

PROTOCOL TITLE: Manual vs. custom knee study

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Randomized prospective evaluation of total knee replacement component alignment using manual vs custom instrumentation

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1. Objectives

1. To determine whether the low-dose, biplanar x-ray imaging (EOS) has the same accuracy as computed axial tomography (CT)
2. To validate low-dose, biplanar x-ray imaging (EOS) as a tool to evaluate 3-dimensional alignment of Total Knee Replacement implants.
3. To evaluate differences in total knee replacement implant alignment in patients whose arthroplasty is performed using manual or custom instrumentation derived from preoperative CT

2. Background

Achieving optimal prosthetic alignment of the femoral, tibial and patellar components during Total Knee Replacement (TKR) is of great importance as it contributes to better function, less pain and improved quality of life.^{1,2} TKR requires accuracy in the execution of bone cuts in the correct orientation to the coronal, sagittal and axial planes. Malposition potentially leads to increased mechanical stress on the bearing surfaces and inevitably to earlier loosening.³

Computed Axial Tomography (CT) is the gold standard technique to evaluate implant alignment in the coronal, sagittal and axial planes. As such, CT has imaging has been used to create custom instrumentation with purported likely improvement in surgical outcomes. Customized instrumentation created from a preoperative CT has been shown to be safe and effective⁴, with no reported difference in patient outcomes and similar total knee arthroplasty component alignment.⁵⁻⁶ However, taking into consideration CT's high levels of radiation, cost expenses and its inability to obtain images of the limb in weight-bearing position, CT scan cannot be used routinely as a postoperative tool to evaluate TKR implant positioning.

The imaging system manufactured by EOS Imaging (formerly Biospace Med, Paris) is a biplanar, low-dose radiation, full body, high resolution, radiological imaging system allowing simultaneous acquisition in the coronal and sagittal planes and in standing position.⁷ EOS' main benefits are the considerable reduction in radiation dose (up to 1000 times less than for CT and ten times less than the plain radiography) by using a gaseous detector. George Charpak, the inventor, was awarded the Nobel Prize in 1992 for this work.⁸ Moreover, the EOS system can provide 3D images by using the appropriate software algorithms, thus providing a low-radiation alternative to CT.⁹⁻¹⁴

3. Inclusion and Exclusion Criteria

3.1 INCLUSION CRITERIA:

- ☐ Radiographically confirmed diagnosis of osteoarthritis (OA)
- ☐ Failure of non-operative treatment for the diagnosis of symptomatic Osteoarthritis
- ☐ Age greater than 18 years
- ☐ Desire to proceed with elective TKR
- ☐ Completion of informed consent and signature of written consent form

3.2 EXCLUSION CRITERIA:

- ☐ Ligamentous instability that may necessitate a constrained TKR implant

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- ☐ Retained hardware in the distal femur or proximal tibia of the operative extremity
- ☐ Medical contraindication to undergo preoperative CT, or inability to tolerate preoperative CT

4. Study-Wide Number of Subjects

112

5. Study-Wide Recruitment Methods

Subjects will be enrolled in the study in the Northwestern Medicine outpatient orthopaedic surgery clinic [259 E. Erie, 13th floor] at their pre-operative clinical appointment with either Dr. David Manning or Dr. Matthew Beal. The principal investigator or sub-investigator will complete the informed consent process and obtain the written consent form.

6. Multi-Site Research

N/A

7. Study Timelines

1.1. All subjects will follow the time points below:

- Baseline (pre-operative)
- 6 weeks post-operative
- All primary analyses of the study will be completed by 2015.

8. Study Endpoints

1. To determine whether the low-dose, biplanar x-ray imaging System (EOS) has the same accuracy as CT in the evaluation of TKR implants
2. To validate EOS as a tool to evaluate 3-Dimensional alignment of TKR implants in the coronal, sagittal and axial planes
3. Evaluate differences in component alignment of patients whose arthroplasty is performed by using manual or custom instrumentation derived from a preoperative CT scan.

9. Procedures Involved

Subjects will undergo standard of care preoperative low-dose, biplanar x-ray (EOS) and standard of care preoperative CT of the surgical extremity. All subjects' preoperative standard of care CT will be used for surgical planning of bony resection during total knee replacement. They will then be randomized in a single-blinded fashion into one of four groups: Group A, using customized instrumentation derived from preoperative CT for both the femoral and tibial preparation; Group B, using customized instrumentation derived from the preoperative CT for the femoral preparation and manual instrumentation for the tibial preparation; Group C, using manual instrumentation for both the femoral and tibial preparation; and Group D, using customized instrumentation derived from the preoperative CT for the tibial preparation and manual instrumentation for the femoral preparation. The 4th randomization arm is being added in order to

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have fair comparison between the custom and manual instrumentation and prevent treatment bias and include all iterations.

Following randomization, they will undergo elective, primary knee replacement utilizing standard Medacta GMK Sphere implants. Dr. David Manning or Dr. Matthew Beal will be the attending surgeon for all subjects. Subjects will be admitted to the orthopaedic service following total knee replacement for standard postoperative care. Postoperative follow-up appointments will be arranged at the standard time points: at three weeks and at six weeks. A standard postoperative radiograph will be obtained at 6 weeks using EOS, and the TKR implant alignment will be evaluated in the coronal, sagittal and axial planes. All TKR implant alignment measures for both the pre and post op radiographs will be done by the manufacturer of the EOS Imaging system since they have the technical expertise to perform the measurements. TKR implant alignment will be compared to the preoperative plan that was created using the preoperative CT.

Only 13 out of the total 20 patients currently enrolled in the study have undergone surgery. Upon approval from the IRB, we can randomize the remainder of enrolled patients and the remaining 60 to include the 4th arm. We feel that the addition of the 4th arm strengthens the study and dataset more so than the randomization bias weakens the study design. We are prepared to report this bias in publication.

The following data will be collected from each consented subject's chart: Name, MRN, date of surgery, name of surgeon, operative time, total blood loss, discharge hemoglobin data, hemoglobin delta between pre-op and morning after surgery, and total tourniquet time.

10. Data and Specimen Banking

All information regarding the nature of the proposed investigation provided to the investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the subject, or the appropriate regulatory authority) will be kept in confidence by the principal investigator. All personal information will be treated as strictly confidential and not made publicly available. All records are stored in a locked filing cabinet and password protected computers which are accessed only by the Principal Investigator, Co-Investigator, and authorized study staff. All identifiable data will be destroyed a year after the study is complete.

11. Data and Specimen Management

The primary outcome measure of total knee arthroplasty component alignment will be measured on the postoperative EOS image obtained at the six week follow-up appointment. Alignment will be measured in the coronal, sagittal and axial planes and compared to the preoperative plan created with the preoperative CT. All TKR implant alignment measures for both the pre and post op radiographs will be done by the manufacturer of the EOS Imaging system. All radiographs sent to EOS Imaging will be fully de-identified and will be

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transmitted securely using Box.com in a dicom format.

Secondary outcomes of operative time and intraoperative blood loss will be obtained from the medical record. Wilcoxon Rank-Sum test will be used to compare the coronal, sagittal, and axial alignment measurements between groups. Student's t-test will be used to compare the secondary outcome measures of operative time and intraoperative blood loss between groups.

A power analysis was performed to determine appropriate sample size for each group to determine a 1 degree difference in component alignment. Previous literature has noted standard deviation in axial alignment with custom instrumentation is 1.5 degrees¹⁵. With a p-value of 0.05 and a power of 0.8, our power analysis determined that each group needed to include 25 subjects to be appropriately powered. The planned sample size of 28 subjects in each group was chosen to fulfill this power analysis.

12. Provisions to Monitor the Data to Ensure the Safety of Subjects

N/A

13. Withdrawal of Subjects*

N/A

14. Risks to Subjects*

Procedures such as X-rays and CT scans will be used during this research study. The cumulative radiation exposure from these tests is considered small and is not likely to adversely affect the patient or their disease. However, the effects of radiation add up over a lifetime. It is possible that having several of these tests may add to the patient's risk of injury or disease. When deciding to enter this study, the patient will be asked about their past and future contact with radiation.

There are no other known risks involved in this study since both type of knee implants are FDA approved standard implants used by Dr. Manning and Dr. Beal in surgery.

The EOS imaging system is being used to obtain full standing radiographs. This is within its FDA approved capacity.

The ad hoc analyses of the EOS radiographs for TKR alignment is independent of the patient's care at NMG and performed after the surgery and post-operative care has been completed. The radiographs obtained in EOS are obtained for the patient's standard of care with their surgeon.

15. Potential Benefits to Subjects

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The subjects are not likely to have any direct benefit from being in this research study. However, the subject may benefit from the knowledge that they are helping to improve our understanding of how best to treat future patients that undergo total knee arthroplasty.

16. Vulnerable Populations

N/A

17. Community-Based Participatory Research

N/A

18. Sharing of Results with Subjects

No results will be shared with the subjects.

19. Setting

All research will be conducted in the orthopaedic surgery clinic [259 E. Erie, 13th floor].

- All subjects will be identified during their pre-operative visit with Dr. Manning or Dr. Beal.
- All consent will be obtained at the orthopaedic surgery clinic [259 E. Erie, 13th floor].

20. Resources Available

Dr. Manning and Dr. Beal has been conducting clinical research for the last 8 years of their careers Furthermore, Dr. Manning and Dr. Beal will have support from joints fellow Dr. Kevin Hardt and the research coordinator in the department that will facilitate the identification, consent and collection of data expeditiously. Northwestern Memorial Hospital cares for approximately 700 orthopaedic joint surgery patients per year, from which the study population will be derived. Lastly, coordinator and statistical arrangements are already in place and are ready to implement.

21. Prior Approvals

N/A

22. Recruitment Methods

Subjects will be enrolled in the study in the outpatient clinic [259 E. Erie, 13th floor] at their pre-operative clinical appointment with either Dr. David Manning or Dr. Matthew Beal. The principal investigator or sub-investigator will complete the informed consent process and complete the written consent form.

23. Local Number of Subjects

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24. Confidentiality

N/A

25. Provisions to Protect the Privacy Interests of Subjects

Only the Principal Investigator, Co-Investigators, and authorized study staff will access to the data collected through the study. All research team members will be required to complete the CITI research training along with other requisite training required to access medical records.

26. Compensation for Research-Related Injury

N/A

27. Economic Burden to Subjects

All procedures performed in the study are part of the subject's standard of care while undergoing treatment with Dr. Manning and Dr. Beal. All costs incurred from the study procedures, visits, etc. will therefore be billed to the patient's insurance. The patient will therefore incur no cost from the study.

28. Consent Process

All subjects will be consented during the patient's pre-operative clinic visit with Dr. Manning or Dr. Beal by either Dr. Manning, Dr. Beal, Dr. Kevin Hardt, or the authorized research coordinator. The patient will be given the choice to take a copy of the consent home to review prior to making a decision regarding their participation in the study. All the patient's questions will be answered prior to obtaining informed consent.

29. Process to Document Consent in Writing

All consent will be documented in writing using the IRB approved consent form.

30. Drugs or Devices

N/A