Study Title: ToKa HTO Virtual Clinical Trial

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Sponsor:	Royal Exeter & Devon NHS Trust
Funder:	Arthritis Research UK
Chief Investigator Signature:	

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. SYNOPSIS

Study Title	ToKa HTO Virtual Clinical Trial	
Internal ref. no. / short title	NA	
Study Design	Virtual comparative trial	
Study Participants	Imaging data derived knee OA cohort	
Planned Sample Size	20	
Planned Study Period	12 months	
	Objectives	**Endpoints**
Primary	Safety comparison between existing HTO device (Tomofix) & ToKa	Calculation of bone and device load environment using Finite Element Analysis (FEA)

2. ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
FEA	Finite Element Analysis
GCP	Good Clinical Practice
GP	General Practitioner
HTO	High Tibial Osteotomy
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
OA	Osteoarthritis
SOP	Standard Operating Procedure
TKR	Total Knee Replacement

UKR	Unicompartmental Knee Replacement

3. BACKGROUND AND RATIONALE

High Tibial Osteotomy (HTO) is an alternative to knee replacement in suitable patients with early knee osteoarthritis (OA), it is particularly suited to patients with single compart disease who otherwise would be suitable for unicompartmental knee replacement (UKR)[1]. OA of the knee is very common and increasing driven by the ageing of the population[2]. The current limitations of HTO are related to the difficulty of achieving the desired correction due to a challenging surgical technique and soft tissue irritation due to the use of generic stabilisation plates[3]. This study will examine the safety equivalence of a new patient specific HTO process which has patient specific 3D printed plates, ToKa, with the existing most commonly used HTO procedure using the Tomofix plate. Importantly this study will be undertaken as a *Virtual Trial*, existing anonymised 3D imaging data will be used to create the virtual patient cohort. This cohort will receive both procedures, which for this type of procedure is only possible in a virtual scenario.

The main question to be addressed is: "Is the ToKa procedure as safe as the most commonly used existing HTO procedure?". In this context safety concerns the mechanical loads placed upon the tibia and the support plate.

The interventions will all be made on computer models, the 3D imaging data will be used to create the intact (un-operated) models of the subject tibias. Each model will then be virtually operated upon, with both the ToKa and Tomofix procedures. The models will then be loaded with physiological loads experienced during function and the mechanical states compared[4].

In order to build the cohort of virtual patients existing anonymised CT data from patients with knee OA will be used. The exclusion criteria are: previous knee or osteotomy surgery, abnormal anatomy of the tibia, poor quality CT data. This study will use data from 20 patients, allowing paired comparison between each intervention in each virtual patient increasing the study power. There are no previous studies of this type to base a power analysis upon, thus the data will be critically evaluated and should increased numbers be required an extension to the ethics will be made. The study findings will be relevant to a knee OA population.

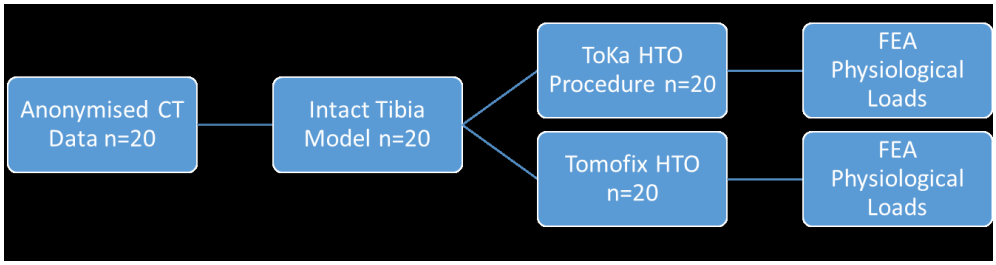
4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Objectives	**Outcome Measures/Endpoints**
Primary Objective To investigate whether the new ToKa HTO procedure is as safe as the currently widely used Tomofix HTO	The key outcome measures are the mechanical load variables describing the mechanical loads present in the tibia and implanted devices during physiological loading as determined by FEA.

5. STUDY DESIGN

The study design is a virtual clinical trial in which BOTH interventions are applied to the virtual population. This is only possible in a virtual scenario. This allows powerful paired analysis.

Flow diagram:



6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

Anonymised CT data sets from patients with moderate to severe knee OA.

6.2. Inclusion Criteria

- Appropriate existing CT data of lower limb.
- Male or Female, aged 18 years or above.
- Diagnosed with moderate to severe OA of the knee.

6.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Abnormal anatomy of tibia or presence of pathology other than OA, e.g. bone tumour.
- Previous knee or osteotomy surgery.
- Presence of metal-work.

7. STUDY PROCEDURES

7.1. Recruitment

Data obtained by querying hospital PACS systems for suitable patients with suitable radiological examinations, anonymised by hospital before transmitting to research team.

7.2. Informed Consent

We believe this is not required for anonymous use of existing imaging data.

7.3. Screening and Eligibility Assessment

CT data to be reviewed by surgical member of team to ensure subjects meet the inclusion criteria and that none of the exclusion criteria apply.

7.4. Randomisation, blinding and code-breaking

NA

7.5. Baseline Assessments

Intact tibia models will be loaded with physiological loads to establish a per subject baseline value for mechanical load variables.

7.6. Subsequent Visits

NA

7.7. Discontinuation/Withdrawal of Participants from Study

NA

7.8. Definition of End of Study

The end of study is the date of the final FEA analysis has been performed.

8. INTERVENTIONS

The interventions will all be made on computer models, the 3D imaging data will be used to create the intact (un-operated) models of the subject tibias. Each model will then be virtually operated upon, with both the ToKa and Tomofix procedures. The models will then be loaded with physiological loads experienced during function and the mechanical states compared[4]. The time point for the comparison will be 6 weeks simulated post-operation.

9. SAFETY REPORTING

NA

10. STATISTICS AND ANALYSIS

10.1. Description of Statistical Methods

All study practices and statistical methods are based on the International Conference on Harmonization

(IHC) document "Statistical Principles for Clinical Trials."

Data will be summarised by treatment group. Baseline characteristics, and safety outputs total overall columns will be included to summarise all subjects.

For all baseline, demographic, safety and efficacy outputs data will be summarised by treatment group. In summary tables of continuous variables, the minimum and maximum statistics, the arithmetic mean and median, the 95% confidence interval, standard deviation, and standard error will be presented will to the same number of decimal places as the original data.

In summary tables of categorical variables, counts and percentages will be used. The denominator for each percentage will be the number of subjects within the population treatment group unless otherwise specified.

All hypothesis testing will be carried out at the 5% (2-sided) significance level unless otherwise specified.

Two one-sided test (TOST) procedure will be used to test equivalence[5].

10.2. The Number of Participants

This study will use data from 20 patients, allowing paired comparison between each intervention in each virtual patient increasing the study power. There are no previous studies of this type to base a power analysis upon, thus the data will be critically evaluated and should increased numbers be required an extension to the ethics will be made. In order to generate the virtual cohort we will request ethics for anonymous re-use of imaging records for 30 patients, allowing for drop out due to issues with images or patient anatomy.

10.3. Analysis of Outcome Measures/Endpoints

Two one-sided test (TOST) procedure on the mechanical load variables. The primary outcome measure will be maximum mechanical stress (von Mises stress) in the device under physiological loading experienced during gait and stair function at a simulated six weeks post-operatively. The secondary outcome measure will be the maximum mechanical strain (von Mises strain) in the bone around the screws holding the HTO plates.

11. DATA MANAGEMENT

11.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

Additionally, Renishaw plc. will be granted access to anonymised data for the purposes of pre-operative planning software development specifically for and only relating to the ToKa device.

11.2. Data Recording and Record Keeping

Data will stored according to University of Bath's research data storage policy
http://www.bath.ac.uk/research/data/policy/research-data-policy.html

Anonymised data stored by Renishaw plc. will be stored according to their data storage policy:

http://www.renishaw.com/en/data-protection-statement--7425

12. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

13.2. Approvals

The protocol will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.3. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

13.4. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All

documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

14. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

15. REFERENCES

1. Harris JD, McNeilan R, Siston RA, Flanigan DC. Survival and clinical outcome of isolated high tibial osteotomy and combined biological knee reconstruction. *Knee* 2013;20-3:154-61.
2. Arden N, Nevitt MC. Osteoarthritis: epidemiology. *Best Pract Res Clin Rheumatol* 2006;20-1:3-25.
3. Niinimaki TT, Eskelinen A, Mann BS, Junnila M, Ohtonen P, Leppilahti J. Survivorship of high tibial osteotomy in the treatment of osteoarthritis of the knee: Finnish registry-based study of 3195 knees. *J Bone Joint Surg Br* 2012;94-11:1517-21.
4. Bergmann G, Bender A, Graichen F, Dymke J, Rohlmann A, Trepczynski A, Heller MO, Kutzner I. Standardized loads acting in knee implants. *PLoS One* 2014;9-1:e86035.
5. Walker E, Nowacki AS. Understanding equivalence and noninferiority testing. *J Gen Intern Med* 2011;26-2:192-6.

16. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	Version_0_02_UoB	24/10/2017	Alisdair R. MacLeod, Richie Gill	Anonymised data access will also be granted to Renishaw plc. who are now partners in developing ToKa software
2	Version_0_03_UoB	23/01/2018	Richie Gill	Amended number of data sets access requested for