INFORMATION SHEET AND CONSENT FORM

(Applicable to patients capable of giving personal consent)

INFORMATION SHEET

Dear Sir/Madam,

A medical-scientific research project is scheduled at the *II^a Clinica Ortopedia e Traumatologica dell'Istituto Ortopedico Rizzoli IRCCS di Bologna (Italy)*. The project's title is:

Clinical Evaluations of the TOKA Customized Device for High Tibial Osteotomy in the Treatment of Knee Osteoarthritis: a Pilot Study

This research will take place at the *Istituto Ortopedico Rizzoli IRCCS di Bologna (Italy)* and is sponsored by 3D Metal Printing, a medical device manufacturer located at the University of Bath's Innovation Centre, United Kingdom.

To carry out this research we need the collaboration and availability of people who, like you, meet the appropriate scientific requirements suitable for the evaluation that will be carried out. Before deciding whether you'd like to give your consent to participate to this study, you should carefully read the following pages, ask questions if you do not understand the contents of this document or need further clarification. Furthermore, we also advise you to seek advice from family members and your GP for a second opinion, prior to making your decision.

What the study proposes

Osteoarthritis of the inner part of the knee is a common condition in physically active patients over the age of 30. The surgical treatment for these patients affected by this specific disease, is high tibial osteotomy (HTO). Today, this procedure is considered to be the most accredited and joint preserving option when compared to more invasive surgical procedures such as total knee replacement.

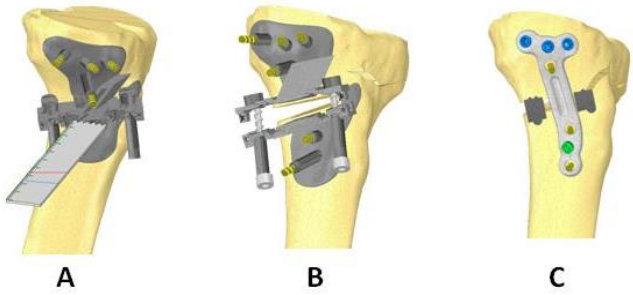
The TOKA® HTO surgical procedure consists of a personalised (custom-made) fixation plate and surgical guide that is built upon the patient's three-dimensional (3D) radiological image CT scan. This allows the optimal adaptation of the device in relation to the patient's bone shape. TOKA® medical devices will be custom-built using a biocompatible material (titanium) which is normally used to fix bones in orthopaedic surgery. Such devices are not CE marked. CE marking is a legal requirement only for mass produced products, including medical devices, that are commercialised in European countries.

This research study aims to deliver a true personalised surgery using additively manufactured "3D printed" patient specific surgical guides and an implantable device (titanium plate) designed for a specific patient. Therefore, according to European's medical device regulations, the device is not classed as mass produced, under the manufacturer's Declaration of Conformity to European standards defining the CE marking requirements.

Because of the features described above, the TOKA® medical device is described as a First-in-human trial, even though additively manufactured, custom-made medical devices are nowadays widely used in orthopaedic surgeries. Your surgeon will conduct a standard and widely performed surgery called High Tibial Osteotomy (HTO) using a unique surgical guide and stabilise the osteotomy with a titanium custom plate and locking screws.

The surgical treatment consists of the tibial osteotomy (Figure - A), which is an operation aimed at correcting the axis of the lower limb by realigning the tibia with a special guide (Figure - B) and fixing the new alignment by

inserting a personalised plate attached to the bone with locking screws (Figure - C), so that the weight distribution is even. This conservative surgical procedure makes it possible to avoid or delay total knee prosthesis.



The study aims to assess the effectiveness of knee realignment achieved and the functional performance of the knee joint after osteotomy.

In this study, 25 patients with the same condition as yours will be surgically treated using the TOKA® procedure to maintain tibial realignment after osteotomy.

What your participation in the study involves

Doctors and health care professionals will assist you and provide you with the necessary care as per normal clinical practice while performing this surgical treatment. Furthermore, regardless of treatment, this research study requires:

NORMAL CLINICAL PRACTICE

- **5 questionnaires required** to understand your health and the functionality of the treated limb. The questionnaires will take around 15 minutes to complete. Routine questionnaires will be provided at the beginning of treatment and during routine appointments at 1, 3, 6 and 12 months.

- **Diagnostic tests:**
  - A computerised tomography (CT) of your knee assessing the state of cartilage and subchondral bone before the start of the treatment.
  - Preoperative frontal knee radiography and post-surgery at 1, 3 and 12 months.
  - Preoperative lateral knee radiography and post-surgery at 1, 3 and 12 months.
  - Preoperative load bearing panoramic X-ray of the lower limbs and post-surgery at 6 months. The X-ray is to be performed standing including both lower limbs.

IN ADDITION TO NORMAL CLINICAL PRACTICE

- **Gait analysis** at the *Laboratorio di Analisi del Movimento e Valutazione Funzionale – Clinica Protesi (IOR, Bologna, Italy)* to analyse the biomechanics of the lower limbs. This examination will be carried out at the beginning of treatment and during the 6-month follow up appointment.

- **Diagnostic tests:**
  - A computerised tomography (CT) of the knee to assess the condition of cartilage and underlying bone at the 6-month follow up appointment.
  - A load bearing lateral and frontal X-ray of the lower limbs at 24 months post-surgery.

All personal data collected will be anonymised by the researchers by allocating a code to the procedure known only to researchers; it will then be processed, analysed and published in an eventual form devoid of any aspect

that can identify the patient. Furthermore, your diagnostic images will be used for future research to improve personalised surgery.

The study will last for a total of 32 months, but you will only be involved for 24 months from the start of the surgical treatment. There will be 25 people participating to this research study who will be chosen amongst those who are suffering from medial knee osteoarthritis like you.

Your cooperation will be required in the following areas:

1. Willingness to complete questionnaires both before surgery and at 1, 3, 6, 12, 24 months after surgery;
2. Willingness to undergo the above-mentioned diagnostic tests, both in pre and post-operative phases.

Your participation in the study does not entail any additional costs compared to standard clinical practice.

Insurance: The manufacturer sponsor of the study has undertaken a specific insurance policy for potential damages caused by the study, indemnifying each effected patient up to €1.500.000 (€5.000.000 cumulatively for the study) in accordance with the current law (DM 14/7/2009).

What are the benefits you will receive by participating in the study?

It is anticipated that by participating in this study you will benefit from the use of a custom device, which is designed to fit your unique tibial bone to ensure a more accurate realignment compared to normal clinical practice and a reduction of surgical time. Furthermore, your personalised fixation plate is designed for greater tissue conservation (skin and muscles) and reduced bleeding with a minimal surgical incision.

The study will also provide useful information to researchers to improve personalised osteotomy using TOKA®, a knee-preserving treatment for degenerative osteoarthritis disease to potentially avoid or delay knee replacement.

The expected benefits originate from comparing the mechanical evaluation of standards vs. personalised surgical procedures.

What are the risks of participating in the study?

Participation to this study could involve some additional risks compared to standard practice related to the additional investigation planned:

1) **Computerised tomography** may involve certain risks related to the ionising radiation used during the treatment, commonly used in the clinical study of the knee. The risks associated with exposure to ionising radiation are related to DNA alterations with possible onset of mutations and neoplasms. Such occurrences are exclusively due to massive doses of radiation and prolonged exposure. In particular, the scans will have a maximum duration of 30 seconds and, according to the available scientific literature, the patient will be subjected to an exposure of 12.6 micro Sieverts (unit of measurement for ionising radiation actually absorbed by the tissue).

2) For your information and for a comparison on the exposure, the actual **X-ray** exposure of the knee is 4 micro Sieverts.

3) **Gait analysis** consists of a non-invasive test, evaluating patient movement capabilities by recording their walk through a system of infrared cameras and 2 walking platforms fitted with sensors.

Potential risks related to TOKA® High Tibial Osteotomy treatment are similar to the ones from standard High Tibial Osteotomy performed with conventional, mass produced surgical devices currently available:

- Infection risks,
- Mechanical failure of the fixation plate,
- Unsuccessful re-alignment of the knee's mechanical axle.

Because of the nature of the "first in human" study, unknow side effects could potentially develop during the course of the treatment such as an insufficient mechanical resistance of the medical device. This risk in particular has been studied and reproduced in a laboratory using similar stress conditions of a human knee with quality and safety tests as required by international standards. TOKA® components have been virtually tested by simulating human activity under extended endurance. All tests have been satisfactory.

Your surgeon will provide you the specific information about the Consent Form of this surgical treatment which you will receive before the intervention as per standard clinical practice.

What happens if you decide not to participate in the study?

Participating to this study is voluntary. You can refuse to participate in the study or withdraw from the study at any time without giving any explanation and without any penalty or negative consequence. Your refusal to participate or your decision to terminate your participation in the study will not affect the necessary medical assistance; the best possible care will still be provided. If you decide to not take part in this study, you will still receive the current available High Tibial Osteotomy (HTO) surgery with standard size medical devices.

Doctors will also be able to stop the study at any time, and he will explain the reasons for doing so.

Information about the results of the study

If you are interested, the research's results will be available for your consultation at the end of the end of the study.

Additional information

For more information and communication, the following staff will be available:

Prof. Stefano Zaffagnini- tel. 051-6366075

Istituto Ortopedico Rizzoli, Clinica Ortopedica Traumatologica II Via Pupilli 1 - 40136, Bologna

You can request additional information about the study's participant' rights by contacting *the Segreteria Locale del Comitato Etico AVEC, via Pupilli 1, Istituto Ortopedico Rizzoli 40136 Bologna, tel. 051 6366480- Email: segreteria.ce@ior.it*

The proposed protocol of this study has been written according to the (European Union) Good Clinical Practice Standard and the most up to date version of the Helsinki Declaration and approved by the Ethical Committee - Area Vasta Emilia Centro della Regione Emilia-Romagna (CE-AVEC) presso l'Azienda Ospedaliero – Universitaria di Bologna, Policlinico S. Orsola-Malpighi.

CONSENT FORM

I,_____

hereby declare to have received by Dr. _____

a comprehensive explanation regarding the request to participate in this experimental study as reported in the attached information sheet, a copy of which was delivered to me in sufficient time

Date: _____

I also declare that I was able to discuss these explanations, that I could ask all the questions I felt were necessary, and that I have since received satisfactory answers. Furthermore, I also declare that I was given the opportunity to inform myself regarding the details of the study with someone I trust.

I therefore freely accept to participate to this study, having fully understood the meaning of the request and having understood the risks and benefits involved.

- ☐ I accept
- ☐ I do not accept

_____ _____

Date Patient's signature

_____ _____

Date Doctor's signature who informed the patient

In the event the patient cannot read or sign:

I,_____

hereby declare that Dr. _____

exhaustively explained to _____

the details and the characteristics of this experimental study as reported in the attached information sheet, and that the applicant freely agreed to join the study after he/she was given the opportunity to ask all the questions he/she deemed necessary.

_____ _____

Date Independent witness signature