December 14, 2017

Research Study Proposal

Title of Study: A Prospective Study to Examine Patient Satisfaction, Function, and Limb Alignment Outcomes for Mako versus Non-Mako Total Knee Replacements

A. Background and Statement of Context

In recent years, orthopedic surgeons have increasingly embraced robotic-assisted surgical techniques to improve the accuracy and precision of total hip and knee arthroplasty, and partial knee arthroplasty. The stages of computer-assisted surgery include preoperative imaging and planning, intraoperative design and execution, and postoperative evaluation [1]. Several prior studies have attempted to validate the clinical efficacy and cost efficiency of robotic assisted total hip replacement [2-6]. However, few studies have addressed the clinical and radiographic outcomes of robotic assisted total knee arthroplasty (TKA), with no consensus in regards to meaningful clinical value [7]. In November 2015, as a pioneer user, Virtua Joint Replacement Institute (JRI) adopted the Mako System (Stryker, Kalamazoo, MI) - a robotic-arm assisted surgery technology based on CT image guided navigation. Today, 5 surgeons have performed a total of 471 TKA cases done to date using the Mako device. This study is aimed at contributing to the nascent body of literature on robotic-assisted TKA (RA-TKA) by comparing the patient reported outcomes and accuracy of implant placement for patients receiving RA-TKA versus TKA with traditional mechanical guides (MG-TKA).

B. Study Questions/Objectives and Hypotheses

Study Objectives

The purpose of this study is to compare the efficacy (patient reported outcomes and radiographic results) for RA-TKA versus MG-TKA. Specifically, when compared to their control group counterparts that undergo MG-TKA, we hypothesize that the intervention group treated with RA-TKA will, following surgery, experience:

1. Higher patient reported Forgotten Joint Score (FJS), 3 months, 6 months, 12 months, 2 years, and 5 years postoperatively (primary outcome measure).

2. Higher patient reported Knee injury and Osteoarthritis Outcome Score (KOOS), 3 months, 6 months, 12 months, 2 years, and 5 years postoperatively.

3. Higher patient reported Veterans Rand 12-item Health Survey Score (VR-12), 3 months, 6 months, 12 months, 2 years, and 5 years postoperatively.

4. Fewer radiographic outliers (deviation greater that 3 degrees from planned mechanical limb alignment). The radiographic analysis will be performed postoperatively using long limb plain radiographs.

C. Study's Alignment with Virtua's Mission, Vision, Values and Strategic Imperatives

Though the Virtua JRI remains at the forefront of RA-TKA, through this study Virtua Health may become the first health system to report better clinical outcomes of TKA utilizing RA-TKA versus the standard MG-TKA. Moreover, these data may help demonstrate greater value achieved by the application of RA-TKA in TKA practiced at Virtua, and provide an evidence-base of higher quality and value to insurers and population-based health providers.

D. Study Design

Type of Study Design

This is a randomized, controlled, prospective, single-blind study.

Study Inclusion Criteria

Patients who meet all of the following inclusion criteria may be eligible to participate in the study:

1. Age 18 or older

2. Diagnosed with primary osteoarthritis and cleared to undergo total knee arthroplasty at the Virtua JRI

3. Willing to provide informed consent, participate in study, and comply with study protocol

Study Exclusion Criteria

Patients who meet any of the following criteria may not be eligible to participate:

1. Pregnant or contemplating pregnancy prior to surgery;

2. Worker's compensation or personal injury related to knee (clinical outcomes have been shown to be less predictable and often poorer in this patient group; there may also exist potential issues with reimbursement)

3. Post-traumatic arthropathy (clinical outcomes have been shown to be less predictable; pre-operative deformity and risk factors are greater and difficult to propensity-match between groups)

4. Self-pay patients or patients whose insurance are known to typically decline reimbursement for preoperative CT scans

E. Study Procedures

During the preoperative office visit, the surgeon will inform the patient that appears to meet study eligibility criteria about the study, and discuss the differences between the two surgical techniques (RA-TKA versus MG-TKA) including their potential risks and benefits. The surgeon will make clear to the patient that consenting to be a part of the study means that the patient has agreed to be randomly assigned to one of the two surgical groups. Currently at the Virtua JRI, the decision to use RA-TKA for a TKA procedure is driven by the surgeon's preference. The surgeon will therefore let it be known to the patient that the only difference the patient will experience as a result of being a part of this study is that the decision to use the Mako technology for their procedure will now be left to chance.

Patients who are deemed eligible to participate in the study and are willing to participate will be asked by the surgeon to complete the research informed consent. This document will be summarized verbally by the surgeon and potential participants will be given the opportunity to ask questions about the protocol or their involvement prior to providing consent. Those who agree to participate and provide research informed consent will be enrolled in the study, and given a copy of the research informed consent document. The patient's informed consent would be added to the patient's chart.

A computer-generated randomization scheme will be employed and the randomization outcomes will be sealed in opaque envelopes. Two to three weeks ahead of the consented patient's surgery, a JRI office staff will pick an envelope from the randomized stack, unseal the envelope, and based on the outcome (even or odd), assign the patient to one of the two surgical groups. While the study intervention group (even) will receive RA-TKA, the control group (odd) will receive MG-TKA. The office staff will inform the surgeon and Mako representative if the patient was assigned to the RA-TKA group. The patient will not be told which group they are assigned to in order to eliminate subjective bias from the self-reported patient outcomes as a result of the patients knowing what procedure they had. Because patients undergoing RA-TKA require 4 stab incisions separate from the TKA incision for pin placement, it will become obvious to patients undergoing MG-TKAs that they did not have RA-TKA. In order to blind the patient to which treatment group they have been randomized to, patients enrolled in the MG-TKA group will have 2 stab incisions made. This is similar to prior published orthopedic surgery studies where patients in the control group for arthroscopic intervention were given sham portal incisions to preserve blinding (12-13).

In line with routine pre-operative planning, all study patients will be scheduled to undergo pre-operative CT scans within 2 to 3 weeks of surgery. At their 2-week post-operative office visit, all study patients will be scheduled to undergo post-operative CT scan before their 6-week post-operative visit so that component rotation could be compared to pre-operative target values.

Anesthesiologists will use their usual pre-operative and intra-operative techniques for all study participants. Post-operative care will be standard between groups. As with standard practice, pre-operative and post-operative range of motion will be recorded.

F. Statistical Analysis and Sample Size Justification

Statistical Methods

The primary outcome measure is the difference in mean Forgotten Joint Score (FJS) between the two groups of patients for which the two sample t-test will be utilized. The FJS is a self-completed 12-item questionnaire used to assess patients' awareness of their artificial joint during activities of daily living on an awareness scale of 0 (never) to 4 (mostly). There is a 6th response of "not relevant for me", and this is treated as a missing value and not included in the number of completed items. All the responses are summed up and divided by the number of completed items, and the mean value is then multiplied by 25 to obtain a total score from 0 to 100. This score is then subtracted from 100 to change the direction of the final score in such a way that higher scores indicate a higher degree of forgetting the artificial joint [8]. The FJS (Appendix 1) will be administered to the patients during their regularly scheduled 3, 6, and 12 months, 2 year, and 5 year postoperative office visits.

A second outcome measure is the difference in Knee injury and Osteoarthritis Outcome Score (KOOS) between the two groups of patients for which the two sample t-test will also be utilized. The KOOS is a knee-specific instrument used to evaluate short-term and long-term symptoms and function in subjects with knee injury and osteoarthritis. It consists of 42 questions in 5 subscales; Pain, other Symptoms, Function in daily living (ADL), Function in Sport and Recreation (Sport/Rec), and knee-related Quality of Life (QOL). All questions are assigned a score of 0 (No Problems) to 4 (Extreme Problems). Scores are transformed to a 0 to 100 scale, with zero representing extreme knee problems and 100 representing no knee problems [9]. The KOOS will be administered to the patients during their regularly scheduled 3, 6, and 12 months, 2 year, and 5 year postoperative office visits.

A third outcome measure is the difference in mean scores for the Veterans RAND 12 Item Health Survey (VR-12) between the two groups for which the two sample t-test will be utilized. The VR-12 is a 12-item questionnaire corresponding to eight principal physical and mental health domains including general health perceptions, physical functioning, role limitations due to physical and emotional problems, bodily pain, energy-fatigue, social functioning and mental health. The 12 items are summarized into two scores: a Physical Component Score (PCS) and a Mental Component Score (MCS) which then provides an important contrast between the respondents' physical and psychological health status [10]. The VR-12 will be administered to the patients during their regularly scheduled 3, 6, and 12 months, 2 year and 5 year postoperative office visits.

The radiographic outcomes will be studied in two ways.

1) The mechanical alignment of the entire post-operative limb will be measured at 6 weeks by long-limb radiograph cassettes and compared to the pre-operative plan for accuracy and deviation less than or greater than 3 degrees from the intended target. From each treatment group, the percentage of patients with radiographic outliers (deviation greater that 3 degrees from the expected implant placement) will be compared. The z-test for proportions will be used for this assessment.

2) Pre-operative and post-operative CT scans will be performed on all patients and component rotation will be measured and compared to pre-operative target values for each. The rotational femoral component angle is defined as the angle between the surgical epicondylar axis and the posterior condylar line of the femoral component. The rotational tibial component angle is defined as the angle between a line connecting the centre of the tibial component and the medial third of the tibial tubercle and a line perpendicular to the posterior condylar line of the tibial component [14]. A Mann-Whitney U test can determine statistically significant differences ($p < 0.05$) in absolute value from the target angles between the two treatment groups using these parameters. Fisher's exact probability test will be used to compare the quality of implantation, measured against the ideal position, between the two systems with these parameters ($p < 0.05$). The correlation between error in rotational alignment and the functional score for both groups can be measured using Spearman's correlation coefficient by rank test ($p < 0.05$). Preoperative and postoperative posterior femoral condylar offsets will be measured in the sagittal plane for the preoperative femur and the femoral component. The maximum thicknesses of the medial and lateral posterior condyles will be measured from the edge of each condyle to a line tangential to the posterior cortex of the femoral shaft [15].

Two blinded reviewers will assess each patient film to assure intra-observer and inter-observer reliability. The chance-corrected κ-coefficient will be calculated to determine intra- and inter-observer agreement [16].

All statistical analyses will be conducted at the 0.05 level of significance.

Power/Sample Size

Giesinger et al. [11] reported that for 98 TKA study patients, their 2-month, 6-month, 1-year, and 2-year postoperative FJS mean (standard deviation) were respectively: 20.9 (17.4), 41.7 (25.9), 67.3 (27.2), and 80.8 (25.8). For the purpose of our power analysis therefore, we find it reasonable to assume a 10 point difference in mean FJS between the two patient groups as the effect size to detect and a standard deviation of 27.2. For an 80% power at a 0.05 level of significance, the minimum required sample size for each group is 118. To account for possible crossovers, we apply a 5% markup against the statistically derived sample size to arrive at a minimum of 124 patients needed for each group for a total of 248 patients to be enrolled in the study.

G. Study Duration and Subject Enrollment Feasibility

Between Jan 1, 2017 to November 16, 2017, the Virtua JRI averaged about 128 TKA cases a month. If we assume that 25% of eligible patients can be enrolled into the study, then we estimate to average about 32 study patients per month. For the 248 patients needed in total for the study therefore, we anticipate an 8-month study enrollment completion timeline.

H. Study Limitations

The main limitation we anticipate is with regards to the possibility of patients declining to participate in the study due to concerns of leaving their surgical assignment to chance. By assuming only a 25%

enrollment rate however, combined with the large volume of TKA cases we see at the Virtua JRI, the projected 8-month enrollment completion timeline is very realistic.

I. Stakeholder Communication Plan

The physician assistants (PAs) will play a crucial role in enrolling patients for the study. All the PA's at the Virtua JRI will be trained on the study protocol so that they are well equipped to address patients' questions/concerns. The PAs will also take the lead on administering the patient reported outcomes surveys (FJS, KOOS, VR-12) and they will receive the relevant training to administer these effectively.

J. Dissemination Plan for Study Findings

The Virtua JRI surgeons plan to publish the study outcomes in a reputable peer-reviewed orthopedic journal such as the Journal of Arthroplasty.

K. Itemized Study Budget

Department	Estimated Labor Hours	Estimated Supply Cost ($)
Virtua Clinical Research Department – Statistical/IRB/Manuscript support	80	
Virtua Voorhees Radiology		$24,800 (Estimated $100 per post-operative CT scan for 248 study patients)
Leg length software for radiographic assessment of implant placement		$15,000 (3 units at $5,000 per unit)
Funding Source(s): Virtua Foundation		

Protection of Human Subjects

Throughout the study, the study investigators (Virtua JRI surgeons, PAs, and statistician), will be the only ones with access to the data collection database. Following the completion of the study, all personal health information collected, including name, gender, age, significant medical comorbidities, and postoperative complications, will be de-identified as soon as possible prior to data analysis and any subsequent publications or research submissions. Patients would be told participation is purely voluntary with no monetary reimbursement and that being assigned to one of the two surgical groups comes with minimal risk.

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Appendix 1: Forgotten Joint Score Questionnaire

Item	Are you aware of your artificial joint:
1	in bed at night?
2	when sitting on a chair for more than one hour?
3	when you are walking for more than 15â€‰minutes?
4	when taking a bath/shower?
5	when traveling in a car?
6	when climbing stairs?
7	when walking on uneven ground?
8	when standing up from a low-sitting position?
9	when standing for long periods of time?
10	when doing housework or gardening?
11	when taking a walk or hiking?
12	when doing your favorite sport?