PG, Ko CY. "Appropriateness criteria to assess variations in surgical procedure use in the United States. ArchSurg. 2011, 146:1433-1440
5) Carr A, Robertson O, Graves S, Price A, Arden N, Judge A, Beard D. "Knee replacement" *Lancet* 2012, 379:1331-1340