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February 15, 2019

Dear Clinicaltrials.gov administration,

This cover letter accompanies a protocol being submitted for NCT02998372. The study is supported by an NIH grant (R21 AR069150). The study primarily focuses on computational simulation of function for knees with patellar instability. For validation of the models, simulated data was compared to pre-operative and post-operative measures of patellar tracking and patellofemoral contact pressures determined by computational reconstruction of functional activities performed by patients during MRI scans. Prior to the proposed study, imaging with accompanying kinematics, pressure data and computational models was available for seven subjects being treated for patellar instability. The grant application proposed adding 5 additional subjects and models to the study. Because the subjects would be evaluated pre-operatively and post-operatively, the study was designated as a clinical trial, although the surgical approach was left up to the surgeon as opposed to being specified within the protocol. Therefore, the study was registered on clinicaltrials.gov based on the aims and goals listed for the grant application.

Patient enrollment has now been completed for the study. Only three of the proposed five subjects that were to be evaluated pre-operatively and post-operatively were enrolled. Additional pre-operative imaging from other sources was used to complete creation of the necessary number of models.

The attached protocol is an abbreviated version of the NIH grant application that includes the development of computational models and the analysis of the five subjects. That is the clearest document to describe the relationship between the clinical trial portion of the study and the overall stated goals.

Please let me know if you have any questions about this document.

Sincerely,

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Computational Simulation of Patellar Instability

Specific Aims

1. **Dynamic computational simulation of patellar instability**

Use multibody dynamic computational simulation to replicate lateral patellar maltracking in patients being treated for patellar instability. Knee models representing patients with recurrent instability will be used to characterize patellar lateral maltracking and pressure applied to patellofemoral cartilage during simulated functional activities. The models will be individually validated against previously acquired and newly generated data from in vivo motion. The source of the in vivo data will be computational reconstruction of in vivo function performed with the patients that the simulation models are based on.

2. **Characterize influence of surgical stabilization on knee function for individual patients**

The multibody dynamic models will be used to simulate MPFL reconstruction and tibial tuberosity medialization. MPFL reconstruction will be simulated with variations in the femoral attachment position, while the magnitude of tuberosity realignment will be varied. The actual surgical procedures performed on the patients will be simulated, with the influence on lateral tracking and contact patterns compared to in vivo results to validate simulation of the surgical procedures.

3. **Compare surgical options as a function of patellofemoral anatomy**

Variations in patellar tracking and contact pressure will be compared between MPFL reconstruction and tuberosity medialization. Techniques to alter trochlear dysplasia and tuberosity lateralization will also be developed and applied to the models. Simulations performed while varying anatomy will establish ranges over which each surgical option limits patellar maltracking without elevating contact pressures.

Approach

Aim 1: Simulation of instability

Models for dynamic simulation of knee function will be developed to represent 12 knees with recurrent patellar instability. Simulation of motion will be performed using multibody dynamics software. Springs will be used to represent the anterior and posterior cruciate ligaments, the medial and lateral collateral ligaments, the posterior capsule, the patellar tendon, and the lateral and medial retinaculum. Quadriceps muscle forces will be applied to the patella through springs representing the quadriceps tendon. Medial and lateral hamstrings forces will apply one-third of the quadriceps force to the tibia along the long axis of the femur.

Solid bodies representing the femur, patella, and tibia will include the corresponding cartilage for each bone. Cartilage contact at the tibiofemoral and patellofemoral articulations will be governed by simplified Hertzian contact. Patellofemoral and tibiofemoral kinematics and detailed pressure maps will be characterized during post-processing by applying rigid body translations and rotations exported from the simulation to the bone models, reproducing the simulated joint motion. At flexion angles with the patella engaged with the trochlear groove, starting at 15°, muscle and ligament force vectors exported from the simulation will be applied to the patella. Overlap between cartilage on the femur and patella will be combined with the elastic modulus and Poisson's ratio of the cartilage to determine reaction forces on elements on the surface of the patella based on linear elastic theory, referred to as the discrete element analysis technique. The position of the patella within the trochlear groove will be iteratively modified until the joint compression, lateral force and tilt moment are balanced, producing a pressure pattern based on the applied force and area for each element. Tibiofemoral and patellofemoral kinematics will be quantified from the motion of local coordinate axes embedded in each bone based on anatomical landmarks using the floating axis coordinate system.

High resolution MRI scans of subjects with patellar instability are currently available for 7 subjects from a previous study (3T scanner, extremity coil, proton density-weighted images, sagittal plane, 0.3 mm in plane resolution, 1.5 mm slice thickness). Models will be reconstructed from these scans, allowing representation of cartilage surfaces and attachment points for the ligaments, patellar tendon, and quadriceps tendon. Five additional subjects scheduled for surgical stabilization for recurrent patellar instability will be recruited to meet the proposed sample size of 12 models.

The 5 recruited subjects will participate in pre-operative computational reconstruction of in vivo knee function with closed chain loading conditions. The technique uses high resolution MRI scans to create computational models of the femur, patella and tibia, as well as the cartilage. Low resolution scans are acquired during isometric quadriceps contraction with the knee positioned at multiple flexion angles, with the aid of a MRI-compatible loading frame that applies a spring-loaded force of 60 N to 85 N along the axis of the body at the foot. Shape matching algorithms align models of the bones from the high resolution images, with attached cartilage, to bones reconstructed from lower resolution scans with the knee flexed.

Models of each knee will be used to simulate the in vivo function. The muscle forces will be ramped up until the reaction force at the foot reaches the spring force applied in vivo. A direct comparison of tibiofemoral and patellofemoral kinematics and contact pressures between computational and in vivo data will be performed. The accuracy of computational simulation will be reported in terms of root mean square errors between the computational and in vivo data, along with correlation coefficients evaluating the accuracy of variations in output related to changing the flexion angle and between knees. Once the pre-operative models are validated by comparison to the output from reconstruction of in vivo function, they will be used to represent a dynamic squatting

Aim 2: Simulation of surgical stabilization

Accuracy of the post-operative models will be assessed in the same manner as the pre-operative models. The newly enrolled subjects will be treated surgically, with the procedure performed based solely on clinical evaluation, and will participate in post-operative computational reconstruction of in vivo knee function. All models will be modified to represent the post-operative condition based on the imaging data and the surgical notes. The post-operative models will be used to simulate function and compare kinematics and contact pressure data to the data determined from the subjects.

Aim 3: Compare surgical options

The simulation models will be used to represent two primary surgical options: reconstruction of the medial patellofemoral ligament and realignment of the tibial tuberosity, while also varying parameters related to knee anatomy. The kinematics and pressure output from all the simulated surgical variations will be compared between the 12 models at individual degrees of knee flexion with repeated measures ANOVA's combined with post-hoc Student-Newman-Keuls tests, with significance set at $p = 0.05$. The analyses will focus on relative variations in the kinematics and pressure measurements, with the pre-operative condition treated as the control for each knee, with the goal of each procedure to reduce lateral patellar shift and tilt without increasing the contact pressure.

Analyses will be performed for various combinations of tibial tuberosity position and depth of the trochlear groove. For each combination, the statistical analyses noted above will be performed to compare the influence of the various surgical procedures on patellar tracking and contact, with an emphasis on determining the limits at which each procedure becomes ineffective in reducing lateral tracking without overloading cartilage. In addition, for each procedure multivariable linear regression analyses will be performed to relate the anatomical parameters to the change in the output parameters.