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Protocol

Clinical Investigation

Study Title	"Clinical Evaluations of the TOKA Customized Device for High Tibial Osteotomy in the Treatment of Knee Osteoarthritis: a Pilot Study"
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1. Device description

Product Description:

The product is a customised medical device (implantable plate and accessories) for use in opening wedge high tibial osteotomy (HTO), designed and manufactured in compliance with the relevant medical standards. It can be inserted in the IIb risk class, given the rules outlined in Annex IX (Classification Criteria) within the Medical Device Directive 93/42/EEC, in particular:

- Rule 8: All implantable devices and long-term surgically invasive devices are in Class IIb. Examples: Nails and plates

The device is designed using CAD files, created from the medical device software ScanIP to handle the imaging data. As per normal routine HTO procedures, the surgical planning is done by the surgeon using X-rays to obtain key information, such as the correction angle desired, the hinge point positioning and the cut orientation. The CAD files are then imported and manipulated using an internal software. This allows the positioning of the bone geometries in accordance with the surgeon's plan and assists with the creation of plate and surgical guide/accessory geometries via the recording of screw and cut positioning and orientation. Note that the software does not automatically generate the surgical plan or make any treatment decision (i.e. opening angle, hinge point, screw locations).

The TOKA® (Tailored Osteotomy Knee Alignment) medical device consists in implantable and non-implantable components for opening wedge HTO. The core implantable product comprises:

- **Custom fixation plate**
  - ⇒ Made of Ti-6Al-4V ELI Grade 23 titanium powder
  - ⇒ Typically includes 7 holes for locking screws
  - ⇒ Will be patient specific
  - ⇒ Will be flush against bone
  - ⇒ Will have no sharp edges or protrusions that could cause irritation
  - ⇒ The head of the screws will not protrude substantially from the plate

- **Locking screws**
  - ⇒ Made of Ti-6Al-4V
  - ⇒ Typically, 7 screws are to be used with the plate

The non-implantable components comprise the following:

- **Surgical guide**
  - ⇒ Made of Ti-6Al-4V ELI Grade 23 titanium powder
  - ⇒ Typically, 7 drill tube guides are to be used
  - ⇒ Will be flush against bone
  - ⇒ Should be the minimum size required for adequate functionality, especially in the horizontal direction

- **Pins**
  - ⇒ Made of stainless steel
  - ⇒ 2 pins per set

- **Opening Screws**
  - ⇒ Made of Ti-6Al-4V ELI Grade 23 titanium powder
  - ⇒ 2 identical opening screws per set
  - ⇒ Length of shaft is currently 40mm (should not change patient-to-patient)

- **Drill Bits**

⇒ Made of stainless steel 316L
⇒ Typically, 7 drill bits are to be used with the plate
⇒ Dimensions are analogous to locking screws

- **Wedges**
  ⇒ Made of Ti-6Al-4V ELI Grade 23 titanium powder
  ⇒ Exact dimensions will be patient specific
  ⇒ Include 'anterior' and 'posterior' labels and features to ensure correct positioning
  ⇒ Should have a feature to allow easy removal.

- **Saw blade guides**

  ⇒ Made of stainless steel
  ⇒ 2 blades per set: one for biplanar and for main cut
  ⇒ Blades laser marked to indicate cutting depth.

- **Allen Key and Hex bit**

  ⇒ Made in stainless steel 316L

- **K-wires and K-wire tubes**

  ⇒ Made in stainless steel 316L / Ti-6Al-4V
  ⇒ 2 K-wires and K-wire tubes to be provided

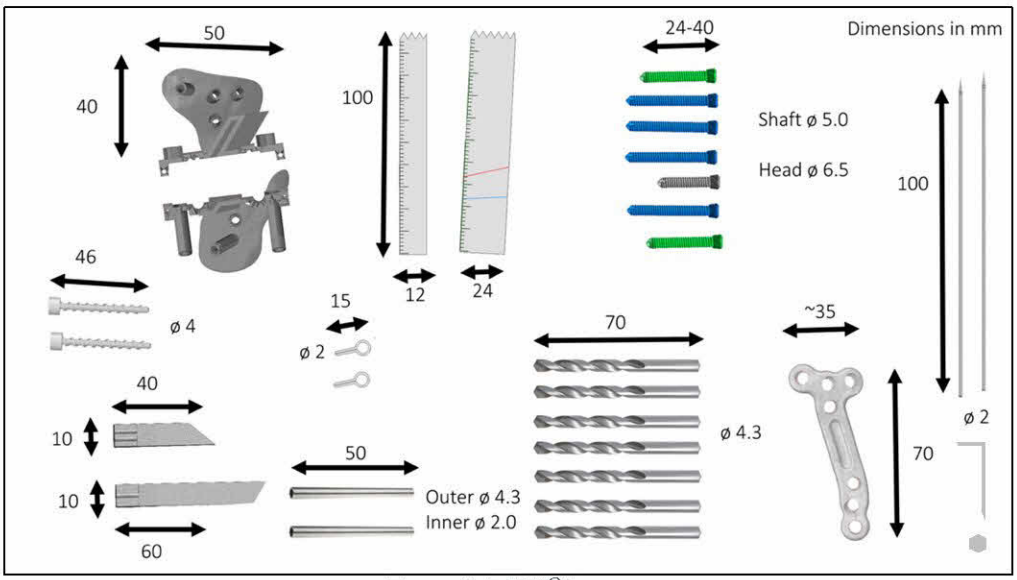

Figure 1: TOKA® Inventory

All these components will be supplied within a TOKA® box with a transport document identifying the parts and the purpose of the product (as indicated in the contract), and it will be labelled according to the standard operating procedure (SOP) in the Quality Manual (Appendix 1). More specifically, the product will be sent to the pharmacy within the Rizzoli Orthopaedic Institute.

TOKA® is categorised as a custom-made device and the main aim is to overcome the difficulties that the current HTO procedure encounters. Given that the components are patient-specific, TOKA® is able to resolve the problems of existing generic HTO plates and the additional presence of a custom-made surgical guide allows a substantial reduction in surgical time. This surgical guide also permits the surgeon to perform the HTO procedure with a high degree of accuracy, as it precisely aligns the tibia to the pre-specified amount, via screws threaded to a pre-determined length. Moreover, the customised characteristic is highly beneficial to the patient

in that it is likely that adverse effects, such as soft-tissue irritation, are less likely to occur compared to the typical devices used.

Key Features include:

- 3D-printed custom surgical guide enables accurate plate positioning on tibia and guides open wedge cut profile (angle and depth)
- Spacers/wedges maintain accurate open wedge cut angle after removal of jig
- 3D-printed custom plate fits individual patients' tibial profile
- Product to be supplied non-sterile (sterilised on site by autoclave). Validated sterilisation protocol will be supplied (Appendix 2).

2. Background & rationale

Osteoarthritis (OA) of the knee carries a huge personal and societal burden. Up to 28% of the population over 40 in the UK have knee pain, with half of these people having radiographic OA (Palmer). Knee OA is becoming more common; this is driving the growing demand for knee replacement, which currently records over 100,000 procedures performed annually in the UK alone, increasing by 5% per year (NJR 2014 – 2016). With the continuing trend of the ageing population (The United Kingdom Knee Osteotomy Registry), the demand for knee replacement is set to more than double by 2030 (Patel). Total knee replacement (TKR) is currently the treatment of choice for end-stage OA and is highly effective for patients with low activity, but there is a significantly higher risk of early revision for young (40-65) and active individuals, who represent 1/3 of patients. More specifically, patients aged 64 years or less at time of primary surgery have more than double the revision rate of those aged between 65 and 74 years. Based on datasets from six countries, mean revision rates of about 6% after five years and 12% after ten years, are to be expected for TKR in older aged patients (Labek), which signifies an even higher number for the younger patient population. Given that OA is becoming more common, the increase in numbers of primary knee replacement will be associated with increased revision rates. It is predicted that the UK revision rate will have increased by over 300% by 2030 (Patel).

A more conservative approach to treating OA is represented by unicompartmental knee replacement (UKR). Irrespective of the product used, the revision rate for medial UKR in national datasets is higher than those for TKR (Labek), giving ten-year revision rate at almost 19% (University of Lund). The Joint registry gives comparable results of 85.71% survival rates, meaning 14.29% revision rates after a period of 11 years.

Revision knee surgery is significantly more expensive and carries much higher risks than primary knee surgery, as well as providing generally worse outcomes compared to the primary surgery (Kallala).

As mentioned previously, whilst knee replacement provides treatment for patients with end-stage disease, it is not recommended for the early stages of knee OA and severity of radiological OA is a key factor used by surgeons when deciding whether to perform knee replacement (Verra). The stage of knee OA is mainly based on radiographs (x-rays) (Kellgren), but there is a poor relationship between symptoms and radiographic appearance (Bedson). A significant number of individuals find themselves in the treatment gap, suffering pain and disability from knee OA but are not yet suitable for knee replacement (London). As well as the pain and disability these individuals suffer, there is a financial societal burden. Considering only the UK population aged 40 to 65 years (21 million people), of this working age group 2.9 million people have radiographic knee OA resulting in annual burden of £24 billion.

An alternative to knee replacement (TKR & UKR) is high tibial osteotomy (HTO). Here the native joint is preserved by re-aligning the tibia to off-load the worn areas of the knee, which is stabilised by a plate. Well performed HTO can delay the need for knee replacement by approximately 10 years and in some cases, it can be the definitive treatment, avoiding the need for further surgery altogether. Ten-year survival of HTO is reported to range from 92% (Schallberger) to 73% (Niinimaki); a recent review of 69 studies including 4557 participants reported an average ten-year survival of 84.5% (Harris). Gathering further information and data, a study using a meta-analysis (Kim) obtained 5-year and 10-year survival rates of 95.1% (95% CI: 93.1 to 97.1) and 91.6% (95% CI: 88.5 to 94.8%) respectively.

Opening wedge HTO may be performed with or without bone grafting and the comparative radiological outcomes relating to these two methods are still very controversial (Han) (Samy). A meta-analysis looking at 25 studies showed that there were similar rates of radiological union and correction maintenance, in particular the RCT within this analysis was found to yield similar bone union period, union rate and correction loss rate between the patients with bone graft and those without filling (Han). As a result, the evidence currently present is not sufficient to strongly support the superiority of an opening wedge HTO with bone graft to one without bone graft. Moreover, it can be noted that the opening wedge HTO procedure without bone grafting is particularly advantageous, as it is successful at reducing surgery time and patient complications/morbidity (Han) (Samy). However, the surgical procedure using bone grating may present some favourable outcomes for large correction angles, with an opening distance of approximately over 15mm (Han).

A recent economic model to compare the age-based cost-effectiveness of OA found that HTO was a more cost-effective treatment for younger patients compared to UKA and TKA (Konopka) (Smith) due to the preservation of the natural joint and allowing patients to return to active lifestyles. The main driver of the cost-effectiveness of HTO was the patient-reported measure of well-being and was essential when comparing the operative interventions. Whilst HTO is recommended for younger patients, TKA is the more common treatment for knee OA despite reported dissatisfaction with the functional outcome following the procedures. On the other hand, knee surgeons are concerned about performing HTO due to surgical complexity, and the link between surgical inaccuracy and poor patient outcomes (Akizuki). Potential improvements in technical accuracy during surgery is therefore an important factor for surgeons and decision-makers, as surgical outcomes also have downstream economic impacts, such as economic inactivity and revision risk.

The main existing HTO treatment pathway uses standardised plates (e.g. DePuy's Tomofix plate), which are generally available in few sizes. These require significant surgical time to fit due to the large number of measurements, and the use of radiography is required during theatre. A major reason for patient dissatisfaction is also the fact that it may cause soft tissue irritation. Furthermore, current solutions don't provide any planning support to surgeons. Alignment is estimated using the patient's 2D x-ray and the surgery requires significant skill and experience to achieve the desired correction throughout the lengthy operation.

To improve on these shortcomings, 3D Metal Printing are developing a technology called TOKA®, which comprises of customised 3D printed components made of a standard medical grade titanium alloy to be used in the opening wedge HTO operation. The technology will include a surgical guide to ensure precision surgery, and an anatomical stabilisation plate that is implanted into the patient. The parts are to be individually produced using the patients' CT scans enabling TOKA® to overcome the problems of existing generic HTO plates and give the potential to substantially reduce surgical time and cost.

HTO, in particular using the TOKA® product, is an excellent method to treat the early onset of unicompartmental knee OA. It allows the preservation of all the natural structures within the knee, while considerably reducing pain and allowing the patient to return to an active lifestyle.

In the worst-case scenario, if serious adverse reactions were to occur, a removal of the implant would be required, followed by the implantation of the routine device used in the centre under investigation.

UKR or TKR would be the only other alternatives to an HTO and require more of the natural joint structures to be removed, which is therefore more invasive and less beneficial.

The TOKA® solution has been used in multiple cadaver tests, is set to undergo a feasibility study later this year and virtual testing has been performed. It is estimated that it achieves similar, if not superior, survival rate results to the current pathway for HTO (i.e. between 75% and 94.8% for 10-year survival rates). The clinical results of opening wedge HTO are strongly related to the accuracy of correction achieved surgically, so the high precision achieved by TOKA® is extremely beneficial (MacLeod).

Therefore, it can be concluded that the benefit of using the TOKA® device for opening wedge HTO compared to other procedures (e.g. UKR, TKR) as well as other HTO devices, outweighs the overall risk.

Total Knee Replacement is the most common procedure undertaken in the NHS. The world's first knee osteotomy register (UK Knee Osteotomy Registry), with only 49 currently registered surgeons, recorded 1,776 procedures during 2014-2017. However, given that few surgeons are registered, a large amount of cases are not reported. Therefore, we estimate that the total number within the UK is approximately 3,000 annually. A further 11,000 are treated with UKR annually (NJR, 2017), and the vast majority would qualify for TOKA® patient-specific technology. The total UK patient population eligible to receive the TOKA® treatment within the health economic report is estimated at 14,000.

Consequently, it is important to be able to measure the performance of the device, and thus an initial study needs to be performed. This investigation has the potential to demonstrate the improved outcomes for patients, as well as the fact that opening wedge HTO surgery can be performed in a straightforward, simple manner with high accuracy, enabling more patients to be offered the surgery. At this point in time, a preliminary pilot study will suffice to gauge an initial understanding of the beneficial results of the surgery, and possibly influence surgical practice with the aim of improving patient outcomes and satisfaction.

Unlike the bi-dimensional planning, the three-dimensional planning allows to avoid mistakes due to changes to the sagittal plane during the correction of the coronal plane (tibial slope increase).
The personalised surgical planning together with the (patient specific) cutting surgical guide allow surgeons to perform a safer and more accurate osteotomy, avoiding compromising the lateral hinge which will make the osteotomy unstable.
Moreover, the surgical planning and the use of the surgical guide present the benefit to avoid an incomplete osteotomy, responsible of potential fractures of the tibial plane during the opening of the osteotomy.

Furthermore, the pre-planning of the osteotomy using patient specific stabilising plate, instrumentation and surgical guides introduces a great simplification for the surgeons to achieve the planned correction, overcoming a critical surgical step not always easy to achieve.
The result is a great reduction of the surgical time and improved surgery performance.
This HTO surgical procedure has been tested on several cadaveric tests.

3. Study objective

The main aim of this pilot study is to assess the clinical performance of the personalised HTO using the TOKA® device and procedure to be able to conduct an RCT in the near future. A more detailed description of all the primary and secondary objectives can be found in Chapter 8.2.

4. Risks and benefits

The risks and benefits relating to the device and surgery are outlined in more detail in Chapter 2; however, a brief overview of the main aspects is mentioned again in this section.

It can be established that for relatively young patients, the technology will provide a cost-effective treatment for early-stage knee OA as opposed to patients living in constant pain, undergoing regular physiotherapy or pain management until they are old enough for a total knee replacement. The overall benefits for the patient are that it is a joint-preserving treatment for knee OA, and that it gives the opportunity to return to a normal active lifestyle. In addition, through preserving their natural joints, patients will gain extra time before needing a joint replacement, and for some patients this will be their definitive treatment. Joint disease carries a significant detrimental burden in terms of quality of life as well as a considerable societal burden. Some additional benefits related to the use of the TOKA® are that it achieves an accurate correction, has decreased invasiveness, has comparable, if not improved, adverse event rates with current treatments, and has a reduced cost.

Therefore, although there are many risks associated with the medical device given the nature of the HTO procedure (e.g. infection, soft tissue irritation etc), it can be concluded that it is also likely to be extremely beneficial, and so the evaluation of the overall risk is acceptable.

5. Ethical considerations

Regulatory approvals from the Research Ethics Committee and the Rizzoli Research Authority will be obtained prior to starting the study. Furthermore, the protocol and study follow Good Clinical Practice principles and abide by the ethical principles discussed in the declaration of Helsinki, the Council of Europe Convention for the Protection of Human Rights and Dignity of the Human Being in the Application of Biology and Medicine (Convention of Oviedo 04/04/1997) and Italian Codes of medical ethics of health care professions, current Regulations and current anti-corruption laws.

6. Obtaining participant consent

If the potential participants have given verbal agreement to enrol in the study, we will obtain written consent of participation, using Appendix 3, when they attend the hospital after patient recruitment. The patient will meet one of the clinical investigation team to sign an Ethics Committee approved study consent form. They will also give their availability for the recording of the pre-operative and post-operative data, which will need to be collected and includes: the planned medical imaging and functional assessment (gait analysis) mentioned in Chapters 8.9 and 8.12, routine demographics and medical history data (to be inserted separately in the patient's record – cartella clinica), Knee Osteoarthritis Outcome Score (KOOS) (Appendix 4), the EQ-5D score (Appendix 5), the Tegner score (Appendix 6), the knee society system score (KSS) (Appendix 7), pain measurements by Visual Analogue Scale (VAS) during rest and activity (Appendix 8). Collecting the pre-operative data will take approximately 60 minutes.

We will ask for specific patient consent to use the anonymised medical images for further research on personalised devices.

Two copies of written consent will be obtained: one original and one photocopy. The original will be kept by the research team in the patient's records (cartella clinica) and one will be returned to the patient. Routine care for these patients from their clinic appointment will have already included several radiographs of the affected knee and an assessment of their active and passive range of motion of the knee. All information collected pre-operatively will be used to compare post-operative progression.

7. Pre-clinical trials and previous clinical experience

Currently, the device has undergone no clinical experience. However, a preIDEAL framework is currently being used, which precedes the standard IDEAL framework commencing with first in-man studies. This is done to aid in the safe introduction of the novel technique and device.

1. Firstly, Laboratory/Experimental testing was performed using composite tibiae and finite element simulation to evaluate the influence of plate design variables [including geometry (TOKA® vs Tomofix) and screw positioning] on clinical factors [plate stress and interfragmentary movement (IFM)]. The geometry of the novel TOKA® plate was structurally optimised (MacLeod).
2. Moreover, to test the safety of the device, *in silico* virtual trials have been done (Appendix 9), which simulate the presence of the fixation plate within patients and give an understanding of the device performance (strains in the bone around the screws, movement at the facture/osteotomy site, stress of plate: maximum, minimum, von Mises).
3. Surgeon training was conducted prior to cadaver tests using models, videos and planning software.
4. Lastly, a number of cadaver tests have been performed to optimise the design and analyse the finer details of the surgical procedure. Following these tests, a validation process was undertaken to examine the agreement between pre-operative plan and post-operative correction (Appendix 10).

A feasibility study is also planned later this year in collaboration with the Royal Devon & Exeter NHS Foundation Trust. This study is still at the stage of obtaining all the necessary documentation for the MHRA.

8. Clinical investigation information

8.1. Description of the clinical study

This preliminary pilot study is a single-centre, prospective, uncontrolled, 32-month study to assess the performance of personalised opening wedge HTO treatment using the TOKA® device and procedure. The medical device being examined is a custom-made device and therefore does not require a CE mark. Furthermore, the study will serve as a useful method of gathering clinical data and measuring device performance, as well as establishing a potential commercial relationship with the hospital administration.

8.2. Primary and secondary objectives

Primary Objective:

- Pilot study to assess the morphology of the knee joint and the improvement of OA following the TOKA® treatment, to be able to conduct a future RCT.

Secondary Objectives:

- Pilot study to Assess the functional outcome of the knee joint and the improvement of OA following the TOKA® treatment, to be able to conduct a future RCT.

8.3. Outcomes

Primary Outcomes:

The morphology of the knee joint is assessed by:

- Verifying the matching between the planned correction and the post-operative imaging results, along with the investigation of the maintenance of the desired correction at the follow-up meetings. These results are measured through the correction angle, hip-knee-ankle angle (HKA - mechanical axis), Mikulicz point (recorded as a percentage of the tibial width from the medial to the lateral region) and posterior slope, using the imaging techniques outlined in the tables below.

Secondary Outcomes:

The functional outcome of the knee joint is assessed by:

- Performing a gait analysis of the patients pre-operatively and post-operatively.
- The use of clinical scoring (Appendix 4-8).

8.4. Inclusion and exclusion criteria

Inclusion Criteria:

- Patients undergoing opening wedge HTO at the Rizzoli Orthopaedic Institute
- Patients must have completed a consent form for the study
- Patients must be prepared to comply with the pre and post-operative investigations, rehabilitation, attendance schedule and questionnaire schedule of the study
- Patient in whom any varus deformity present is <20°
- The diagnosis is of unicompartmental medial osteoarthritis of the knee
- Patient has primary diagnosis of Non-Inflammatory Degenerative Joint Disease (NIDJD)
- BMI<40

- Age range 40 to 65 years

Exclusion Criteria:

- Refusal to consent to the study
- Pregnancy
- Prisoners
- A patient known to have substance abuse or psychological disorders that could interfere with their ability to comply with the post-operative rehabilitation and assessment schedules
- Patients unable to read or understand the patient information leaflet and consent form
- Patient has a known sensitivity to device materials.
- Patient has a Body Mass Index (BMI) ≥ 40.
- Patient has an active or suspected latent infection in or about the affected knee joint at time of study device implantation.
- Patient has received any orthopaedic surgical intervention to the lower extremities within the past year or is expected to require any orthopaedic surgical intervention to the lower extremities, other than the HTO to be enrolled in this study, within the next year.
- Patient requires bilateral HTO or has a history of unsuccessful contralateral partial replacement or HTO.
- Patient has chronic heart failure (NYHA Stage ≥ 2)
- Patient has a neuromuscular or neurosensory deficiency, which limits the ability to evaluate the safety and efficacy of the device.
- Patient is diagnosed with a systemic disease (e.g. Lupus Erythematosus) or a metabolic disorder (e.g. Paget's disease) leading to progressive bone deterioration.
- Patient is immunologically suppressed or receiving steroids in excess of normal physiological requirements (e.g. > 30 days).
- Patient has very poor bone quality, with extensive bone deterioration that could compromise the use of the implanted device.

8.5. Study Population

The study population comprises 25 adult patients aged between 40 and 65 years, enrolled consecutively, under the care of the Rizzoli Orthopaedic Institute, who are undergoing opening wedge HTO for the treatment of medial compartment OA of the knee. The study team believe the research burden on study participants is moderate with one pre-operative visit required and 5 visits required for post-operative follow-up after 1, 3, 6, 12 and 24 months. The team are confident that study dropout rates will be relatively low, and will also utilise letter, e-mail and SMS communications to encourage patient attendance at all follow up time frames. As such, it has been advised that this population number is sufficient to meet the pilot study aims.

8.6. Identifying potential study participants

Patients will be identified as potential participants in one of two ways. Firstly, by their surgeon when they are initially listed for opening wedge HTO surgery at their out-patient consultation at the Rizzoli Orthopaedic Institute. The surgeon will outline the study, provide the patient with the study consent form containing information about the study (Appendix 3) and ask permission to the patient to allow one of the research team to contact them to discuss the study further. Alternatively, potential participants will be identified from the current surgical waiting list as suitable for inclusion by a member of the direct care team. In this latter case, one of the direct care team will telephone the patient requesting permission for one of the research team to contact them by telephone to discuss the study and to enquire if the patient would be interested in participating in the study. Information about the study will be sent to potential participants in advance of the research team contacting them. The number of patients approached and invited to take part in the study will be recorded.

The patient will have an opportunity to further discuss the research project as well as provisionally agree or decline enrolment during this telephone call.

The Rizzoli Orthopaedic Institute carry out approximately 200 HTO procedures per year. We understand that studies have, on average, a low percentage of potential participants who choose not to be part of the research. Consequently, we believe it is reasonable to recruit about 10 cases per month (i.e. 60% participation rate). However, we will allow for 6 months to achieve our sample size of 25 in case recruitment is slower than anticipated.

8.7. Study settings

The study will be conducted in the 2nd Orthopaedic and Traumatology Clinic at the Rizzoli Orthopaedic Institute in Bologna, which is an IRCCS hospital, and hence places particular importance on research assignments. This centre is also the orthopaedic clinic for the Faculty of Medicine at the University of Bologna. The procedure with the novel device under investigation will be performed at the Rizzoli, thus the data will also be collected there, more specifically in the Movement Analysis Laboratory and Functional - Clinical Evaluation of Prostheses. However, the specific data collected pre and post intervention will be sent to the company manufacturing the device under investigation (3D Metal Printing) in the UK.

To be able to identify all the investigation centres involved in the study, page 1 and 2 have been inserted to provide essential information relating to the investigation.

8.8. Study flow and timeline

Study flow is outlined and summarised in Appendix 11.

8.9. Pre-operative radiological & functional assessment

The 25 patients enrolled in this study investigating the medical device (TOKA®) will undergo a pre-operative CT scan of the affected leg, which will be through the hip, knee and ankle. The CT scan will be conducted according to hospital routine protocol. Other pre-operative scans needed are AP, lateral 30°, merchant view and hip and lower limb panoramic frontal load bearing X-rays (also conducted according to hospital routine protocol).

These images are then used to perform a pre-operative plan, by the surgeon and the support staff, to enable the creation of the custom-made TOKA® components. The procedure for determining the key variables (Mikulicz point, hinge point, correction angle and opening distance) is done following a modification of Miniaci's Method for opening wedge osteotomy cases, which is the process used in the Rizzoli Orthopaedic Institute for routine opening wedge HTO cases. This method consists in 6 main steps:

1. The tibial plateau width is measured just below the joint line. Subsequently, a line is drawn from the centre of the femoral head to the centre of the talar dome, which represents the pre-operative weight-bearing or Mikulicz line. This line intersects the tibial plateau at a point termed the Mikulicz point and is typically recorded as a percentage of the tibial width from the medial to the lateral region.

2. Fujisawa's point is then marked and is typically just lateral to the lateral tibial eminence (usually around 62.5% of the tibial width from medial to lateral). Another line is drawn from the centre of the femoral head though the marked Fujisawa's point. This line is extended to indicate the post-operative ankle centre.

3. The hinge point is then identified by extending a line perpendicularly from below the subchondral sclerosis of the lateral tibial plateau till approximately 18mm in males and 15mm in females.

4. Following this step, two lines are drawn – one from the hinge point to the pre-operative ankle centre and another from the hinge point to the post-operative ankle centre. The angle between these two newly marked lines is termed the correction angle and an example can be seen in the figure below.

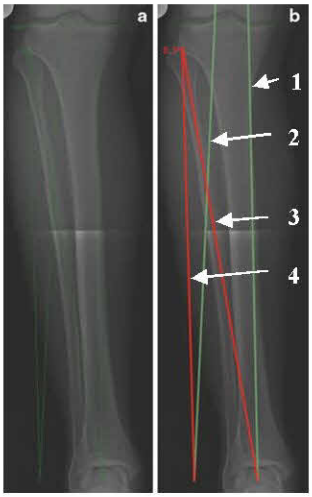

Figure 2: (1) Mikulicz line; (2) Line from centre of femoral head through Fujisawa's point and up to extrapolated post-operative ankle centre; (3) Line from the hinge point to the pre-operative ankle centre; (4) Line from the hinge point to the post-operative ankle centre

5. The obliquity of the osteotomy plane (located above the pes anserinus and projects towards the fibula head) from the vertical line drawn in step 3 is annotated (usually approximately 110°). The proximal osteotomy cut is then projected at this angle.

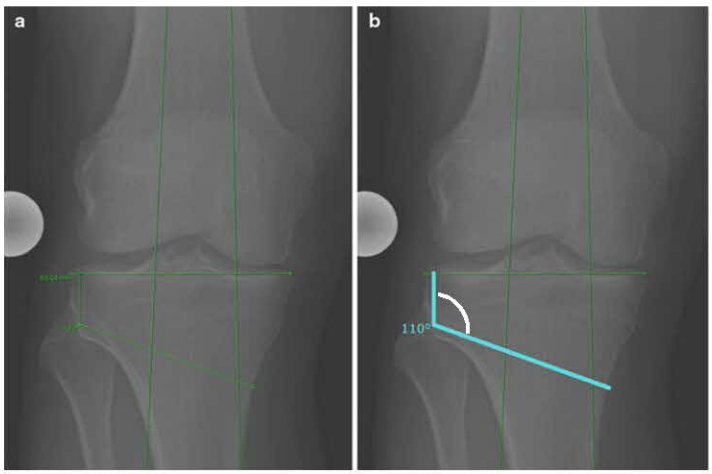

Figure 3:Proximal osteotomy cut at 110° angle

6. Finally, the projected proximal osteotomy cut is moved distally by the previously calculated correction angle to obtain a planned opening. The distance between the proximal osteotomy cut and this distally moved line is the opening distance (Elson).

After the annotation of all these points, lines and angles, the surgeon or investigation team refers them to the TOKA® design team and precision custom-made osteotomy components are generated via modelling software.

Aside from the pre-operative diagnostic images, all study participants will also need pre-operative functional assessments. This will mainly consist in a gait analysis for each patient, which will allow measurement of the location of the loading of the knee joint during functional activity. The analysis will take place at the Movement Analysis Laboratory and Functional-Clinical Evaluation of Prostheses within the Rizzoli Orthopaedic Institute and will be performed by members of the clinical investigation team. The measurements will only take between 10 to 30 minutes. In addition, clinical scores will be registered.

All the pre-operative data needed for each patient undergoing opening wedge HTO with the TOKA® product can be summarised in the table below.

	X-Ray (AP)	X-Ray (lateral 30°)	X-Ray (merchant view)	Hip and Lower Limb Panoramic (frontal load bearing)	CT	GAIT	Clinical scores (KOOS, EQ-5D, Tegner, KSS, VAS)
Pre-operative data	✓	✓	✓	✓	✓	✓	✓

8.10. Admission to hospital for surgery and hospital stay

The admission into the hospital will occur using the routine procedures that the Rizzoli has already put in place and comply with for every HTO case they encounter.

8.11. Surgical procedure

The surgical procedure is one of the most crucial aspects. Surgeon training is given through a video supplied with the TOKA® product, as well as the written instructions in the user manual. A copy of the User Manual and procedure steps can be found in Appendices 12 and 13 respectively. Note that prior to performing the opening wedge HTO surgery, the sterilisation of all the components needs to be performed by using the validated instructions supplied in Appendix 2.

8.12. Post-operative follow-up

For this specific study, participants will be reviewed at 1, 3, 6, 12 and 24 months post-operatively. The table created below shows the post-operative material required for each patient follow-up.

Post-operative follow-up (months)	X-Ray (AP)	X-Ray (lateral 30°)	X-Ray (merchant view)	Hip and Lower Limb Panoramic (frontal load bearing)	CT	GAIT	Clinical scores (KOOS, EQ-5D, Tegner, KSS, VAS)
1	✓	✓					✓
3	✓	✓					✓
6		✓	✓	✓	✓	✓	✓
12	✓	✓					✓
24		✓	✓	✓			✓

As can be seen, the study will terminate at 24 months, after which patients may return to the usual post-operative management schedule (if any is needed).

8.13. Radiation Risk Assessment

Below is a table of the routine and study medical imaging required, which can be used to produce a radiation risk assessment:

Procedure	Pre-Op	Post-Op	Follow-up [month]	No.	Additional Procedure dose	Routine care No.
X-ray (AP)	✓	✓	1, 3, 12	4	≈ 4μSv	4
X-ray (Lateral 30°)	✓	✓	1, 3, 6, 12, 24	6	≈ 4μSv	5
X-ray (Merchant view)	✓	✓	6, 24	3	≈ 4μSv	2
Hip and Lower Limb Panoramic (frontal load bearing)	✓	✓	6, 24	3	≈ 4μSv	2
CT	✓	✓	6	2	≈ 12.6μSv	1

Participants will generally be aged between 40 and 65 years of age. The younger patients will have slightly higher risks, given that they are more sensitive to radiation and they have a longer lifetime for the development of radiation effects (ionising radiation can cause cancer, which manifests itself after many years or decades). Moreover, a category of individuals that could be greatly affected from radiation risks are pregnant women, who are inserted in the exclusion criteria information and so are excluded from the investigation.

For routine clinical care of opening wedge HTO treatment, 14 radiological tests are usually done compared to the 18 planned as part of this investigation. Essentially, in routine clinical care, the 24-month follow-up tests, as well as the standard CT performed at the 6-month follow-up (note that this may be performed sometimes for further evaluations), are not performed.

In the table above, it can be seen that approximately 12μSv is the radiation dose associated with the additional x-rays as part of the study, whereas approximately 12.6μSv is the radiation dose for the extra CT scan performed. These values add to a total of 24.6μSv. If we take into consideration that the average annual radiation dose in the UK is equivalent to 2.7mSv, then 1μSv is comparable to slightly over 2 hours of natural UK background radiation. Another method of comparison to get a better understanding of the figures could be represented by radiation doses during flights. It is estimated that a transatlantic flight (around 6 hours) leads to about 0.08 mSv, and therefore, 1μSv is comparable to about 4.5min on a plane (Public Health England).

This signifies that the figures of additional radiation exposure relating to this study can be compared to about one day of natural UK background radiation or slightly under 2 hours of a transatlantic flight.

With participants' consent, we will use the anonymised data for research on the personalised device, allowing minor optimisations of plate design and surgical technique.

Although there are some additional radiation risks associated with the alternative routine, it can be concluded that this added diagnostic imaging only adds a low extra dosage. These additional examinations are also likely to be extremely beneficial for the assessment of the performance of the device, and so the evaluation of the overall radiation risk is acceptable.

Aside from the risk posed by the radiation, there are also aspects relating to risks of the procedure and device. TOKA® is designed using a risk-based approach, which places great importance on the safety of the patient. Several methods used for assessing the risks are virtual modelling and simulations, along with animal and cadaver tests. Moreover, the design and development of TOKA® follows ISO 14971 to allow conformance to

international risk management standards. The latest risk management table and report can be viewed in Appendices 14 and 15 respectively.

8.14. Interruption of study and patient withdrawal

Following an interruption of the study for any reason, a standard operation procedure must be put in place and enforced to ensure an organised and adequate end to the investigation in order to manage/finalise patient treatment.

All individuals who have not yet been treated with the medical device, but have either:

- Signed written consent,
- or have verbally agreed to enrol in the study, via direct consultation with the surgeon or via telephone call with an investigation team member,

need to be informed promptly that the investigation has been interrupted, and so they will be treated using the routine procedure for opening wedge HTO provided in the specific centre where the study is taking place.

Alternatively, for the individuals who have been treated with the medical device, and that consequently needed to attend follow-up meetings, a new post-operative schedule is used consisting in Rizzoli Orthopaedic Institute routine procedures, shortening the timeline to 12 months instead of 24 months. The table created below shows the routine post-operative material required for each patient follow-up in the event of an interruption of the study.

Post-operative follow-up (months)	X-Ray (AP)	X-Ray (lateral 30°)	X-Ray (merchant view)	Hip and Lower Limb Panoramic (frontal load bearing)	CT	GAIT	Clinical scores (KOOS, EQ-5D, Tegner, KSS, VAS)
1	✓	✓					✓
3	✓	✓					✓
6		✓	✓	✓			✓
12	✓	✓					✓

If the patient should notice any signs of adverse event following the follow-up period of 12 months, then he/she should immediately contact the investigation team for a consultation.

Conversely, if the patient were to withdraw from the study at any point after the surgery, then the data may still be used. As a result, a higher number of patients is recruited to take into account dropout rate, given that if there is a withdrawal before the 24-month follow-up, then this will considerably impact the study timeline (may result in up to a 2-year delay). Therefore, to ensure a minimum of 20 patients are investigated, then 25 are enrolled, which should suffice given the current Rizzoli Orthopaedic Institute dropout rate of up to approximately 13%.

More information on the suspension or early interruption of the study can be found in Chapter 13.

7. Data collection

The knee unit research coordinator or the research nurses employed by the Rizzoli Orthopaedic Institute will collect the pre-operative consent, the pre and post-operative clinical scores. All patients will be given a unique

number for identification and the date of collection will be recorded. Data will be entered onto the study database and the accuracy of the entry will be double checked again by other research coordinators or nurses.

Furthermore, the gait analysis data will be collected at the Movement Analysis Laboratory and Functional-Clinical Evaluation of Prostheses within the Rizzoli Orthopaedic Institute and referenced again by that unique patient identification number and date of collection.

Each surgeon involved will be responsible for clinic data and communications, operation note details, reporting on X-ray finding, which will need to be sent to the sponsor (3D Metal Printing) for component generation.

All other data will be stored on Rizzoli secure computers and it will typically be entered into an Excel spreadsheet.

Clinical scores in use will be as follows:

- Knee Osteoarthritis Outcome score (KOOS)
- The EQ-5D score
- The Tegner score
- The International Knee Society System score (KSS)
- Pain measurements by Visual Analogue Scale (VAS) during rest and activity.

All the data collected will be inserted into the patient's Case Report Form (CRF), of which the template can be seen in Appendix 16. Aside from the clinical scoring, it will contain the following pre-operative and post-operative information: correction angle, HKA angle, Mikulicz point (recorded as a percentage of the tibial width from the medial to the lateral region) and posterior slope. This data will be monitored periodically by a member external to the Rizzoli Orthopaedic Institute.

8. Quality assurance

It is important to note that the medical device does not require a CE mark given that it is a customised product. ISO 9001:2014 and ISO 13485:2016 accreditations are to be obtained from BSI this year with the successful admission to phase 2 audits, following the completion of phase 1 on the 26th February. The phase 2 audit is planned on the 29th April to the 1st May, and certifications are scheduled to be received a few months after the 26th June. The study may be monitored, or audited in accordance with the current protocol, Good Clinical Practice (GCP), relevant regulations and standard operating procedures to ensure that quality standards are maintained.

Furthermore, to ensure that the device is being manufactured to a high-quality standard, data sheets for the titanium powder material, as well as the 3D printers used, are inserted in Appendices 17 and 18 respectively.

9. Auditing

Internal audits will be conducted periodically (every 3 months) to ensure that the investigation is being carried out according to protocol and that patient safety is achieved. Note that members of the Ethics Committee may also perform audits, if found necessary, to verify conformity and patient safety.

The audit must be performed by individuals who are qualified through training and/or experience and must undertake a fair and comprehensive audit of clinical investigation study files.

The auditors should allow 1-3 days for the conduct of a research audit and they must review all documentation provided, against known Governance approval documentation. Subsequently, they should record any findings or discrepancies on the Audit Checklist given in Appendix 19.

Audit findings may be classified into three groups and require the adoption of different measures, which can be seen below.

Category	Implication	Action required
Critical finding	Major breach of GCP, Declaration of Helsinki or protocol procedures without notification to Competent Authorities. Causes harm or increased immediate risk to study participants and/or affects the integrity of the study data.	Immediate cessation of all study activities until findings have been resolved.
Major finding	Breach of GCP, Declaration of Helsinki or protocol procedures without notification to Competent Authorities. Could cause harm to participant or integrity of study data if unresolved in a timely manner.	Findings are required to be investigated and resolved within 1 month. A follow-up visit may be arranged.
Minor or other finding	Low risk to participants but requires resolution before end of study.	Findings are required to be resolved by the next audit (3 months)

10. Deviation from protocol

Investigators must communicate/report deviations from protocols to the sponsor and Ethics Committee, especially if the deviation compromises patient safety.

11. Adverse events

An adverse event (AE) is defined as "any untoward medical occurrence in a clinical trial subject and which does not necessarily have a causal relationship with the treatment."

A device related AE is defined as "an event that causes or has the potential to cause unexpected or unwanted effects involving the safety of device users (including patients) or other persons"

A serious adverse event (SAE) is "any untoward and unexpected medical occurrence" that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

Some AE and SAE are not unexpected in orthopaedic surgery and may not require reporting at all. Examples may include:

- Post-operative respiratory tract infections
- Urinary tract infections
- Dermatological events
- Pain in the contra-lateral knee
- Joint disease progressing in other joints and requiring treatment

Some AE and SAE are not unexpected in orthopaedic surgery and may require documenting without further reporting. Examples may include:

- Local knee issues such as discomfort, swelling, pain provided no more significant reason found for them
- Wound infection, deep vein thrombosis (DVT)

Other 'important medical events' may also be considered serious if they jeopardize the participant or require an intervention to prevent one of the above consequences. The Chief Investigator will advise on such matters.

Participants will be asked to inform their surgeon if any complications or adverse events occur and similarly request the surgeons to specifically ask their patients for this information at each clinic attendance.

A meeting of the research team will be held on a 3 monthly basis to discuss progress of the study, any specific problems and to consider whether there are any justifications for stopping the study. If adverse events that compromise patient safety occur the surgeon may decide to revert to the routine care procedures and replace the current implant with the standard device used for opening wedge HTOs in the Rizzoli. The identification of any unexpected complications that would require an early termination of the study are not anticipated, as HTO is a well-established procedure.

All serious and non-serious complications that relate to the investigation, including those occurring during the surgical procedure and throughout the post-operative evaluations, will be documented on the appropriate data forms with specific details of the symptoms, their severity, duration and outcome. All other serious adverse events which are fatal will also be recorded.

Any such events occurring in the immediate peri and post-operative events should be reported to the Chief Investigator by the surgeon in charge of the case who will contact the study sponsor. Similarly, if any such adverse events are identified in clinic, the surgeon concerned should report these events back to the Chief Investigator to be logged and the sponsor will be informed.

SAE's will be reported to the sponsor within 24hrs of the investigator being aware of the event. Any SAE occurring to a participant will be reported to the Ethics Committee that gives a favourable opinion of the study where, in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs will be submitted within 15 working days of the Chief Investigator becoming aware of the event.

12. Protocol amendments

Following the positive opinion of the Ethics Committee, all the amendments that the sponsor or investigation team would like to make must be informed to the Ethics Committee. In particular substantial amendments require more scrutiny compared with the non-substantial amendments.

The chief investigator, with the collaboration of the research team is responsible for deciding whether an amendment is either substantial or non-substantial. This decision is based upon the significant impact an amendment may have on the following:

- The scientific validity of the study
- The management of the investigation
- The performance and safety of the medical device used
- The safety, physical or mental integrity of the patients enrolled
- Ethical aspects of the clinical investigation

It is important to note that not all amendments require authorisation by the Ethics Committee before being enforced. Such amendments that need only be transmitted for informative purposes must not have immediate or direct implications on the safety, ethics and scientific validity of the investigation. Once again, it is the responsibility of the chief investigator and the research team to determine the assignment of the amendments to each category.

13. Early interruption or suspension of study

The early interruption or suspension of the study can be initiated by either the Ethics Committee, the investigation team or the sponsor.

These can occur if there is the presence of reasonable doubts regarding the safety of the patients or the scientific research around the device in question.

However, if the investigating team or sponsor learns of new factors relating to the conduction of the investigation or the medical device that may influence the safety of the patients enrolled in the study, then it must implement measures to protect the individuals from any risks. These measures, which may include the early interruption or suspension of the study, and the problems that the measures intend to address, need to be informed to the Ethics Committee. It must also be noted that in the case of the suspension of the study, the investigation cannot be restarted until a notification of the substantial amendment is sent, followed by a positive opinion from the Ethics Committee. More information on protocol amendment can be found in Chapter 12.

If there is an early interruption or suspension of the study not related to safety considerations, the sponsor needs to justify the decision taken.

14. Confidentiality & conflicts of interest

The study staff will ensure that the participants' anonymity is maintained, and the participants will be identified only by participants ID number on all electronic databases. All documents will be stored securely and will only be accessible by study staff and authorised personnel. Furthermore, the study will comply with the General Data Protection Regulation (GDPR) requirements and the requirements displayed in the contract. All Rizzoli staff involved will be compliant with the code of confidentiality and will adhere to Good Clinical Practice principles.

The data associated with the study will be kept electronically on the hard drives of computers within the Rizzoli Orthopaedic Institute and within the 3D Metal Printing office (note that the data given to the sponsor will only have a patient ID and cannot trace back to the names of the individuals in the study). It will be stored on encrypted and password protected computers. The data will only be accessible by members of the clinical investigation team, along with members of staff who will require access to the data to ensure compliance with the protocol and conformity to all study regulatory requirements.

At the end of the study, all research data will be archived, and radiographs and scans will remain on secure systems.

Both members of the TOKA® design team and the clinical investigation team in the Rizzoli Orthopaedic Institute will complete the necessary applications regarding the clinical investigation to the ethics committee.

Furthermore, it must be noted that there are no conflicts of interest within this investigation.

15. Dissemination of results

Only the clinical investigation team at the Rizzoli Orthopaedic Institute, as well as the individuals involved in the study, who are employed by the manufacturer of the device, will be informed of the results. The participants will also be informed in writing of the results, by the clinical investigation team at the Rizzoli Orthopaedic Institute, if they so desire. Additionally, results may be published, but only patient identification numbers will be used to maintain anonymity.
The main investigator undertakes to produce the final report, publish all the data collected as described in the protocol and to ensure that the data is reported responsibly and consistently. In particular, the publication of the data deriving from this study will take place regardless of the results obtained. The transmission or dissemination of data, through scientific publications and / or presentations in congresses conferences and seminars, will take place exclusively following the merely statistical elaboration of the same, or in any case in an absolutely anonymous form.

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17. Appendices

17.1. Appendix 1: SOP 26 Product Identification and Traceability

17.2. Appendix 2: Validated Sterilisation Instructions

17.3. Appendix 3: Study Consent Form

17.4. Appendix 4: KOOS

17.5. Appendix 5: EQ-5D

17.6. Appendix 6: Tegner Score

17.7. Appendix 7: KSS

17.8. Appendix 8: VAS and Pain Medication Sheet

17.9. Appendix 9: Virtual Trial Report

17.10. Appendix 10: Pre-operative Plan vs Post-operative Correction Validation Report

17.11. Appendix 11: Study Flow and Timeline

17.12 Appendix 12: User Manual

17.13 Appendix 13: Procedure Steps

17.14 Appendix 14: Risk Management Table

17.15 Appendix 15: Risk Management Report

17.16 Appendix 16: Patient Case Report Form (CRF)

17.17 Appendix 17: Fatigue Testing & Titanium Powder Data Sheet

17.18 Appendix 18: User guide - Renishaw additive manufacturing systems

17.19 Appendix 19: Audit Table