PACKAGE INSERT

OPRA™ Implant System

Integrum

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INTRODUCTION

DESCRIPTION

The Osseoanchored Prostheses for the Rehabilitation of Amputees (OPRA™) device is an implant system for direct skeletal anchorage of amputation prostheses. The OPRA™ Implant System constitutes a rehabilitation alternative for transfemoral amputees when treatment with socket prostheses is or is anticipated to be insufficient.

PRINCIPLE OF OPERATION

The OPRA™ Implant System consists of an anchorage element (Fixture) and a skin-penetrating device (Abutment). The Fixture is surgically inserted in the medullary canal of the remaining femoral skeleton and, after a healing time of approximately six months, the Abutment is connected to the Fixture. The amputation prosthesis is then attached directly to the external part of the Abutment, via the OPRA™ Axor™ II. For further information, please see the OPRA™ Axor™ II Instructions For Use.

The postoperative rehabilitation is standardized with controlled levels of loading. Full weight bearing with definitive prosthesis is normally permitted approximately 6 months after Stage 2 (S2).

Recommended follow-ups comprise clinical, mechanical and X-ray checks-ups.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician.

OPRA™ IMPLANT SYSTEM

MANUFACTURER

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DIRECTIONS FOR USE

The OPRA™ Implant System is implanted in two surgical stages: Stage 1 (S1) and Stage 2 (S2). Figures 1 and 2 show the components as implanted after the surgical stages. Instructions for the surgeries are found in the Surgical treatment Stage 1 (S1) and Surgical treatment Stage 2 (S2) Sections.

PRODUCT LIABILITY

Integrum AB is responsible for the product's performance only when the product is used in accordance with this Instruction for Use.

SYSTEM DESCRIPTION

The implant components are described below, divided into the two surgical stages and external prosthetic components.

IMPLANT COMPONENTS FOR THE STAGE 1 SURGERY (FIGURE 1):

- Fixture
- Central Screw
- Healing Cylinder
- Graft Screw
- Washer

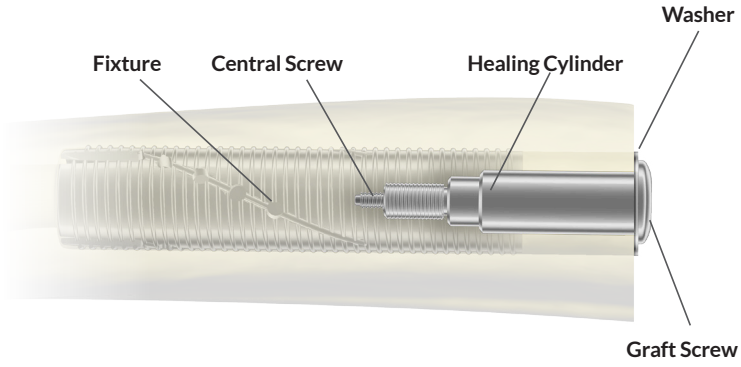


Figure 1: Components - S1: Fixture, Central Screw, Healing Cylinder, Cylinder Screw and Graft Screw inserted in the bone.

IMPLANT COMPONENTS FOR THE STAGE 2 SURGERY (FIGURE 2):

- Abutment
- Abutment Screw

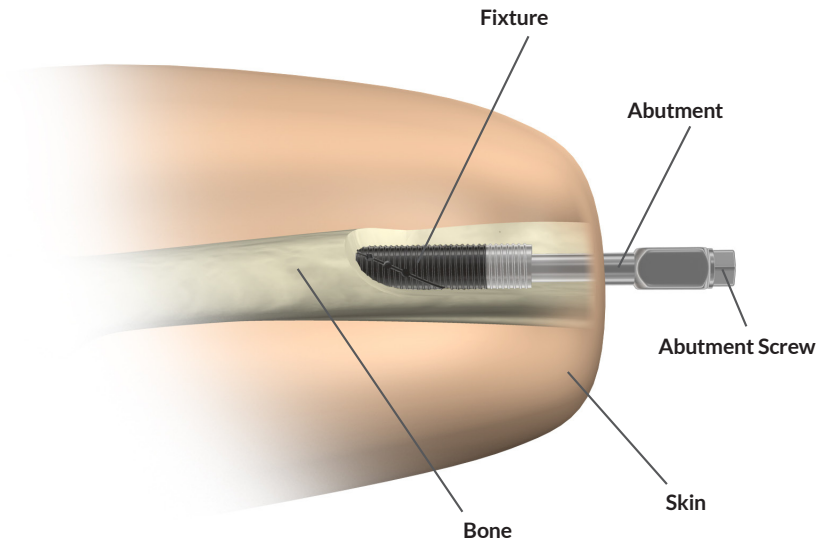


Figure 2. Components - S2: Abutment and Abutment Screw inserted in the Fixture. (superior cortex removed for visualization of the device).

EXTERNAL PROSTHETIC COMPONENTS:

The implant components should be connected to external prosthetic components through the connection device Axor™ II. For detailed information, see the Axor™ II Instructions For Use.

The external prosthetic connection device, Axor™ II, provides a standard connection to other prosthetic devices. The standard interface is a 4-hole connection for female or male connection shown in Figure 3 below. The OPRA™ Implant System is intended for use with commercially available non-microprocessor controlled prosthetic knees and microprocessor controlled prosthetic knees that do not include powered activation of flexion and extension of the prosthetic knee.

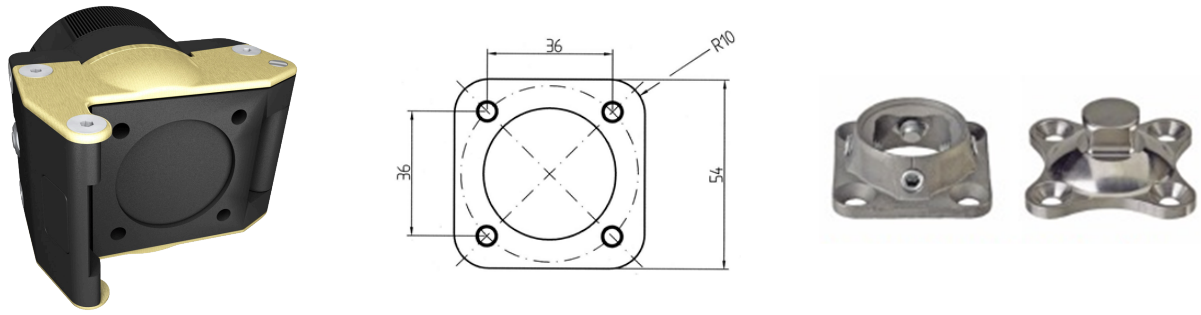


Figure 3: Pictures showing the standard interface prosthetic connection

LIST OF COMPONENTS

Table 1: List of OPRA™ Implant System Components

DESIGNATION		Ref.no.
Central Screw		1353
Healing Cylinder -12		1795
Graft Screw F/G		1959
Healing Washer 17 x 0,5 -12		1797
Healing Washer 21 x 0,5 -12		1798
Healing Washer 17 x 5 -12		1816
Healing Washer 21 x 5 -12		1817
Healing Washer 17 x 10 -12		1818
Healing Washer 21 x 10 -12		1819
Fixture	**Diameter Ø (mm)**	
Fixture BioHelix -12	Ø 16	1800
Fixture BioHelix -12	Ø 16.5	1801
Fixture BioHelix -12	Ø 17	1802
Fixture BioHelix -12	Ø 17.5	1803
Fixture BioHelix -12	Ø 18	1804
Fixture BioHelix -12	Ø 18.5	1805
Fixture BioHelix -12	Ø 19	1806
Fixture BioHelix -12	Ø 19.5	1807
Fixture BioHelix -12	Ø 20	1808
Fixture BioHelix -12	Ø 21	1809
Fixture BioHelix -12	Ø 22	1810
Fixture BioHelix -12	Ø 23	1811
Fixture BioHelix -12	Ø 24	1812
Fixture BioHelix -12	Ø 25	1813
Abutment	**Length (mm)**	
Abutment 12 x 78	78	1820
Abutment Screw	**Length (mm)**	
Abutment Screw 87	87	1999
Abutment Support		1479
Axor™ II		1288
Connector		IBK0003
Soft Tissue Support Pylon		IBK0041
Soft Tissue Support Pylon II		1290
Soft Tissue Support Plate Small		IBK0042
Soft Tissue Support Plate Large		IBK0043
Extension Plate 5 mm		1165
Extension Plate 10 mm		1166
Extension Plate 15 mm		1167

MARKING, PACKAGING, STORAGE AND STERILITY

Components are marked with serial number and size when appropriate.

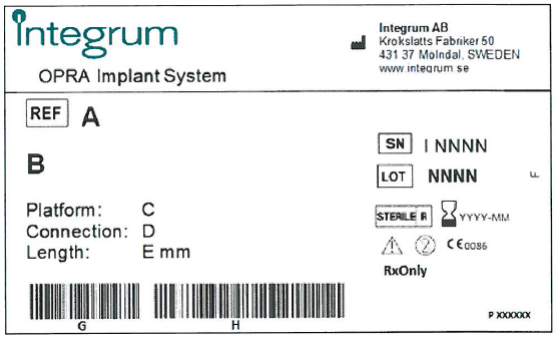
Each component is supplied in separate packaging. All items can be stored at ordinary room conditions.

All implant components are delivered sterile.

Inspect packages for puncture or other damage prior to surgery. If the packaging is damaged or if sterility cannot be guaranteed for any other reason, please return the device to Integrum AB. Do not re-sterilize the components.

LABELS

The label is specified in Figure 4. The inner packaging comes with 5 labels. On the outer packaging there is 1 label.



A	REF number
B	Component Name
C	Platform (if applicable)
D	Ø / Connection (if applicable)
E	Length (if applicable)
F	Unique label identification number and rev (XXXXXX-XX)
G	Device identifier (DI)
H	Production identifier (PI)
SN	I NNNN (if applicable)

Figure 4. Label specification with UDI

IDENTIFICATION AND TRACEABILITY

For purposes of traceability, attach the label from inner packaging to the patient's medical records when installing the component.

SINGLE USE

The OPRA™ Implant System is intended for single use and must under no circumstances be reused. There are risks of mechanical fatigue and infection if the implant is reinstalled in another patient.

Components must unconditionally be rejected and returned to Integrum AB if:

- The packaging is damaged.
- The expiration date has passed.
- Sterility, for any other reason, cannot be guaranteed.
- They have been in contact with a patient, even if not installed.

INDICATIONS AND CONTRAINDICATIONS

INDICATIONS

- The OPRA™ Implant System is indicated for patients who have transfemoral amputation due to trauma or cancer and who have or are anticipated to have rehabilitation problems with, or cannot use, a conventional socket prosthesis. The OPRA™ Implant System is intended for skeletally mature patients.
- The patient failed to receive benefit from socket prostheses or is expected to not tolerate socket use due to problems such as:
    - o Recurrent skin infections and ulcerations in the socket contact area
    - o Pain
    - o A short stump preventing the use of socket prosthesis
    - o Volume fluctuation in the stump
    - o Soft tissue scarring
    - o Extensive area of skin grafting
    - o Socket retention problems due to excessive perspiration
    - o Restricted mobility

CONTRAINDICATIONS

The contraindications for the OPRA™ Implant System follow:

- The patient's skeletal growth is not complete. Completed skeletal growth is defined through the finding of generally closed epiphyseal zones on X-ray.
- The patient has atypical skeletal anatomy which may affect treatment with OPRA™.

  Examples of atypical skeletal anatomy:
    - o Skeletal dimensions outside defined interval.
    - o Development anomalies.
    - o Conditions which are not amenable to device insertion such as deformities, fracture, infection.
- The patient would have less than 2 mm of remaining cortex bone available around the implant, if implanted.
- The patient has osteoporosis.
- The patient is older than 65 years or younger than 22 years.
- The patient's body weight is higher than 220 lbs including the prosthesis.
- Do not treat patients with the following concurrent diseases:
    - o Severe peripheral vascular disease.
    - o Diabetic mellitus with complications.
    - o Skin disorders involving the residual extremity.
    - o Neuropathy or neuropathic disease and severe phantom pain.
    - o Active infection or dormant bacteria.
    - o Metabolic bone disease and/or metastatic lesions in the residual femur.
- The patient is pregnant.
- The patient is not expected to be able to comply with treatment and follow up requirements.

WARNINGS

- The OPRA™ Implant System is a sterile single use device. Do not use past the expiration date or if the package is opened or damaged.
- Smoking negatively impacts anchoring of the OPRA™ Implant System in the femur.
- Healing problems can occur in obese patients.
- Patients with the OPRA™ Implant System that undergo elective surgery for any reason are risk for infection so they should be treated with antibiotics prophylactically (e.g. cephalosporin intravenously).
- Patients with a medical history of previous infection on the amputated side should be carefully evaluated with laboratory analysis including sedimentation rate, CRP, WBC to verify there is no on-going infection. Further dormant bacteria should be excluded, especially in the skeleton. We recommend intramedullary culturing.
- Joint problems that might affect ambulation (i.e joints of the contralateral limb, the sacroiliac joint, the ipsilateral hip joint i.e. inflammatory, non-inflammatory disease or rheumatoid arthritis) may negatively affect the outcome of the treatment.
- Extension defects in hip joints should be avoided. Extension defects exceeding 10 degrees result in adverse bio-mechanical stress of the implant system, which could lead to impaired gait pattern and increase the risk of complications.
- Concurrent diseases might affect a patient's treatment with the OPRA™ Implant System.
- The following drugs may negatively affect the anchoring of the OPRA™ Implant System in the femur and cause loosening of the Fixture:
    - o Steroids for systemic use.
    - o Chemotherapy agents.
- A patient will typically not be a suitable candidate for treatment with the OPRA™ Implant System if:
    - o The patient is using the prosthesis every day per week more than 13 hours; or
    - o The patient does not report more than moderate trouble and moderate reduction of quality of life.

In these instances, alternative treatments, such as socket modifications, general amputee rehabilitation, or soft tissue or bone surgery might better address rehabilitation problems.

- The following drugs should not be used, as they may affect bone remodeling, during the first year of treatment:
    - o NSAID (Non Steroid Anti Inflammatory Drugs) and ASA (acetylic salicylic acid) two weeks preoperatively or for continued use postoperatively.
    - o Bisphosphonates.
    - o Other drugs that might affect bone remodeling.

MRI SAFETY INFORMATION

Non-clinical testing has demonstrated that the OPRA™ Implant System is MR Conditional. A patient with this device can be safely scanned in an MR system meeting the following conditions:

- Static Magnetic field of 1.5 and 3.0 T
- Maximum spatial field gradient of 4500 gauss/cm (45 T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2 W/kg (normal operation mode) when the implant is at least 20 cm out of isocenter.

RF heating tests of the OPRA™ Implant System showed high expected temperature increase for a wbSAR of 2W/kg after 15 minutes of continuous scanning when at the isocenter. Moving the device 20 cm out of iso center, as listed in the

conditions above, reduced heating to 3.9°C.

In non-clinical testing, the image artifact caused by the device extends approximately up to 45 mm from the OPRA™ Implant System when imaged with a gradient echo pulse sequence and a 3.0 T MRI system. It is likely that clinical MR protocols may show smaller artifacts.

PRECAUTIONS

- For at least 6 months after Stage 1 (S1) surgery, the Fixture must not be subjected to direct load. Full load with definitive prosthesis is normally permitted approximately 6 months post-operatively Stage 2 (S2) following check-up by the physician responsible for the treatment.
- Mobilization must be carried out according to individualized training programs.
- OPRA™ is intended for use with normal physical activity. Instructions on physical activity are included in the Patient Labeling.
- Please note both uni- and bilaterally amputated patients have been treated with the OPRA™ Implant System. However only a few bilateral patients were treated with the OPRA™ Implant System. Therefore, the outcomes in bilateral patients are unknown and study results cannot support any definitive conclusions.
- If the patient's bone quality is judged to be suboptimal, the mobilization should be carried out at a reduced pace.
- In the event of pain or other discomfort, mobilization should be discontinued until the cause of the symptoms has been established.
- Prosthetic components should be chosen to minimize the risk of overloading the implant system. If the prosthesis is overloaded, the Fixture could be severely damaged.
- Retightening of the Abutment Screw shall only be performed by professionals. If the Abutment or Abutment Screw is replaced, the screw must be retightened by treating physician. Additional appointments may be necessary to ensure that the system is working correctly.
- The components should be inspected for crack formation and signs of wear in the connection to external prosthetic components. Signs of wear in the connection between Fixture and Abutment include dark coloring of secretion or tissue.
- The Abutment Screw should be tightened with a counter torque device clockwise to 12 Nm torque. Tightening must be carried out in accordance with the protocol in section Tightening of Abutment Screw on page 20.
- The healthcare professional should inform the patient of the following special care to be exercised:
    - o While riding a bike, the patient's knee joint might lock in the fully stretched position which can seriously damage the Fixture. The patient should always position the bike seat low enough that the artificial knee cannot fully stretch out while cycling. The patient should never stand up while cycling.
    - o The patient should always check carefully that the prosthesis is adequately attached to the Abutment.
    - o The patient should never try to fix any problems with the device or use any tools on the device as that may damage the Abutment and the Fixture.
    - o The patient should never run, jump or climb, should always use a cane or crutches for longer walks, never lift or carry heavy items and never subject the OPRA™ Implant System to high torques.
    - o The patient should always protect the Abutment when he or she is in hot or cold places.
        - o In the sauna, wrap a wet towel around the Abutment to protect it from heat.
        - o Protect the amputated limb when in a cold environment.
    - o The patient should always avoid damaging themselves or others with the Abutment.
    - o Protecting the Abutment during sleep is recommended. The protection will be provided by your prosthetist.

- If the OPRA™ Axor™ II is damaged in any way, the patient should contact his or her prosthetist.
- If the OPRA™ Axor™ II has been immersed in water, the patient should contact his or her prosthetist.
- Change of Abutment must be considered if:
    - o There is movement in the connection between Fixture and Abutment, despite repeated tightening;
    - o Dark-colored secretion continues, despite repeated tightening; or
    - o The Abutment is deformed or mechanical complication is suspected.

TEAM ASSESSMENT

INTRODUCTION

To assess whether a patient is suitable for treatment with the OPRA™ Implant System is a major undertaking. We recommend the following guidelines developed by The Center of Orthopaedic Osseointegration at the Department Orthopaedics at Sahlgrenska University Hospital Gothenburg, Sweden. Team assessment is performed to reach consensus in relation to benefits and risks with the treatment. The team consists of at least one orthopaedic surgeon, one prosthetist and one physiotherapist. Thorough analysis and clinical examination of the patient is completed.

Q-TFA

In order to establish the suitability for treatment, the patient is asked to answer the Q-TFA (Questionnaire for Persons with Transfemoral Amputations). The answers to the Q-TFA should be reviewed by the team and the patient together to determine suitability. Questions 1,2,3,4 and 5 relate to frequency of prosthetic usage.

A patient will typically not be a suitable candidate for treatment with the OPRA™ Implant System if:

- The patient is using the prosthesis every day per week more than 13 hours; or
- The patient does not report more than moderate trouble and moderate reduction of quality of life.

In these instances, alternative treatments, such as socket modifications, general amputee rehabilitation, or soft tissue or bone surgery might better address rehabilitation problems.

PROFESSIONAL EVALUATION

The prosthetist should carefully examine the present prosthetic solutions and state, based on the prosthetist's best knowledge, whether new sockets or other solutions could have a major benefit for the patient.

The orthopaedic surgeon should carefully inform the patient about the surgical protocol and the potential risks of the treatment. The prosthetist and the physiotherapist should carefully inform the patient about the details of the rehabilitation program and the prosthetic solutions available for the OPRA™ Implant System. The patient should receive the OPRA™ Patient Labeling.

The patient should be given ample time for additional information requests. No decision on treatment should be taken at the team assessment. The recommendation is to wait 10-14 days for contemplation by the patient to make an informed decision.

PATIENT INFORMATION

Ensure that the patient receives the OPRA™ Patient Labeling, where hazards and warnings are clearly stated.

SURGICAL TREATMENT STAGE 1 (S1)

PREOPERATIVE EVALUATION

CLINICAL EXAMINATION

Preoperative amputation status includes:

- Registration of active and passive hip mobility. Extension defects in hip joints should be avoided. Extension defects exceeding 10 degrees result in adverse biomechanical stress of the implant system, which could lead to impaired gait pattern and increase the risk of complications.
- Assessment of the residual extremity with regard to skin, soft tissue and skeleton.
- Laboratory analysis: The recommendation is to make a complete kidney and liver function analysis to determine the patient's capability to synthesize all type of oral or intravenous antibiotics, in case of post-operative or later infections that may occur during the long-term use of this device.

X-RAY

Preoperative X-ray examination of the residual bone is carried out in frontal and lateral projection, with a ruler.

To optimize the survey of the residual bone's distal parts where the degree of mineralization is lower, supplementary soft tissue examination is also recommended on two levels.

Survey of skeletal structure

Particular attention is focused on:

- The skeletal dimension.
- Skeletal quality.
- Any development anomalies.
- Any residual conditions after fracture, infection etc.

COMPUTED TOMOGRAPHY

Preoperative Stage 1 (S1) computed tomography examination is carried out.

The purpose of the examination is:

- To complement survey of the skeletal structure.
- To verify that the length of the residual bone provides space for external prosthetic components. This is done by determining the normal anatomical femur length.
- To provide a reliable basis for planning the Fixture dimension.

TECHNICAL SPECIFICATION

- Skeletal window.
- Overall view of the frontal and lateral projection including the whole femur bilaterally. The purpose of this overall view is to make it possible to measure the length of the femur and to ensure that the cross section projections are at right angles (±10°) in relation to the longitudinal axis of the femur.
- Cross section covering the residual bone's distal 120 mm. Section thickness maximum 3 mm. Section distance 3 mm. To ensure adequate planning of the Fixture diameter, all cross sections must be documented in 1:1 scale and have a scale of length enclosed.

BONE QUALITY

This treatment has mostly been used for patients who have had their amputation for some time. In the OPRA™ clinical study, an average of more than 10 years had passed since the amputation. Amputation leads to reduced function as compared to an able bodied person and the skeleton will not be loaded in a normal physiological way, thus the cortical bone quality in the diaphyseal part of the femur bone tend to change over time. This bone may change to more like spongious or trabecular bone. To some extent, bone quality can be judged by x-ray. Evaluation of bone quality should be performed preoperatively. At least 2 mm of remaining bone tissue should be available around the implant.

Depending on the bone quality, different drills are used during the surgical procedure. Bone grafting is not recommended except for the distal end of the bone, and bone grafting should always be performed distally. Please see the OPRA™ Stage 1 - Surgical Technique Manual for further details.

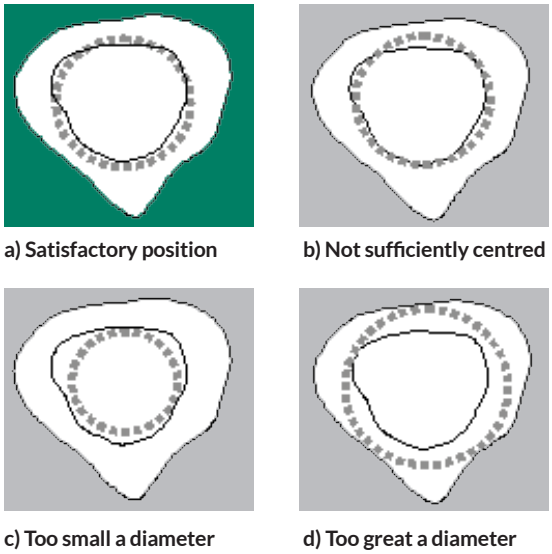
DETERMINING NORMAL ANATOMICAL FEMUR LENGTH

Femur length is measured bilaterally. The measurement originates from the proximal boundary of the trochanter major to central knee joint line and central residual bone's distal end respectively. Via secondary comparison the distance from the residual bone to normal anatomical position of the knee joint line can be determined. The minimum recommended distance to provide space for external prosthetic components is 200 mm. The recommended remaining length of the bone is 130-350 mm measured from the top of the greater trochanter to the distal bone end.

PLANNING OF FIXTURE DIAMETER AND POSITIONING

In all cross sections corresponding to 80 mm (approx. 27 cross sections) of the residual bone, where it is planned to place the Fixture, a circle is drawn so that the thickness of the cortical bone does not fall below 2 mm anywhere on the circumference and optimal endosteal contact is maintained (Figure 5). The resulting diameter of the circle determines the Fixture size and the location of the circle determines the positioning of the Fixture.

Other preoperative evaluation is carried out in accordance with the procedures of the treating unit.



a) Satisfactory position **b) Not sufficiently centred**

c) Too small a diameter **d) Too great a diameter**

Figure 5. Planning of Fixture diameter and positioning.

The estimated size of the Fixture must be within the intervals of 16.5-19.5 mm. If the dimension is not within this interval, this constitutes a contraindication to treatment based on atypical skeleton anatomy.

PREOPERATIVE PREPARATIONS

STOCK CHECK

Ensure that all Fixture sizes and other relevant components are in stock. Check particularly that the planned Fixture size, as well as 0.5 mm larger and 0.5 mm smaller diameters, are available.

ANTIBIOTIC PROPHYLAXIS

The procedure is carried out under antibiotic prophylaxis. Use e.g. penicillinase stable penicillin (isoxa penicillin) such as Cloxacillin 2 g x 3 IV or cephalosporins such as Cefuroxime 1.5 g x 3 IV. In case of over-sensitivity to the above preparations, Clindamycin 600 mg x 3 IV should be used. Antibiotic infusion should be started at least 30 minutes before the planned start of surgery.

SETTING UP

The positioning of the patient on the operating table must allow for fluoroscopy using a C-arm in two right angle levels. Prepare for possible autologous bone transplantation from the iliac crest. Preferably the bone should be harvested ipsilaterally.

SURGICAL INSTRUMENT MANAGEMENT

Instructions for cleaning and sterilization of the surgical instruments are provided in Appendix 1.

SURGICAL TECHNIQUE

The surgery should be carried out in accordance with the stepwise instructions and illustrations in OPRA™ Stage 1 – Surgical Technique. The surgery should be performed by a trained physician with expertise in orthopedic surgical techniques.

POSTOPERATIVE MANAGEMENT

X-RAY

Postoperative X-ray evaluation is carried out in frontal and lateral projection. Fixture position and signs of any possible complications are evaluated.

ANTIBIOTIC PROPHYLAXIS

Intravenous antibiotic should be administered within one hour of surgery and maintained as intravenous administration for 24 hours. Oral administration of antibiotics is then continued until two days after suture removal. Use oral antibiotics which correspond to the parenteral treatment.

SUTURE REMOVAL

Sutures should be removed after approximately 3 weeks.

MOBILIZATION BETWEEN S1 AND S2

Mobilization including joint movement, strength and fitness training is carried out under the supervision of a physiotherapist. Prevention of extension defect is an important element.

If skin status permits use of socket prosthesis, preoperative prosthesis-wearing patients can begin using adapted socket prosthesis 1-3 weeks after suture removal. If a socket is used between S1 and S2, make sure that there is no end-bearing in the socket to reduce the risk of loading the Fixture.

FOR AT LEAST 6 MONTHS AFTER STAGE 1 (S1), THE FIXTURE MUST NOT BE SUBJECTED TO DIRECT LOAD.

SURGICAL TREATMENT STAGE 2 (S2)

PREOPERATIVE EVALUATION

X-RAY

Preoperative X-ray examination of the residual bone is carried out in frontal and lateral projection. There must be no signs of the Fixture coming loose or other complications.

PREOPERATIVE PREPARATIONS

STOCK CHECK

Ensure that all relevant components are in stock.

ANTIBIOTIC PROPHYLAXIS

The procedure is carried out under antibiotic prophylaxis. Use e.g. penicillinase stable penicillin (isoxa penicillin) such as Cloxacillin 2 g x 3 IV or cephalosporins such as Cefuroxime 1.5 g x 3 IV. In case of allergy to the above antibiotics, Clindamycin 600 mg x 3 IV should be used. Antibiotic infusion should be started approximately 30 minutes before the planned start of surgery.

SETTING UP

Ipsilateral gluteal support may be used. Sterile dressing should leave at least 15 cm free skin area distally on the residual extremity.

SURGICAL INSTRUMENT MANAGEMENT

Instructions for cleaning and sterilization of the surgical instruments are provided in Appendix 1.

SURGICAL TECHNIQUE

The surgery should be carried out in accordance with the stepwise instructions and illustrations in OPRA™ Stage 2 – Surgical Technique. The surgery should only be performed by a certified orthopedic surgeon.

POSTOPERATIVE MANAGEMENT

DRESSING

Dressing should be changed at 2-3 day intervals until the skin has healed to the bone surface.

ANTIBIOTIC PROPHYLAXIS

Antibiotic prophylaxis should be given up to suture removal + 2 days. Switch to oral administration as soon as possible. Use oral antibiotics which correspond to the parenteral treatment.

SUTURE REMOVAL

Sutures should be removed after approximately 3 weeks.

MOBILIZATION AND TRAINING PROGRAM

Mobilization is carried out under the supervision of a physiotherapist in accordance with general principles for treatment of osseoanchored implants. Initial loading is carried out with a short training prosthesis, followed by training with a full-length prosthesis according to the training program below.

Training prosthesis:

Week 1-2 post-op Stage 2 (S2)

- Stay immobilized.

Week 3 post-op Stage 2 (S2)

- Active movement training of the hip joint without load.

Week 6 post-op Stage 2 (S2)

- Initiate loading with short training prosthesis that only reach to the knee joint, and an initial a load of maximum 20 kg. Avoid rotations.
- Increase approximately 10 kg per week until full bodyweight is reached. However, the load must be adapted to the patient's body size and strength. Exercise 2x15 minutes per day, increasing to 2x30 minutes/day.
- If pain occurs above 5 on a Visual Analogue Scale (VAS) – the patient should abstain from all training for 1-2 days or until pain has decreased to a more pain-free level. Return to training using a decreased load. If pain remains above 5, the patient should contact the treating physician. For Pain Assessment, see page 29.

Week 10-14 post-op Stage 2 (S2)

With training prosthesis, if full body weight is reached and training conducted withoutpain:

- General fitness exercises including kneeling in all four and kneeling down.
- Return to the treating physician for a decision concerning full-length prosthesis.

With Full-length prosthesis:

- Initiate training with full-length prosthesis and an initial load of maximum 20 kg while walking.
- Increase approximately 10 kg per week.
- Use the prosthesis maximum 2x60 minutes daily indoors.
- Walking exercises should be carried out with parallel bars and with 2 crutches.
- In a standing position, the maximum load is half bodyweight.
- Do not use training prosthesis.

As rehabilitation continues, if pain occurs above 5 on a VAS, rest completely from all kinds of training during 1-2 days. Return using decreased load. If pain remains above 5, the patient should contact the treating physician. For Pain Assessment, see page 21.

Week 12-16 post-op Stage 2 (S2)

- Training of balance and gait pattern.
- Always use 2 crutches. Use of stairs.
- Fitness cycling with light load.
- Sitting down and sitting down to standing up.
- Fitness training with training prostheses.

Week 14-18 post-op Stage 2 (S2)

- Prostheses might be used the entire day.
- Transferring of body weight while standing.
- Walking up-hill with two supports.

Week 16-24 post-op Stage 2 (S2)

- Walking exercises with one support at the physiotherapist and at home.
- Always use 2 crutches for longer walks outdoors.
- Walking slightly uphill, in rough terrain, over obstacles.
- Turning.
- Fitness training with full-length prostheses.

Week 22-26 post-op Stage 2 (S2)

If full body weight is reached and training conducted without pain:

- Walking without support during training.
- Return to the treating physician for a decision about the use of one support more frequently while walking.

If the patient's bone quality is judged to be suboptimal, the mobilization should be carried out at a reduced pace.

PROSTHETIC PROTOCOL

OPRA™ AXOR™ II

The OPRA™ Implant System is connected to external prosthetic components through the connection device OPRA™ Axor™ II. For detailed information, see the OPRA™ Axor™ II Instructions For Use.

The external prosthetic connection device provides a standard connection to other prosthetic components that would include the prosthetic knee and foot. A standard European 4 hole male/female mounting system is utilized in the external prosthetic device. This allows the OPRA™ Implant System to be connected to all prosthetic systems that utilize this standardized connection method. This interface connection is described in Figure 6.

The OPRA™ Implant System is intended for use with commercially available non-microprocessor controlled prosthetic knees and microprocessor controlled prosthetic knees that do not include powered activation of flexion and extension of the prosthetic knee.

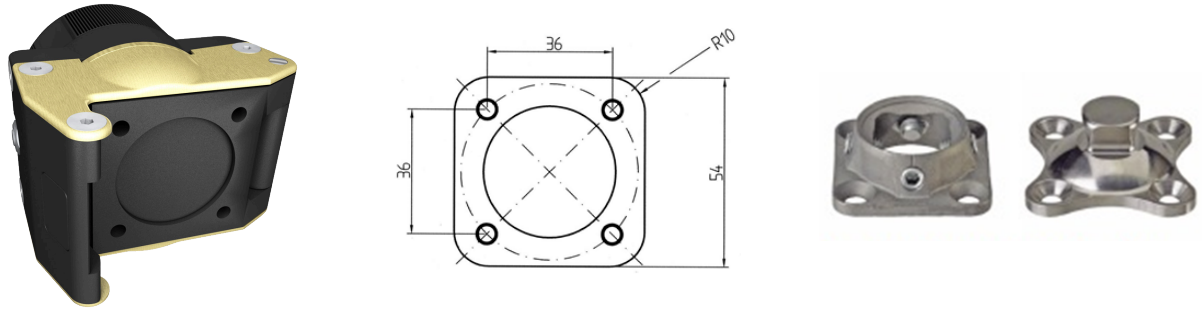


Figure 6: Pictures showing the standard interface prosthetic connection

FOLLOW-UP AND CHECKS

CHECK-UP SCHEDULE

After Stage 2 (S2) the following check-ups are recommended (Table 2):

Action	Day 21	Month 3	Month 6	Month 12	Continued
Amputation status	●	●	●	●	Every 6 months
Inspection of components	●	●	●	●	Every 6 months
X-ray			●	●	Years 2, 3, 5, 7, 10, 15 etc.

Table 2. Check-up schedule.

AMPUTATION STATUS

Clinical examination of the residual extremity comprises the following elements:

- Inspection of skin penetration.
- Inspection of soft tissue configuration when standing.
- Assessment of osseoanchorage:
    - o Pain when loading is a potential sign of loosening.
    - o A mobile implant system is a sign of loosening.
    - o A radiolucent zone around the entire Fixture is a potential sign of loosening.
- Joint evaluation:
    - o Assessment of range of movement in the hip joint, particularly with regard to extension.
    - o Evaluate joints to specifically check for any signs of ipsilateral leg joint disease or contralateral leg joint disease as well as back disorders including the sacroiliac joints.
        - • Examination may include clinical examination, x-ray or MRI.
        - • Symptoms might include pain, swelling, or reduced activity level.
        - • If there are signs of adverse effects on the contralateral extremity, ipsilateral hip joint or the sacroiliac joint, the patient should be evaluated over time according to applicable standard scoring methods (Harris Hip Score, Knee Society Score, etc.) If a reduction in the total score is seen, determine if there are compounding factors that may affect the joint. If the cause of the joint problem cannot be identified, discontinue use of the prosthetic until the adverse effect is reduced or eliminated. In the OPRA™ Implant System study, joint disease related adverse events were not reported up to 2 years of follow up.

POSSIBLE ADVERSE EVENTS

- Superficial infection around the skin penetration area is the most common adverse event during the treatment. Common signs of infection are local redness and swelling as well as discolored secretion. Note that moderately serous or dark-colored secretion may normally occur. In case of suspected superficial infection, culture tests must be taken. Treatment can be carried out by intensifying local cleaning. Antibiotics should be prescribed on relatively wide indications in order to reduce the risk of progressive deep infection.
- In case of pronounced infection with signs of involvement of subfascial tissue as well as possible general effects on the patient, deep infection must be suspected. After culture testing, antibiotic treatment must be started as soon as possible.
- Excessive soft tissue distally on the residual extremity may affect the skin penetration area. In the event of recur-rent infection problems, soft tissue plasty may be considered.
- Restricted extension ability in the hip joint may lead to impaired gait pattern in the patient, with unfavorable mechanical loads on the implant system. Extension defects exceeding 10° must be avoided.

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device:

- Superficial infection.
- Mechanical complication of abutment or abutment screw.
- Pain.
- Loosening of the fixture.
- Deep infection.
- Osteomyelitis (bone infection).
- Injury due to gait instability and/or falls.
- Bone fracture.
- Skin necrosis.
- Pyrexia.
- Soft tissue necrosis.
- Chills.
- Impaired healing.
- Wound necrosis.
- Joint injury.
- Post procedural hematoma .
- Myositis.
- Blister.
- Antibiotic toxicity from repeated administration .
- Sepsis.

INSPECTION OF COMPONENTS

Inspection of components comprises the following elements:

- Assessment of any crack formation as well as signs of wear in the connection to external prosthetic component.
- Assessment of signs of wear in the connection between Fixture and Abutment such as dark coloring of secretion or tissue.

TIGHTENING OF ABUTMENT SCREW

The Abutment Screw should be tightened as follows, with the patient lying on his/her back:

- Set the torque wrench to 12 Nm use a 12 mm socket.
- Hold the square of the Abutment with a 14 mm spanner. Place the 14 mm spanner so that it is pointing downwards and ask the patient to press it gently against the underlying surface.
- Tighten until the torque wrench releases and note how many degrees the Abutment Screw may be turned. Enter this in the medical record.
- If the rotation is more than 3 degrees the screw should be tightened again within 1 week. If the rotation is less than 3 degrees it should be tightened again after 2 weeks.
- If the rotation at the 2-week check is less than 3 degrees it should be checked again after 4 weeks. If there is still rotation, check again after 8 weeks and so on. The period between checks should never be more than 6 months.

POSSIBLE COMPLICATIONS

Abutment change must be considered in the event of:

- Wear, in the following cases;

    o If there is movement in the connection between the Fixture and Abutment. The assessment is done by loosening the Abutment Screw with a 12 mm spanner 2 full turns. Use a counter torque device (14 mm spanner) on the Abutment. Check for rotation by trying to rotate the Abutment manually or by using the 14 mm spanner. Do not use more than 5 Nm torque.

    o If dark-coloured secretion continues, despite repeated tightening. Choose an oversized Abutment i.e. +1 (pressfit diameter increased by 0,01 mm) or +2 (pressfit diameter increased by 0,02 mm) respectively.

- Bent Abutment (the Abutment is deformed or mechanical complication is suspected). Replace with the same Abutment size.

The Abutment should be replaced in accordance with section, Abutment Replacement on page 22.

X-RAY

X-ray examination is carried out in frontal and lateral projection. Assessment of the X-ray examination comprises:

- Signs of loosening of the implant.
- Signs of deep infection.

X-ray examination can also be used for analysis of patients with load pain. Please see the following section, Pain assessment.

PAIN ASSESSMENT

If the patient experiences pain above 5 on a Visual Analogue Scale (VAS), the following procedure should be followed:

- The patient should abstain from all training for 1-2 days or until pain has decreased to a more pain-free level. Return to training using a decreased load.
- If pain remains above 5, the patient should contact the treating physician who should evaluate the cause.

Potential causes of load pain may be:

- Deep infection.
- Skeletal stress fracture.
- Fractured Fixture.
- Commencement of loosening
- General overloading.

The cause of pain can be determined by means of x-ray. Depending on the cause, treatment should be carried out according to the following section, Treatment options.

TREATMENT OPTIONS

A summary of the possible complications and the corresponding treatment options are presented below:

- Suspected overload – Stop using external prosthesis and do not load the implant until pain free or until the cause is defined.
- Superficial infection - Improved hygiene routines and/or antibiotic treatment.
    - o Deep infection - Antibiotic treatment after culturing test of bacteria.
    - o Integrum follows the principles developed for joint arthroplasties. Stable implants are treated without implant removal, which unstable implants normally require implant removal in addition to antibiotic treatment.
- Mechanical complications, due to;
    - o Loose Abutment Screw - Retightening of Abutment Screw.
    - o Bending or fracture - Exchange of Abutment and/or Abutment Screw.
    - o Wear - Exchange of Abutment to an oversized Abutment.
- Severe and persistent pain - Removal of Abutment. If pain remains – Removal of Fixture.
- Skeletal fracture - Treated according to routines for skeletal fractures.
- Loose or fractured Fixture - Confirmation of status by X-ray followed by removal of the Fixture.

FIXTURE REMOVAL

The following options are available if fixture removal is necessary:

- Placement of a new Fixture after the site has healed completely.
- If the Fixture is not replaced, the patient can return to his or her previous condition.

ABUTMENT REPLACEMENT

HANDLING INSTRUCTIONS

- Ensure that the right size of Abutment is in stock.
- Carry out measures under sterile conditions.
- Record the position of the Abutment to the Fixture. With a sterile marker pen, the position of the corner on the Abutment's distal square connection can be marked on the residual extremity.
- Loosen and remove the Abutment Screw and Abutment, using the counter torque device.
- Inspect and clean the Fixture's connecting part.
- Apply new Abutment and Abutment Screw. Observe great care when positioning the new Abutment. Tighten the Abutment Screw in combination with counter torque device to 12 Nm torque. Tighten again after walking with the prosthesis for 5 minutes.
- An appointment for further inspection and retightening within 2 weeks must be arranged.

HYGIENE INSTRUCTIONS

GENERAL INSTRUCTIONS

When the prosthetic phase begins, a strict hygiene regime is required. Hygiene routines should be carried out in accordance with the OPRA™ Patient Labeling, including cleaning of the skin penetration area every morning and evening. It is preferable to use an alcohol-based hand rub before inspection and cleaning. If an alcohol rub is not available, wash hands thoroughly prior to inspecting and cleaning the area. A hand mirror may be useful for inspecting the skin penetration area. The patient should not let other people touch the area immediately around the Abutment.

There are no restrictions regarding bathing and swimming as long as carried out according to instructions for protection of the skin penetration area described below.

INSTRUCTIONS FOR CLEANING THE SKIN PENETRATION AREA

- Moisten a clean gauze bandage or a compress with sterile saline solution (0,9% NaCl). Wind the compress around the Abutment, press it gently against the skin and clean the skin with a circular movement (as with dental floss). Repeat this cleaning twice daily, e.g. morning and evening.
- If there is dry tissue immediately around the Abutment this may be removed using a dry swab or a swab moistened with sterile saline solution (0,9 % NaCl).
- If the skin area closest to the Abutment becomes dry and chapped, a thin application of an ointment, e.g. Vaseline Petroleum Jelly, twice daily is recommended.
- It is not unusual for a small amount of fluid to seep from the skin penetration area, especially in connection with vigorous physical activity. If a small amount of fluid leaks out, wind a clean gauze bandage or compress around the Abutment and to change it daily.
- For bathing or swimming, Vaseline Petroleum Jelly should be gently applied onto the skin penetration area and a silicon liner (provided by the prosthetist) used as a "bathing cap". It is very important to clean the skin penetration area carefully after bathing.

IN CASE OF IRRITATION OR INFECTION

- If the patient has signs of infection he or she should be urged to notify the health care provider and not to self-administer antibiotics.
- If the patient has a cold the skin penetration area may become irritated and it is important to urge extra meticulous hand hygiene when cleaning, using alcohol-based rubs.
- At early signs of infection the patient should be urged to clean one or more times extra during the day.
- If irritation continues, with flushing, swelling, fever and/or aching, the patient should be advised to consult the treating physician.
- In case of high temperature and/or severe pain the patient should be urged to go the hospital emergency department.

MEDICATION

GENERAL RECOMMENDATIONS

For optimum bone healing, advise patients to maintain adequate dietary intake of calcium and vitamins C and D and consider additional daily calcium (1 g) as well as vitamin preparations including vitamins C and D for at least the first 6 months after Stage 1 (S1).

MEDICATION - CONTRAINDICATIONS

Use of the following drugs should be avoided due to their negative effect on the anchoring of the OPRA™ device in the femur as they may cause loosening of the Fixture:

- Steroids for systemic use.
- Chemotherapy agents.

MEDICATION - WARNINGS

Use of medications known to adversely impact bone healing and remodeling should be avoided during the first year of treatment including:

- NSAID (Non Steroid Anti Inflammatory Drugs) and ASA (acetylic salicylic acid) two weeks preoperatively or for continued use postoperatively.
- Bisphosphonates.

CLINICAL CONSIDERATIONS

SUMMARY OF PRIMARY CLINICAL STUDY

The OPRA™ Implant System was evaluated for safety and effectiveness from clinical study data of 65 participants.

SUMMARY OF THE ORIGINAL 51-PATIENT OPRA™ STUDY

The OPRA™ Implant System study was a prospective investigation on bone-anchored amputation prostheses. 51 subjects were treated in the study, which at the time of the last surgery in the study (December 2007), constituted about 1/3 of all patients ever treated with the OPRA™ Implant System or pre- OPRA™ devices. Since the time of this study, the OPRA™ device has undergone incremental improvements for safety. Specifically, the Fixture, the Abutment, and the connection between the Fixture and Abutment have been redesigned with improved mechanical characteristics, both in fatigue and ultimate strength, leading to a stronger and more durable device. The safety device connection (the Axor™ II) between the Abutment and external prosthetic components has been further improved and adds control not only in torsion but also in bending.

STUDY DESIGN

A prospective investigation was performed at Sahlgrenska University Hospital, Gothenburg, Sweden on transfemoral bone-anchored amputation prostheses. The study began in 1999. Each of the 51 subjects served as his/her own historical control, as the study was not randomized. Six subjects were bilateral subjects. Forty-five patients were unilateral subjects. Due to the small sample size of the bilateral patients, this group was unable to be separated and studied alone. The length of the study was 2 years.

Enrollment in the prospective study was limited to patients who met the following inclusion criteria:

- Transfemoral amputee patients with problems using a conventional socket prosthesis or patients anticipated to experience significant problems with socket use.
- Undergone pre-operative Radiographic assessment including CT of the femur stump
- Skeletal maturity
- Normal retained femur anatomy
- Body weight less than 100 kg (225 lb)
- Suitable for surgery based on upon medical history and physical examination
- Ability to comply with the rehabilitative and follow up regimen
- Ability to give written Informed Consent

Patients were not permitted to enroll in the prospective study if they met any of the following exclusion criteria:

- Over 70 years of age
- Severe peripheral vascular disease, diabetes mellitus with complications, skin diseases involving the amputated limb or other diseases that could affect the suggested treatment negatively
- Systemically administrated corticosteroids, chemotherapy drugs or other drugs in a way that could affect the suggested treatment negatively
- Pregnant

The demographics of the study subjects are provided in Table 3.

The general study objectives were:

- To evaluate the performance of OPRA™ Implant System when used for the intended purpose, under normal conditions and according to instructions.
- To evaluate complications with OPRA™ Implant System when used for the intended purpose, under normal conditions and according to instructions.

The primary objective of the clinical investigation was to evaluate the improvement of Prosthetic Use Score captured by the Questionnaire for persons with a Transfemoral Amputation (Q-TFA), comparing the OPRA™ Implant System to Baseline (i.e. to socket prosthesis).

The secondary objectives were:

- To evaluate improvements in functional ability when using the OPRA™ Implant System.
- To evaluate improvements in quality of life when using the OPRA™ Implant System.
- To evaluate the frequency of possible medical complications when using the OPRA™ Implant System.
- To evaluate the type and frequency of mechanical complications when using the OPRA™ Implant System.

Table 3: Demographics

Variable	ITT-Population (n=51)
Gender	
Male	28 (54.9%)
Female	23 (45.1%)
Age at inclusion (years)	44.2 (12.2) 46.4 (19.9; 64.7) n=51
Unilateral/bilateral amputated	
Unilateral	45 (88.2%)
Bilateral	6 (11.8%)
Reason for amputation	
Trauma	33 (64.7%)
Peripheral Vascular Disease	2 (3.9%)
Tumor	12 (23.5%)
Other	4 (7.8%)
Time between amputation and surgery SI (years)	12.1 (11.1) 8.0 (0.9; 41.8) n=51
Age at amputation (years)	32.4 (13.6) 31.6 (13,0; 63,8) n=50
Estimated weight at inclusion (kg)[1]	83.5 (18.6) 83.4 (50.4; 128.8) n=50
Height at inclusion (cm)	172.4 (10.2) 173.5 (154.0; 194.0) n=48
Estimated BMI at inclusion (kg/m^2)[2]	28.1 (4.9) 26.9 (17.4; 42.1) n=48
Smoker at inclusion	11 (21.6%)
Prosthetic user at inclusion	42 (82.4%)
Ever been using prosthesis if not Prosthetic user at inclusion	8 (88.9%)
Level of education	
Primary school	11 (23.9%)
Secondary school	23 (50.0%)
Exam from University	12 (26.1%)
Data missing	5
Civil status	
Single	19 (37.3%)
Married/cohabiting	32 (62.7%)
Nationality	
England	1 (2.0%)
Norway	14 (27.5%)
Spain	11 (21.6%)
Sweden	25 (49.0%)
Employment at inclusion (%)	35.1 (41.7) 10.0 (0.0; 100.0) n=51
Medication at inclusion	
Yes	26 (51.0%)
No	25 (49.0%)

For categorical variables n (%) is presented.
For continuous variables Mean (SD) / Median (Min; Max) / n= is presented.

[1] Weight has been measured without prosthesis. For unilateral patients 12% have been added to calculate the estimated weight, and for bilateral approximately 27.3% have been added.
[2] The estimated BMI is based on estimated weight and height. Height is measured with prosthesis.

REPORTED ADVERSE EVENTS IN 51-PATIENT OPRA™ STUDY

The OPRA™ Implant Study followed subjects for 2 years. Early loosening will, in our experience, be the most common adverse event requiring removal of the OPRA™ Implant System. All of the patients with implant failures showed signs of loosening, pain or infection, within the first year of loading; however, an additional patient was not identified as a failure until later.

Early loosening was the most common adverse event requiring surgical removal of the OPRA™ Implant System and removal was normally performed within the first two years after the Stage 2 surgery. Out of 51 subjects, 4 implant revisions due to loosening of the Fixture occurred. Out of these 4 cases, 3 patients lost their implant within the first year following the Stage 2 surgery and 1 patient lost their implant shortly after the study was concluded. No implant fracture or re-amputation has been reported with the OPRA™ Implant System.

Adverse Events (AE)

Treatment emergent Adverse Events (AEs) were reported in the OPRA™ study. Adverse Events (AEs) were captured from the enrollment of the subject and until the subject had the 24 month visit. An Adverse Event was defined as any undesirable clinical occurrence in a subject whether it was considered related to the OPRA™ Implant System or not. All Adverse Events during the study were to be recorded. An AE could be both objective and subjective. The primary Safety variable was time to revision. Adverse events were captured as the following:

- Onset of Adverse Event
- Pre-specified AEs
- Superficial Infection
- Deep Infection
- Pain
- Mechanical complication of OPRA™
- Skeletal fracture
- Loosening of OPRA™
- Other non-pre-specified AEs
- Severity of Adverse Event

The AEs were classified as mild, moderate or severe with respect to their intensity. The following definitions were used:

- Mild: AE which was easily tolerated.
- Moderate: AE which causes sufficient discomfort to interfere with daily activities.
- Severe: AE which caused marked limitation in activity, some assistance may have been needed, medical intervention/therapy required, hospitalization was possible.

The AEs were evaluated for seriousness. A Serious Adverse Event (SAE) was defined as any untoward medical occurrence that:

- Resulted in death
- Was life-threatening
- Required inpatient hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity

The relationship to the OPRA™ Implant System was classified as:

- Not related: The Adverse Event was definitely not related to the OPRA™ Implant System.
- Probably Unrelated: Cause and effect relationship between the AE and OPRA™ Implant System was not been demonstrated, was improbable, but not impossible.
- Possibly Related: A direct cause and effect relationship between the AE and the OPRA™ Implant System was not been demonstrated, but is possible or likely.
- Related: There is a direct cause and effect relationship between the AE and the OPRA™ Implant System.

There was a total of 101 treatment emergent AEs. Table 4 summarizes all adverse events that were either related or possibly related to use of the OPRATM device. The most frequent AEs related to the treatment during the 2-year study were:

- Infection: 31 (61%) subjects with 44 events
    - o Superficial infection: 28 (55%) subjects with 40 events
    - o Deep infection: 3 (6%) subjects with 4 events
- Pain: 6 (12%) subjects with 6 events
- Injury: 4 (8%) subjects with 4 events
- Loosening of the Fixture: 4 (8%) subjects with 4 events

Table 4 lists the adverse events most frequently reported as related or possibly related to the device.

Table 4: Adverse Events (Safety Population)

System Organ Class PT	ITT-Population (n=51)	
	AEs	Subjects with AEs n (%)
Any AE	84	44 (86.3%)
General disorders and administration site conditions	20	12 (23.5%)
Chills	1	1 (2.0%)
Impaired healing	1	1 (2.0%)
Mechanical complication of implant	9	4 (7.8%)
Pain	6	6 (11.8%)
Pyrexia	2	2 (3.9%)
Wound necrosis	1	1 (2.0%)
Infections	44	31 (60.8%)
Superficial infection	40	28 (54.9%)
Deep infection	4	3 (5.9%)
Injury, poisoning and procedural complications	13	13 (25.5%)
Loosening of the fixture resulting in device removal/failure	4	4 (7.8%)
Fracture	3	3 (5.9%)
Injury*	4	4 (7.8%)
Joint injury	1	1 (2.0%)
Post procedural haematoma	1	1 (2.0%)
Musculoskeletal and connective tissue disorders	3	3 (5.9%)
Myositis	1	1 (2.0%)

Table 4: Adverse Events (Safety Population)

Soft tissue necrosis	2	2 (3.9%)
Skin and subcutaneous tissue disorders	**4**	**4 (7.8%)**
Blister	1	1 (2.0%)
Skin necrosis	3	3 (5.9%)

*** 4 events of trauma resulting in falls**

As shown in the table above, a total of 28 subjects experienced a superficial infection. Three subjects experienced a deep infection. In the study, none of the superficial infections developed into a deep infection; no patient who developed a deep infection had a previous superficial infection.

Table 5 shows the distribution of subjects with treatment emergent adverse events for the different time periods throughout the study. This table shows the number of subjects with treat emergent adverse events whether or not they were deemed to be related, possibly related, or not related to the OPRA™ Implant System. Please note, Table 5 shows 'subjects with events' at each time point; therefore, one subject may be represented multiple times in the table if they experienced an adverse event at more than one time point. However, as Table 5 counts 'subjects with events', not 'total events', if a subject had multiple events occur within one time period, it would only be captured once. Please also note, all adverse events listed in Table 4 are captured in Table 5; however, they are categorized differently, such that major adverse events, such as infection, pain and loosening are called out; while, minor events, such as chills or bruising, are captured as other.

Table 5. Subjects with treatment emergent Adverse Events over time (Safety Population)

Adverse Events	Immed. Post-op Surgery 1 (n=51)	After Immed. Post-op Surgery 1 – Surgery 2 (n=51)	Immed. Post-op Surgery 2 (n=51)	After Immed. Post-op Surgery 2 – 3 months (n=51)	3 months – 6 months (n=51)	6 months – 12 months (n=48)	12 months – End of Study (n=48)
	Subjects with Events n (%)	Subjects with Events n (%); None[x]	Subjects with Events n (%)	Subjects with Events n (%)	Subjects with Events n (%)	Subjects with Events n (%)	Subjects with Events n (%)
Operative Site Events							
Superficial Infection			6 (11.8%)	3 (5.9%)	4 (7.8%)	13 (27.1%)	12 (25.0%)
Deep Infection	2 (3.9%)		3 (5.9%)				
Pain					1 (2.0%)	3 (6.3%)	3 (6.3%)
Onset of loosening of OPRA™ IMPLANT SYSTEM			1 (2.0%)			3* (5.5%)	
Skeletal fracture				1 (2.0%)		2 (3.9%)	1 (2.1%)
Trauma					2 (3.9%)	2 (3.9%)	3 (6.3%)
Mechanical complication of OPRA™ IMPLANT SYSTEM						1 (2.1%)	4 (8.3%)
Systemic Events							
Myocardial infarction; None[x]							
Pulmonary emboli; None[x]							
Urinary tract infection						1 (2.1%)	
Other	3 (5.9%)		6 (11.8%)	1 (2.0%)	2 (3.9%)	4 (8.3%)	4 (8.3%)

Immediately Post-op Surgery is defined within 42 days.

*** 1 patient showed signs of loosening of OPRA™ within the study but the fixture was removed 4 months after the 24 month follow-up**

[x]None; denotes that no events were reported in these categories shaded in dark green in the table.

Serious Adverse Event (SAE)

Among the 84 treatment emergent related and possibly related AEs, the most frequent SAEs were:

- Superficial infection, 4 (7.8%) subjects with 4 (4.8%) events,
- Deep infection, reported by 3 (5.9%) subjects with 4 (4.8%) events,
- Secondary surgical intervention (including reoperation, component replacement/revision, removal): 13 (15.5%) events reported by 13 (25.5%) subjects; of the 13 events, 4 (4.8%) events reported by 4 (7.8%) subjects were specific to implant (fixture) removal (3 implants removed during the study and 1 shortly after the study, giving 4 events in 4 patients).

EFFECTIVENESS OUTCOME IN 51-PATIENT OPRA™ STUDY

The main effectiveness measure was the Q-TFA. The Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) is a self-report measure developed for nonelderly transfemoral amputees using a socket- or osseointegrated prosthesis to reflect use, mobility, problems, and global health, each in a separate score (0-100). The use of the OPRA™ Implant System was able to provide subjects with benefit as measured by increase in prosthetic use (both number of days and hours per day), level of function, and quality of life. The number of subjects stratified by hours per day of prosthesis use are reported at baseline, 12 months and 24 months in Figure 7. Figure 7 shows that the number of subjects using their prostheses more than 12 hours a day increased.

Hours per Day of Prosthesis Use

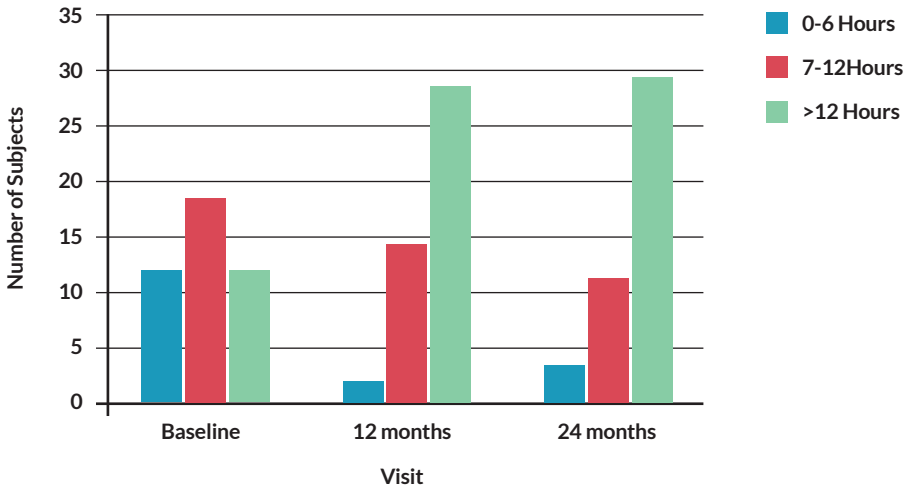


Figure 7: Hours per Day of Prosthesis Use by Visit

The number of subjects stratified by days per week of prosthesis use are reported at baseline, 12 months and 24 months in Figure 8.

Days per Week of Prosthesis Use

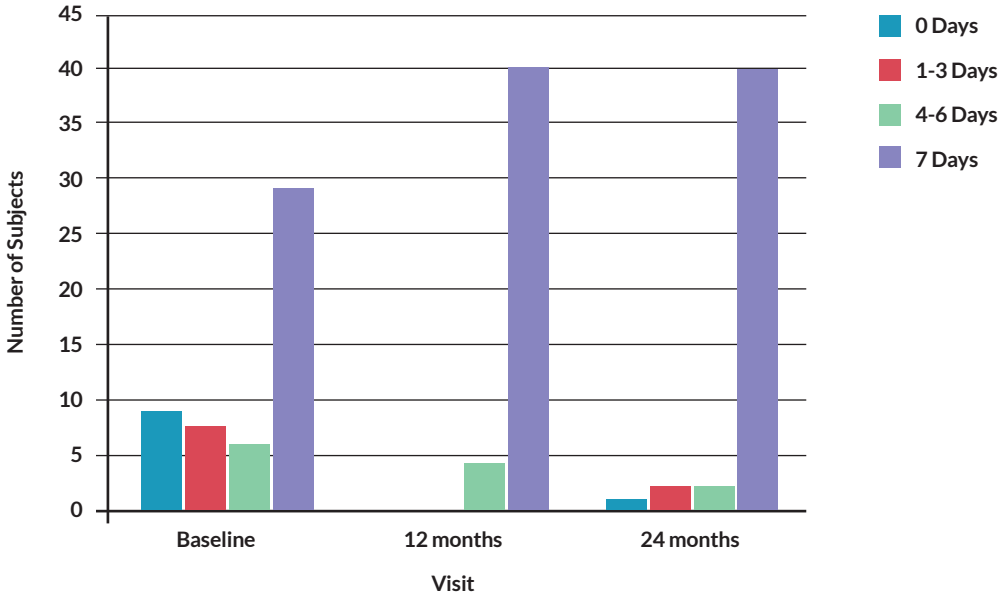


Figure 8: Days of Prosthesis Use per Week by Visit

Figure 8 shows the increase of prosthetic use from baseline to 2 years. The prosthetic use score, level of function, mobility, and improvement in quality of life significantly increased from baseline to 12 and 24 months, while the problem score significantly decreased during the same periods.

As the primary endpoint, the mean Prosthetic use score at baseline was 46.7 (Standard Deviation 36.7) out of 100. The score increased significantly, from baseline to 12 months, mean score 79.7 (22.7) and was sustained at 24 months, mean score 79.9 (27.1). The OPRA™ Implant System was also able to provide subjects with benefits such as longer walking distances, easier attachment and de- attachment of the prosthesis and increased sitting comfort. Cumulative survival rate of the Fixture (defined as lack of Fixture removal or revision) after two years of follow up was 92% and 93% on patient and implant level, respectively, which were calculated based on standard Kaplan-Meier curves and the fact that some patients were bilateral amputees and had 2 implants/fixtures. Note, however, this assumes that non-observed data is non-informative. The average of the Q-TFA Prosthetic Use Score stratified by baseline score and the changes in scores at 12 and 24 months are shown in Figure 9. Figure 9 shows that low prosthetic users (<25) saw a large increase in prosthetic use at 2 years. The moderate prosthetic users saw a slight increase and the high functional prosthetic users saw a slight decrease.

Q-TFA Prosthetic Use Score

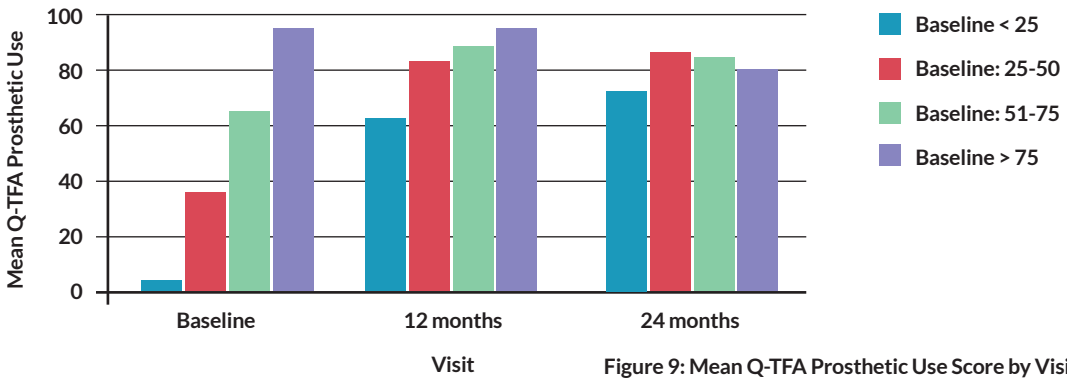


Figure 9: Mean Q-TFA Prosthetic Use Score by Visit

The average of the Q-TFA Problem Score stratified by baseline score and the changes in scores at 12 and 24 months post-procedure are shown in Figure 10. All groups showed a decrease in the problem score at two years.

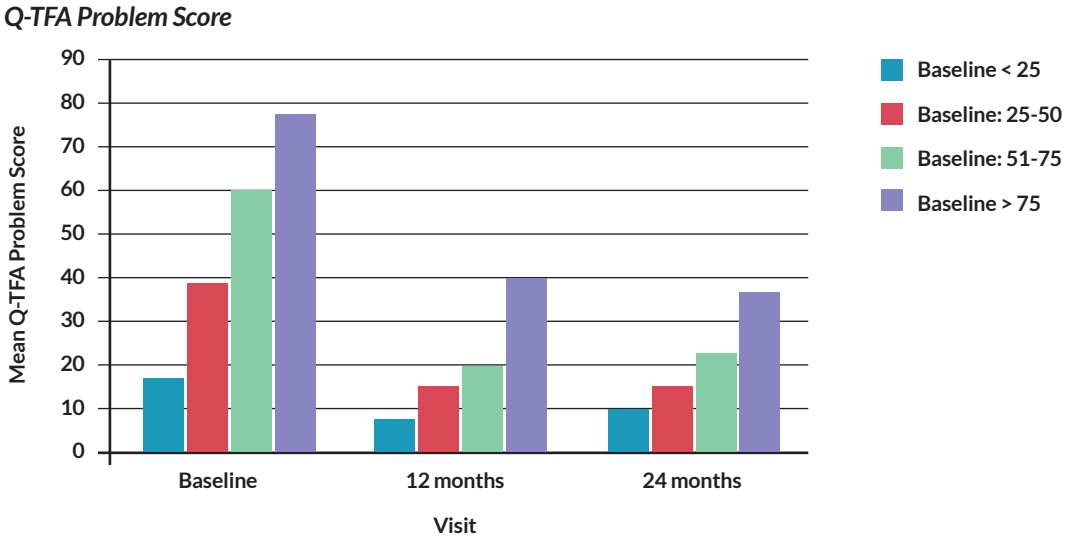


Figure 10: Mean Q-TFA Problem Score by Visit

Patient Preference Information

Integrum also collected patient perspective data from OPRA™ patients after at least 5 years post stage 2 surgery. Specifically, patients from the original OPRA™ study were asked if the advantages outweigh the disadvantages of using the OPRA™ device when taking into account surgeries, rehabilitation and possible complications (complications as abutment changes, superficial infections, etc.). Responses were received 5 years and an average 8.5 years after stage 2 surgery. Responses were recorded using a 5-point scale of "no, highly" to "yes, highly." The vast majority of responses at both time points were that patients "highly" thought the advantages outweighed the disadvantages of the OPRA™ device.

ADDITIONAL ANALYSIS

Integrum performed an additional analysis of the 51 OPRA™ study patients with 14 patients who had stage 1 surgery for the OPRA™ implant at Sahlgrenska University Hospital between March 2007 and November 2011 and met the same eligibility criteria as the OPRA™ study. A summary of these analyses is below.

Table 6 presents baseline and demographic characteristics for the 14 additional patients, which were similar to the original 51 patients from the OPRA™ study with the exception that 100% of the additional 14 subjects were male as compared to the 55%/45% male/female ratio in the original 51 subjects.

Table 6: Baseline and Demographic Characteristics for Additional 14 Subjects

Variable	14 Additional Patients
Gender	
Male	14 (100.0%)
Age at amputation (years)	36.1 (13.0) 33.5 (20; 58) n=14
Reason for amputation	
Trauma	11 (78.6%)
Peripheral Vascular Disease	0 (0.0%)
Tumor	1 (7.1%)
Other	2 (14.3%)
Age at inclusion (years)	45.8 (11.7) 47.5 (27; 63) n=14
Estimated weight at inclusion (kg)	76.8 (12.5) 77 (55; 100) n=14
Height at inclusion (cm)	178.0 (5.8) 177 (170; 190) n=14
Smoker at inclusion	3 (21.4%)
Prosthetic user at inclusion	12 (92.3%)
Level of education	
Primary school	1 (20.0%)
Secondary school	3 (60.0%)
Exam from University	1 (20.0%)
Data missing	9
Civil status	
Single	1 (12.5%)
Married/cohabiting	7 (87.5%)
Missing	6
Nationality	
Sweden	8 (57.1%)
Norway	4 (28.7%)
Spain	1 (7.1%)
Italy	1 (7.1%)
Medication at inclusion	
Yes	3 (25.0%)
No	9 (75.0%)
Missing	2

For categorical variables n (%) is presented.
For continuous variables Mean (SD) / Median (Min; Max) / n= is presented.

For the analysis with 65 subjects, new co-primary safety and effectiveness endpoints combined into a composite overall success endpoint, thus the composite primary endpoint is rate of overall success (i.e., success in both the primary effectiveness and safety endpoints).

With regard to success/failure criteria, the primary endpoint used to determine individual success is:

- Primary safety endpoints:
  - At 2 years: No subsequent secondary surgical interventions and at most 2 superficial infections.
  - At 5 years: No subsequent secondary surgical interventions and at most 3 superficial infections.
- Primary effectiveness endpoints: Patients achieved the minimally clinically important difference (MCID) for the total Q-TFA score (mean of all subscores, i.e., prosthetic use score, prosthetic mobility score, problem score, and global score) of 20.25 points (derived by the applicant) and radiographic success. Radiographic success was defined as "no radiographic loosening of the implant with a radiolucent zone wider than the thread depth sur rounding the entire implant". These endpoints were measured 2 and 5 years after the stage 2 surgery.

Rates of overall success and overall no success (not achieving success in both primary safety and effectiveness) at 2 and 5 years were provided. Proportion of patients who achieved either primary safety endpoints or primary effectiveness endpoints at 2 and 5 years was also assessed, respectively. These analyses included imputations for patients with miss-ing data.

- Secondary endpoint: Proportion of patients who achieved the MCID for the Q-TFA Prosthetic Use subscore (19 points), Prosthetic Mobility subscore (11 points), Problem subscore (-23 points) and Global subscore (33 points), individually.

The MCIDs for change from baseline for the Q-TFA subscales were derived individually and totally by the applicant using the validated SF-36 physical function subscore in a relevant population as an anchor (Escobar et al. (2007) and Keurentjes et al. (2012)).

Table 7 presents the results of the primary effectiveness endpoint with 65 subjects. The data below demonstrates a high proportion of patients with effectiveness success at both time points (70.8% at 2 and 5 years), supporting the device's benefits to patients.

Table 7: Primary Effectiveness Results (Total Q-TFA and Radiographic Success)

Variable	Total (n=65)
Primary effectiveness endpoint: Total Q-TFA ≥ MCID and radiographic success (2 years)	
Success	46 (70.8%)
Not Success	19 (29.2%)
Primary effectiveness endpoint: Total Q-TFA ≥ MCID and radiographic success (5 years)	
Success	46 (70.8%)
Not Success	19 (29.2%)

For categorical variables n (%) is presented.

The additional 14 subjects had a total of 30 treatment related adverse events including 23 surgical interventions, 20 mechanical complications, 2 deep infections, and 6 superficial infections. The surgical interventions addressed the mechanical complications and/or deep infections

Table 8 presents the results of the primary safety endpoint with 65 subjects. At 2 years, 67.7% of patients met the safety endpoint and at 5 years, 43.1% of patients met the safety endpoint. The applicant used the safety criteria outlined above for the analysis with 65 subjects, but the rate of patients without success should be interpreted cautiously as patients who are technically not successful still derive clinical benefit from the device. For example, an uncontrolled fall not related to the device causes a high bending moment on the device and the bone. The device protects the bone from fracture by plastic deformation of the abutment and thereby absorbs energy from the fall and avoids a bone fracture. A femoral bone fracture, which can happen also in socket users, is typically treated with a major surgical intervention and up to 6 months of restricted loading. A bent abutment, however, is replaced under local anesthesia in less than 30 minutes and directly postoperatively, the patient can ambulate without restrictions. However, from a strict safety analysis perspective, this patient would be considered not to be successful under this safety endpoint.

Table 8: Primary Safety Results

Variable	Total (n=65)
Primary safety endpoint (2 years)	
Success	44 (67.7%)
Not success	21 (32.3%)
Primary safety endpoint (5 years)	
Success	28 (43.1%)
Not Success	37 (56.9%)

For categorical variables n (%) is presented.

Table 9 presents rates for overall success at 2 and 5 years. As shown, 47.7% and 35.4% were overall successes at 2 and 5 years, respectively. Notably, only 9.2% and 21.5% did not achieve both effectiveness and safety success at 2 and 5 years, respectively. Thus, at 2 years, 90.8% of patients had some level of success, whether effectiveness, safety, or both. The same is true for 78.5% of patients at 5 years.

Table 9: Overall Successes

Variable	Total (n=65)
2 years	
Overall success	31 (47.7%)
Overall not success	6 (9.2%)
Primary safety success and no primary effectiveness success	13 (20.0%)
Effectiveness success and no primary safety success	15 (23.1%)
5 years	
Overall success	23 (35.4%)
Overall not success	14 (21.5%)
Primary safety success and no primary effectiveness success	5 (7.7%)
Effectiveness success and no primary safety success	23 (35.4%)

For categorical variables n (%) is presented.

Integrum also provided additional data with SF-36 and Q-TFA for the 65 subjects, as presented below.

Table 10 presents changes from before treatment in the SF-36 (Short Form (36) Health Survey, which is a 36-item, patient-reported survey of patient health) to 2 and 5 years for the 65 subjects. As shown, there are statistically significant improvements across most SF-36 subscores 2 and 5 years-post surgery.

Table 10: Change in SF-36-variables from before Treatment to 2 Years and 5 Years

	Change from before treatment to 2 years (n=65)		Change from before treatment to 5 years (n=65)	
Variable		**p-value within group**		**p-value within group**
Physical Function	23.6 (20.2) 25 (-30; 75) (18.4; 28.8) n=62 SRM=1.17 ES=1.11	<0.0001	26.2 (23.1) 25 (-38.1; 85) (20.3; 32.1) n=61 SRM=1.13 ES=1.22	<0.0001
Role Physical	23.0 (41.8) 18.9 (-100; 100) (12.4; 33.5) n=62 SRM=0.55 ES=0.56	0.0002	17.8 (54.2) 0 (-100; 100) (4.0; 31.8) n=61 SRM=0.33 ES=0.43	0.014
Bodily Pain	12.4 (36.4) 10 (-74; 100) (3.1; 21.6) n=62 SRM=0.34 ES=0.46	0.0090	8.17 (32.14) 10 (-69; 90) (-0.11; 16.45) n=61 SRM=0.25 ES=0.30	0.054
General Health	1.40 (18.09) 0 (-42; 52.99) (-3.20; 5.97) n=62 SRM=0.08 ES=0.08	0.55	5.18 (21.57) 5 (-55; 61.65) (-0.39; 10.68) n=61 SRM=0.24 ES=0.30	0.068
Vitality	6.44 (25.62) 5 (-70; 70) (-0.14; 12.95) n=62 SRM=0.25 ES=0.30	0.055	6.81 (23.56) 5 (-55; 70) (0.85; 12.79) n=61 SRM=0.29 ES=0.32	0.023

Table 10: Change in SF-36-variables from before Treatment to 2 Years and 5 Years

Social Function	6.66 (30.92) 0 (-100; 87.5) (-1.16; 14.42) n=62 SRM=0.22 ES=0.26	0.096	7.47 (32.62) 0 (-62.5; 87.5) (-0.76; 15.79) n=61 SRM=0.23 ES=0.29	0.074
Role Emotional	4.77 (50.44) 0 (-100; 100) (-8.18; 17.50) n=62 SRM=0.09 ES=0.11	0.48	5.25 (46.17) 0 (-100; 100) (-6.63; 17.02) n=61 SRM=0.11 ES=0.12	0.39
Mental Health	4.99 (24.40) 8 (-76; 48) (-1.20; 11.10) n=62 SRM=0.20 ES=0.25	0.11	4.23 (22.54) 4 (-56; 52) (-1.57; 9.96) n=61 SRM=0.19 ES=0.21	0.15
Physical Composite	8.80 (10.03) 9.87 (-14.22; 29.83) (6.23; 11.36) n=62 SRM=0.88 ES=1.05	<0.0001	8.76 (10.76) 8.27 (-12.6; 37.04) (6.03; 11.49) n=61 SRM=0.81 ES=1.05	<0.0001
Mental Composite	-0.698 (16.081) 0.426 (-44.799; 33.067) (-4.834; 3.390) n=62 SRM=-0.04 ES=-0.05	0.74	-0.652 (14.725) 0.349 (-35.648; 26.479) (-4.427; 3.087) n=61 SRM=-0.04 ES=-0.05	0.73

For continuous variables Mean (SD) / Median (Min; Max) / (95% CI) / n= / SRM / ES is presented.
For comparison within groups 95% CI based on the Fisher´s Non-Parametric Permutation test for matched pairs was used.
SRM = Standardized Response Mean= mean difference / SD for difference
ES = Effect Size = mean difference / SD for Baseline values
Out of 65 patients, four patients lost their prosthesis and should not be imputed at the 2 and 5 year time points. Of those four patients, one patient had SF-36 data (but no Q-TFA data) at 2 years. Thus, the 2-year timepoint includes n=62 at 2 years and n=61 at 5 years.

Responder analyses for the SF-36 data are presented in Table 11 using the MCIDs from Keurentjes et al. (2012). These data demonstrate that majority of patients had clinically meaningful improvements on the SF-36, especially with regard to physical function, general health, and vitality. It should be noted that the SF-36 records patients' general health and experiences and is not specific to the implant. Thus, some of the variables below, such as social function and emotional role, should not be considered specific to patients' experience with OPRA™.

Table 11: SF-36 Responder Analyses

Variable	Change from before treatment to 2 years (n=65)	Change from before treatment to 5 years (n=65)
Physical Function improvements		
Success	44 (71.0%)	45 (73.8%)
Not success	18 (29.0%)	16 (26.2%)
Role Physical improvements		
Success	32 (51.6%)	28 (45.9%)
Not success	30 (48.4%)	33 (54.1%)
Bodily Pain improvements		
Success	34 (54.8%)	32 (52.5%)
Not success	28 (45.2%)	29 (47.5%)
General Health improvements		
Success	44 (71.0%)	47 (77.0%)
Not success	18 (29.0%)	14 (23.0%)
Vitality improvements		
Success	38 (61.3%)	34 (55.7%)
Not success	24 (38.7%)	27 (44.3%)
Social Function improvements		
Success	26 (41.9%)	28 (45.9%)
Not success	36 (58.1%)	33 (54.1%)
Role Emotional improvements		
Success	15 (24.2%)	19 (31.1%)
Not success	47 (75.8%)	42 (68.9%)
Mental Health improvements		
Success	32 (51.6%)	29 (47.5%)
Not success	30 (48.4%)	32 (52.5%)

For categorical variables n (%) is presented.
Out of 65 patients, four patients lost their prosthesis and should not be imputed at the 2 and 5 year time points. Of those four patients, one patient had SF-36 data (but no Q-TFA data) at 2 years. Thus, the 2-year timepoint includes n=62 at 2 years and n=61 at 5 years.

Table 12 presents change in the Q-TFA variables at 2 and 5 years for the 65 subjects. As shown, there were statistically significant improvements across all Q-TFA variables (total and individual subscores).

Table 13 presents the responder analyses using the anchor-based MCIDs for the Q-TFA. As shown, majority of patients met the MCID for all Q-TFA variables at 2 and 5 years.

Table 12: Change in Q-TFA Variables from before Treatment to 2 Years and 5 Years

	Change from before treatment to 2 years (n=65)		Change from before treatment to 5 years (n=65)	
Variable		**p-value within group**		**p-value within group**
Total Q-TFA score	30.1 (16.0) 29.8 (-7.5; 60.8) (26.0; 34.3) n=61 SRM=1.88 ES=1.55	<0.0001	31.8 (16.4) 30.8 (-6.1; 76.8) (27.6; 36.0) n=61 SRM=1.94 ES=1.64	<0.0001
Prosthetic Use score	35.1 (33.4) 29 (-81; 100) (26.6; 43.7) n=61 SRM=1.05 ES=0.98	<0.0001	39.6 (32.7) 29 (-10; 100) (31.2; 48.1) n=61 SRM=1.21 ES=1.11	<0.0001
Prosthetic Mobility score	16.5 (15.6) 17 (-29; 50) (12.6; 20.5) n=61 SRM=1.06 ES=0.80	<0.0001	20.0 (17.4) 20 (-24; 78) (15.5; 24.5) n=61 SRM=1.15 ES=0.97	<0.0001
Problem score	-29.1 (16.1) -31 (-74.3; 7) (-33.3; -25.0) n=61 SRM=-1.80 ES=-1.53	<0.0001	-28.9 (18.2) -32 (-75.3; 17.5) (-33.6; -24.2) n=61 SRM=-1.59 ES=-1.51	<0.0001
Global score	39.6 (21.5) 34 (0; 92) (34.1; 45.2) n=61 SRM=1.84 ES=2.04	<0.0001	38.5 (22.7) 33 (-18; 100) (32.7; 44.3) n=61 SRM=1.70 ES=1.98	<0.0001

For continuous variables Mean (SD) / Median (Min; Max) / (95% CI) / n= / SRM / ES is presented.
For comparison within groups 95% CI based on the Fisher´s Non-Parametric Permutation test for matched pairs was used.
SRM = Standardized Response Mean= mean difference / SD for difference
ES = Effect Size = mean difference / SD for Baseline values
Out of 65 patients, four patients lost their prosthesis and should not be imputed at the 2 and 5 year time points. Thus, n=61 for the Q-TFA time points at 2 and 5 years. In the overall success analysis, these four patients are not treated as successes.

Table 13: Q-TFA Responder Analysis Using Anchor-Based MCID

Variable	Change from before treatment to 2 years (n=65)	Change from before treatment to 5 years (n=65)
Total Q-TFA score MCID improvements		
Success	44 (71.0%)	45 (73.8%)
Not success	18 (29.0%)	16 (26.2%)
Prosthetic Use score MCID improvements		
Success	32 (51.6%)	28 (45.9%)
Not success	30 (48.4%)	33 (54.1%)
Prosthetic Mobility score MCID improvements		
Success	34 (54.8%)	32 (52.5%)
Not success	28 (45.2%)	29 (47.5%)
Problem score MCID improvements		
Success	44 (71.0%)	47 (77.0%)
Not success		
Global score MCID improvements	44 (71.0%)	47 (77.0%)

Table 13: Change in Q-TFA Variables from Before Treatment to 2 Years and 5 Years

Success		
Not success	44 (71.0%)	47 (77.0%)

For categorical variables n (%) is presented.
Out of 65 patients, four patients lost their prosthesis and should not be imputed at the 2 and 5 year time points. Thus, n=61 for the Q-TFA time points at 2 and 5 years. In the overall success measure, these patients are treated as not successes.

RELEVANT CLINICAL LITERATURE

Several articles have been published based on the same patient population as the OPRA™ study or portions thereof. Key articles are summarized below.

HAGBERG AND BRÅNEMARK (2009) [1]

Hagberg and Brånemark presented 100 patients treated with 106 implants (6 bilaterally; 61% males, 39% females; mean age 43 years; mean time since amputation 11.5 years) between May 1990 and June 2008. Of the 100 patients, 51 are included in the OPRA™ study. The majority had amputations due to trauma (67%) or tumor (21%) (other = 12%). At the time of article publication, 68 patients were using their prostheses (follow-up: 3 months - 17.5 years) and 32 were not (4 are deceased, 7 are before second surgery, 6 are in initial training, 4 are not using prosthesis, and 11 had the implant removed). The majority of treatment failures occurred in patients using pre-OPRA™ systems, before the OPRA™ protocol was established. The implementation of graded rehabilitation is considered to be of utmost importance for improved results.

TRANBERG ET AL. (2011) [2]

Tranberg et al. included post-operative data showing that patients who had an osseointegrated transfemoral prosthesis increased their hip extension by 7.3° (p=0.007), changing from -2.6° (range -13.4° to 10.7°) to -9.9° (range -29.4° to 5°). Moreover, the pre-operative anterior pelvic tilt was reduced by 4.0° (p=0.016), changing from 21.7° (range 11.9-34.8°) to 17.7° (range 5.5-25.7°). Values for hip extension and pelvic tilt changed toward those of controls. These results confirm that patients treated with osseointegrated transfemoral prosthesis encounter significant changes of their kinematic pattern in terms of hip extension and anterior pelvic tilt. Even though the changes were moderate they may, in the long-term have a positive influence on lumbar biomechanics and could contribute to reducing the risk of further problems with low back pain.

NEBERGALL ET AL. (2012) [3]

The study performed by Nebergall et al. addresses radiostereometric analysis (RSA) and periprosthetic bone remodeling, to assess long-term fixation of the implant system (OPRA™). The following number of implants were analyzed with RSA at each follow-up interval: 47 implants at 6 months, 42 implants at 1 year, 40 implants at 2 years, 15 implants at 5 years, 12 implants at 7 years, and 3 implants at 10 years. The RSA analysis for the OPRA™ system indicated stable fixation of the implant (no substantial motion) up to 7 years after the second surgical procedure. At 5 years, the median (Standard Error) migration of the implant was very small (-0.02 (0.06) mm). The rotational movement was 0.42 (0.32) degrees around the longitudinal axis. There was no statistically significant difference in median rotation or migration at any follow-up time. Although some implants showed slight initial motion, the implants had stabilized at the 5-year follow-up. Of the 3 implants that loosened, the motion detected using RSA was only slightly greater than the median degree of motion in the rest of the cohort. Unfortunately, films for the latest follow-up were only available for the failed implants and films were not taken just prior to implant removal. Kinematics at the latest follow-up did not necessarily indicate loosening or substantial migration. Cancellation of the cortex appeared in at least 1 zone in over half of the patients at 2 years but the prevalence had decreased by the 5-year follow-up, indicating a stabilization of bone remodeling. The majority of radiographs showed only minimal amounts of bone remodeling around the implant, and ultimately this remodeling did not compromise implant fixation of performance. Even the cases that experienced more moderate bone loss did not show any indication of loosening or implant failure.

Nebergall et al. concluded that there are several distinct advantages in using the OPRA™ system over the use of a conventional socket prosthesis. The transcutaneous nature of the OPRA™ system permits easy attachment and removal of the artificial limb through a quick-release mechanism. Ease of proper attachment also eliminates discomfort from

wearing a limb that is improperly fitted. Similarly, since the skin-to-prosthesis interface is minimized and since the dermatological problems often associated with prosthesis attachment occur less frequently; there was only 1 superficial infection per patient every 2 years. Nebergall concluded that the OPRA™ system provides a solution for patients who are unsuitable candidates for a conventional socket prosthesis, due either to amputation that has been at too high a level or due to damage to the stump that has been too severe to allow fitting of a socket prosthesis. The rehabilitation problems identified by Nebergall et al. are consistent with the adverse events summarized above.

BRÅNEMARK ET AL. (2014) [4]

The results of the 51-patient OPRA™ study described above were published in Brånemark et al. This article is included for completeness. The authors of this peer-reviewed publication concluded that the high cumulative survival rate at two years (92%) combined with enhanced prosthetic use and mobility, fewer problems and improved quality of life, supported the 'revolutionary change' that patients with transfemoral amputation had reported after treatment with osseointegrated percutaneous prostheses.

TILLANDER ET AL. (2017) [5]

Tillander, et al. studied the risk of osteomyelitis and characterize the clinical effect of osteomyelitis (including risk of implant extraction and impairments to function), and determine whether common patient factors (age, sex, body weight, diabetes, and implant component replacements) are associated with osteomyelitis in patients using the OPRA™ Implant System.

The study retrospectively analyzed 96 patients that included study subjects within the pivotal OPRA™ study described above, custom design and commercial OPRA™ Implant System users receiving femoral implants (102 implants (including bilateral); mean implant time, 95 months) treated between 1990 and 2010 for osteomyelitis. Six patients were lost to follow-up. The reason for amputation was tumor, trauma, or ischemia in 97 limbs and infection in five. All patients were referred from other orthopedic centers owing to difficulty with use or to be fitted with socket prostheses.

Osteomyelitis was diagnosed by medical chart review of clinical signs, tissue culture results, and plain radiographic findings. Proportion of daily prosthetic use when osteomyelitis was diagnosed was semi-quantitatively graded as 1 to 3. Survivorship free from implant associated osteomyelitis and extraction attributable to osteomyelitis respectively was calculated using the Kaplan-Meier estimator. Indication for extraction was infection not responsive to conservative treatment with or without minor debridement or loosening of implant.

Implant-associated osteomyelitis was diagnosed in 16 patients corresponding to a 10-year cumulative risk of 20% (95% CI 0.12–0.33). Ten implants were extracted owing to osteomyelitis, with a 10-year cumulative risk of 9% (95% CI 0.04–0.20). Prosthetic use was temporarily impaired in four of the six patients with infection who did not undergo implant extraction. With the numbers available, we did not identify any association between age, BMI, or diabetes with osteomyelitis; however, this study was underpowered on this endpoint.

The authors concluded that although the overall risk of implant osteomyelitis in patients who receive percutaneous osseointegrated implants after transfemoral amputation increases with time, the improved daily living outweighs the risks and inconvenience of treatment for most patients in this respect.

BRÅNEMARK ET AL. (2018) [6]

Brånemark, et al. presented 5-year outcomes for a subset of patients in the OPRA™ study. Out of 51 patients from the OPRA™ study, 40 patients had five-year follow-up data. The five-year fixture cumulative survival rate was 92% and revision-free rate was 45%. The most common AE was superficial infection, occurring 70 times in 34 patients from baseline to the five-year follow-up. Superficial skin infections were normally treated with oral antibiotics for 10 days, but 16 of them required longer treatment. A total of 85 SAEs were reported in 26 patients:

- Removal of the fixture (4 patients)
- Stump revisions (3 patients)
- Deep infections (11 patients)
- Exchange of abutment and/or abutment screw (15 patients)

Fourteen (14) deep infections were diagnosed in 11 patients during the five-year period. One of these infections caused early loosening/failure of the fixture. Nine patients with deep infections were successfully treated with oral antibiotics, with a mean time of five months. One deep infection had not resolved at the five-year follow-up.

Forty-three (43) mechanical complications occurred in 15 patients, resulting in replacement of the damaged abutment and/or the abutment screw. Accidental overload (falling, stumbling causing the abutment to bend) was the cause in sixteen bent abutments in 9 patients. One patient had the abutment temporarily removed (fixture in situ) four months before the five-year follow-up appointment, due to mechanical problems with the abutment and abutment screw.

Analyses of differences between baseline and the five-year follow-up revealed statistically significant improvements in all four Q-TFA scores ($p<0.0001$) and in the physical function (PF) ($p<0.0001$), role physical (RP) ($p=0.020$) and physical component score (PCS) ($p<0.0001$) on the SF-36. All other differences were non-significant. Details of prosthetic use at baseline showed that 29/42 (69%) used their prostheses on a daily basis for at least 13 hours/day. At 5-year follow-up, this was reported by 28/40 (70%) of the patients.

To address a possible relation between higher prosthetic activity and mechanical complications, the group of 40 patients at the five-year follow-up was divided into those that had experienced any mechanical complication to the abutment and/or abutment screw and those without any such complication and compared with regard to their Q-TFA mobility score at the five-year follow-up. The results showed a statistically significant higher mean mobility score in the group of patients that had had a mechanical complication ($p=0.035$). The group with any mechanical complication ($n=15$) had a mobility score of 74 (SD 20.5, 8-92) as compared to the group without any complication ($n=25$) which had a mobility score of 64 (SD 20.2, 4-97).

In sum, this study demonstrated that 5-year outcomes were similar to those at 2-year follow-up, and that the benefits were clinically relevant. No additional patients lost the anchorage (fixture) of the implant system. Mechanical complications increased and were more frequent in patients with higher activity. Superficial infections per patient and year remained constant. Though the number of deep infections increased, only one implant had to be removed because of infection. This case was an early deep infection before successful osseointegration had been established.

HAGBERG ET AL. (2020) [7]

Hagberg et al. presented long term data with the OPRA™ device, at 2, 5, 7, 10 and 15 years post-S2 surgery. This study includes patients treated in Sweden between January 1999 and December 2017. Thus, original OPRA™ study patients are included, as well as others from the same hospital outside the original OPRA™ study. Integrum is not the sponsor of this study. In addition, several versions of the OPRA™ device are included in this study, and it should be noted that some patients were treated off-label in Sweden. Despite these limitations, the Q-TFA scores generally demonstrated significantly more prosthetic use, better mobility, fewer problems, and an improved global score at 2, 5, 7, and 10 years compared with baseline. At 15 years, there is limited patient data but what is available (see Figure 4 in Hagberg, et al. (2020); $n=11$ for prosthetic use subscore and $n=9$ for other subcores) shows maintenance in the prosthetic use and mobility subscores and improvement in the problem and global Q-TFA subscores from 2 year data.

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6. Brånemark R, Hagberg K, Kulbacka-Ortiz K, Berlin Ö, Rydevik B. Osseointegrated percutaneous prosthetic system for the treatment of patients with transfemoral amputation: A prospective five-year follow-up of patient reported outcomes and complications. J Am Acad Orthop Surg 2018;00:1-9.

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CONCLUSIONS DRAWN FROM THE STUDIES

The clinical experience presented indicates that osseoanchored devices lead to an acceptable level of patient satisfaction and are associated with an acceptable complication risk level. Studies have shown increased prosthetic use, better prosthetic mobility, fewer problems and a better overall amputation situation. There is a definite risk of infection. However, the clinical evidence shows that use of osseoanchored devices leads to manageable infectious complications in transfemoral amputees. Further, longer-term post-marketing data supports the findings from the OPRA™ Implant study and supports a positive benefit/risk assessment.[6] The reported clinical experience with use of the OPRA™ Implant System confirmed associated improvements in patient comfort, function and quality of life. In the OPRA™ clinical study with 51 patients, the cumulative survival rate of the Fixture was high at 92% and 93% on patient and implant levels, respectively, after 2 and 5 years. The number of subjects using their prosthetic device increased during the study, both on an hourly and daily basis, demonstrating patient satisfaction with using the prostheses. In the 65-patient cohort, the cumulative survival rate of the Fixture was 93.6% and 94% on patient and implant levels, respectively, at both 2 and 5 years, with an assumption that non-observed data is non-informative at 5 years.

APPENDIX 1: CLEANING AND STERILIZATION INSTRUCTIONS – SURGICAL INSTRUMENTS

The surgeries should be carried out with the OPRA™ Surgical Instrument Kits for Stage 1 and Stage 2 respectively. The instruments are delivered non-sterile. All instruments are reusable and should be reprocessed by trained personnel according to the procedure below and as described in the "Care, Maintenance, Cleaning and Sterilization Instructions: Integrum Manual Reusable Surgical Instruments". There is no maximum number of reuse cycles, but individual components should be replaced if they are worn or the system is malfunctioning.

The following should be carried out **before the first** surgery:

- Ensure that the instrument kit contains all instruments according to the checklist attached to the surgical manual.
- Make a test assembly of the instruments according to the surgical manual in order to assure the functionality of the instrument kit.
- Clean and decontaminate the instruments according to the "Care, Maintenance, Cleaning and Sterilization Instructions: Integrum Manual Reusable Surgical Instruments". Protect sharp instruments from metal contact in order to prevent blunt edges. Make sure that all instruments are completely dry and pay extra attention to instruments with cavities or channels. If needed, dry with compressed air.

The following should be carried out **after each** surgery:

- Disassemble all instruments before cleaning.
- Instruments with cavities or channels should be rinsed with water and brushed inside before cleaning. Clean and decontaminate according to the "Care, Maintenance, Cleaning and Sterilization Instructions: Integrum Manual Reusable Surgical Instruments". Protect sharp instruments from metal contact in order to prevent blunt edges. Make sure that all instruments are completely dry and pay extra attention to instruments with cavities or channels. If needed, dry with compressed air.
- Make a general inspection in order to assure the functionality of the instruments.
- Assemble all components with threads to check for damages and visually inspect the drills for burrs. Replace any worn or malfunctioning component.

It is the responsibility of the health care facility to ensure that the recommended sterilization process is followed correctly and to verify the sterilization equipment achieves the recommended parameters. Integrum AB is responsible for the instrument's performance only when the instruments are reprocessed in accordance with the recommended procedure.

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CE 2797

Doc.No: 006 194 05 ENG, 2020-11

OPRA™ STAGE 1
FEMUR SURGICAL TECHNIQUE

Implant System for Direct Skeletal Anchorage of Amputation Prostheses

Platform G

Integrum

TABLE OF CONTENTS

APPLICABLE FOR USA

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INTRODUCTION

The Osseoanchored Prostheses for the Rehabilitation of Amputees (OPRA™) Implant System is indicated for patients who have transfemoral amputation due to trauma or cancer and who have or are anticipated to have rehabilitation problems with, or cannot use, conventional socket prostheses. The OPRA™ Implant System is intended for skeletally mature patients.

The patient failed to receive benefit from socket prostheses or is expected to not tolerate socket use due to problems such as:

- Recurrent skin infections and ulcerations in the socket contact area
- Pain
- A short stump preventing the use of socket prosthesis
- Volume fluctuation in the stump
- Soft tissue scarring
- Extensive area of skin grafting
- Socket retention problems due to excessive perspiration
- Restricted mobility

This manual contains stepwise instructions on the surgical procedure for Stage 1 (S1) of the OPRA™ Implant System. In this procedure, the Fixture and the Central Screw are installed and fitted with temporary components for healing. After the healing period, Stage 2 (S2) surgery is performed in order to remove the healing components and place the Abutment and the Abutment Screw.

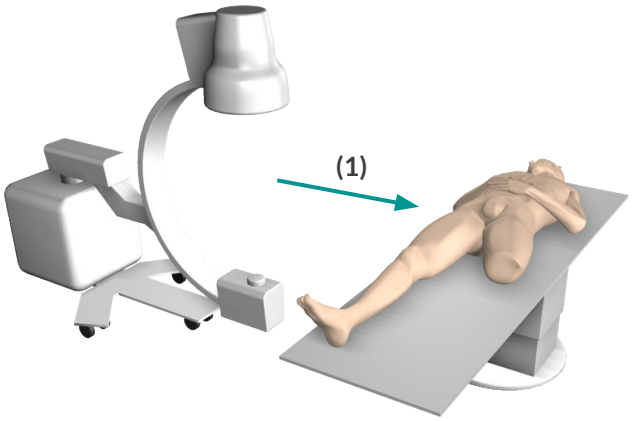
Instructions for S2 are available in OPRA™ Stage 2 (S2) - Surgical Technique.

Please note that this is a short protocol. For further information, including pre- and postoperative management, please see the OPRA™ Implant System - Instructions for Use.

A checklist for the OPRA™ Surgical Instrument Kit is provided separately.

PREOPERATIVE SETUP

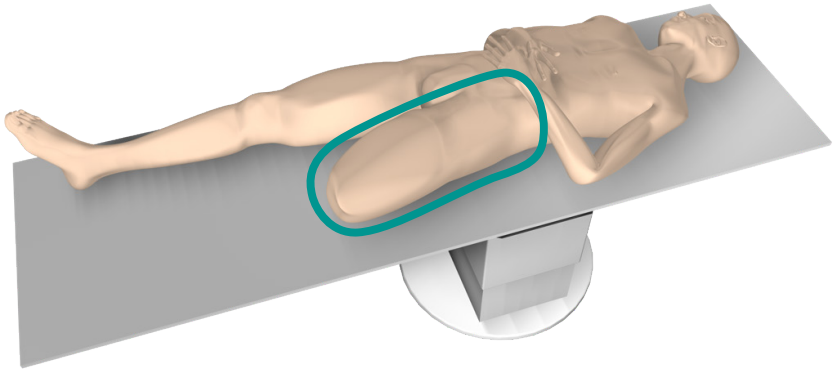
C-BEAM



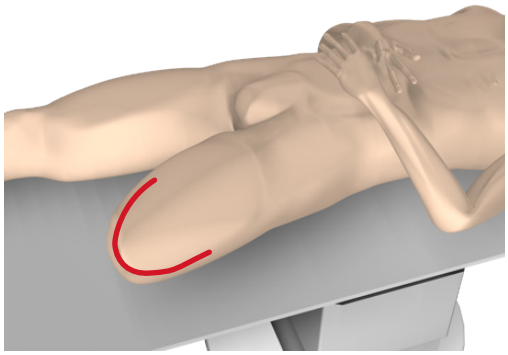
1. The C-Beam should be placed on the contralateral side. Check that the operating table does not interfere with frontal and lateral projections.

WASHING & DRESSING FOR SURGERY

1. Include the hip joint and the ipsilateral iliac crest in the washing/dressing area.



EXPOSURE OF THE FEMUR



1. The picture shows the recommended incision line.

   Expose the femur, preferably using a standard lateral approach.

RECOMMENDED INCISION LINE

START

FIXTURE AND DRILL DIAMETER CORRELATION

FIXTURE Ø (MM)	THREAD PITCH (MM)	FINAL DRILL Ø (MM)	FINAL DRILL Ø (MM)
		Soft bone	*Hard bone*
16,0	1,25	14,5	15,0 15,5*
16,5	1,25	15,0	15,5 16,0*
17,0	1,75	15,5	16,0 16,5*
17,5	1,75	16,0	16,5 17,0*
18,0	1,75	16,5	17,0
18,5	1,75	17,0	17,5
19,0	1,75	17,5	18,0
19,5	1,75	18,0	18,5
20,0	1,75	18,5	19,0
21,0	1,75	19,5	20,0
22,0	1,75	20,5	21,0
23,0	1,75	21,5	22,0
24,0	1,75	22,5	23,0
25,0	1,75	23,5	24,0

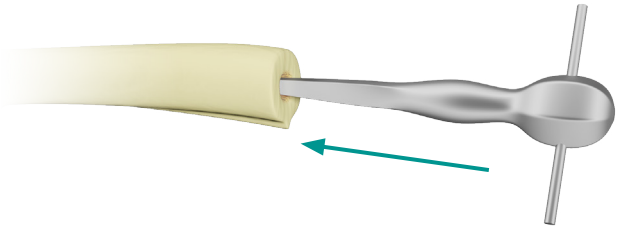
** Use this drill size to prepare the implantation site for the shallow thread Fixture profile. Drill only for a depth of 44 mm.*

1. The table presents the recommended final drill diameter (Ø being the symbol for outer diameter) for each ***Fixture*** diameter, in soft and hard bone respectively.

   Soft bone is defined here as osteoporotic and/or spongious bone normally present in amputees.

   Hard bone is defined here as normal diaphyseal cortical bone.

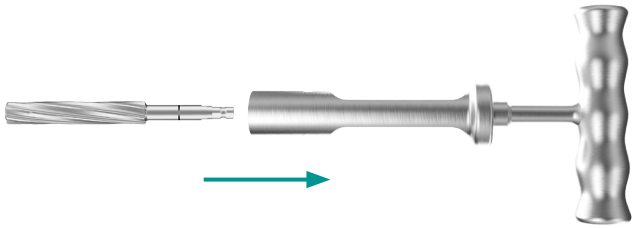
OPENING THE INTRAMEDULLARY CANAL



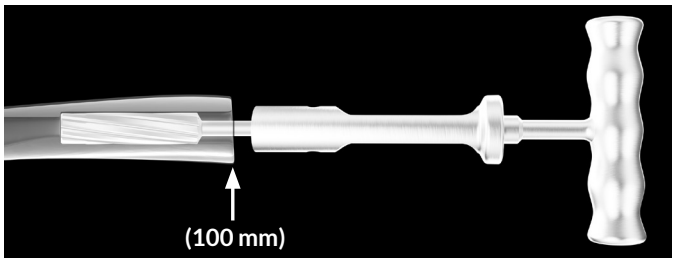
1. Open the intramedullary canal.

DRILLING

DRILLING DEPTH



1. Mount the drill on the ***T-handle Hudson.***

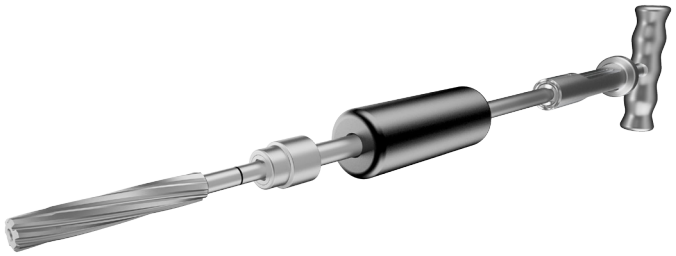


2. Drill to the size of the preoperative planning or adjust peroperatively if needed.

   Try to have a minimum of 2 mm remaining cortical thickness.

   Stop drilling at the 100 mm mark on the ***Drill***.

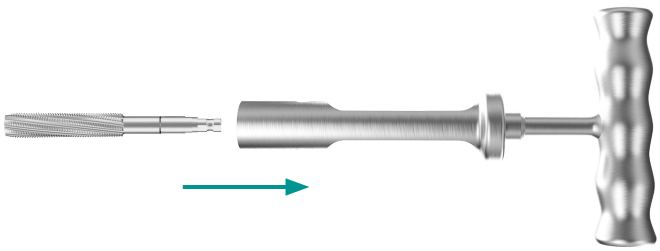
   Save marrow blood and marrow bone from the used drills in a bowl.



3. Optionally, use the ***Drill Rod*** and hand swivel during the drilling procedure.

THREAD TAPS

USING THE THREAD TAPS AS TEST IMPLANTS

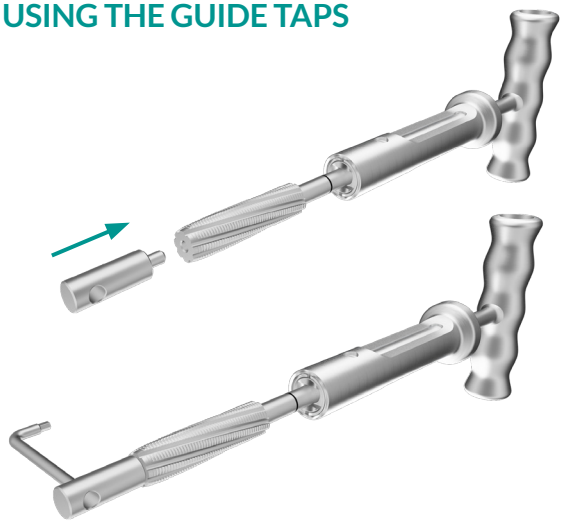


1. Mount the selected ***Thread Tap*** (80 mm test implants). A 16.0 mm ***Thread Tap*** is used as ***Fixture*** test implant 16.0 mm and so on.

2. The selected ***Thread Tap*** is screwed into the bone.

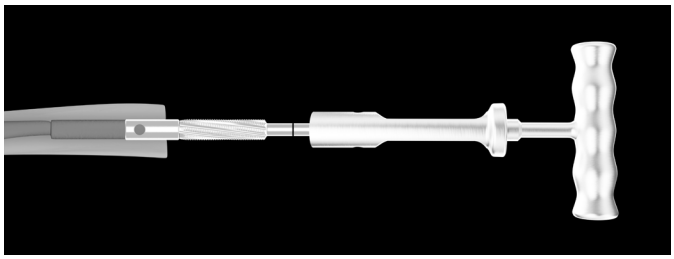
IMPORTANT! Gently move back and forth about 1/3 of a full turn when there is resistance (as tapping in metal), to avoid the thread tap getting stuck in the bone.

USING THE GUIDE TAPS



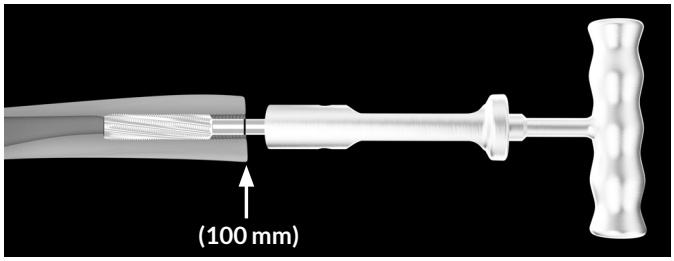
1. Optionally, attach a ***Guide Tap*** (different Ø) to the top of the ***Thread Tap*** to help guide the tap.

2. Tighten the ***Guide Tap*** firmly using an ***Allen Key***.



3. Help to guide the ***Thread Tap*** and keep a straight channel.

THREAD TAP TO CORRECT DEPTH



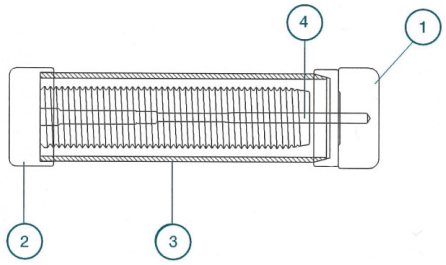
1. Stop at the 100 mm mark on the ***Thread Tap.***

   Unscrew the Thread Tap.

FIXTURE INSTALLATION

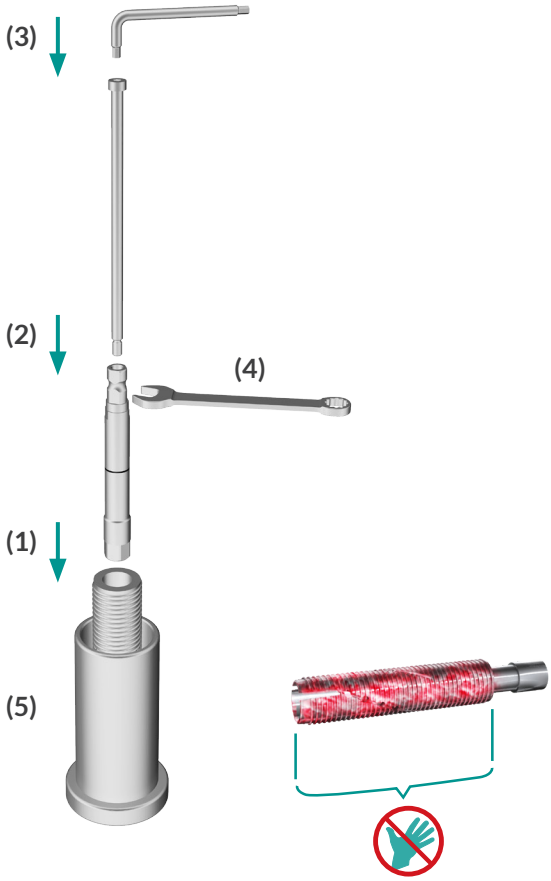
OPENING FIXTURE PACKAGING

The ***Fixture*** is mounted in a protective titanium casing. In connection with the preparation for installation, only sterile titanium instruments may come into contact with the threaded outer surface of the ***Fixture***. In the event of contamination the ***Fixture*** must not be used but must unconditionally be returned to Integrum AB.



1. Unscrew the titanium casing outer lid (1).
2. Hold the titanium casing base lid (2) and pull off the packaging tube (3).
3. Put the ***Fixture*** in the titanium cylinder of the ***Fixture Stand*** and unscrew the titanium casing base lid (2) until it can be removed together with the fastening pin (4).

FIXTURE MOUNTING AND INSTALLATION



1. (1) Attach the ***Fixture Holder Screw G*** to the ***Fixture Holder G***.

   (2) Attach the ***Fixture Holder G*** to the ***Fixture***.

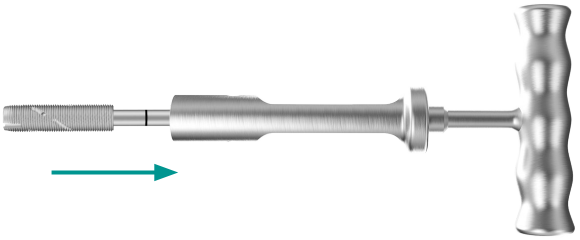
   (3) Use the 2.5 mm ***Allen Key*** to tighten.

   (4) ***Spanner*** 8 mm

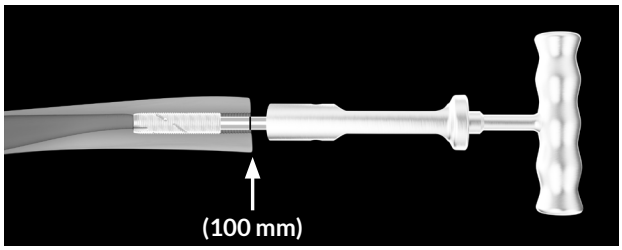
   (5) ***Fixture Stand***

2. Spray marrow blood over the ***Fixture***.

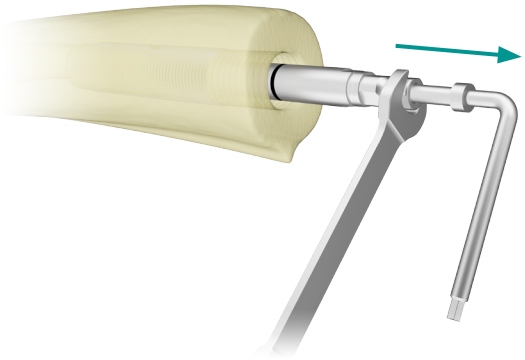
IMPORTANT! Do not touch the ***Fixture***.



3. Connect the ***Fixture Holder G*** to the ***T-handle***.

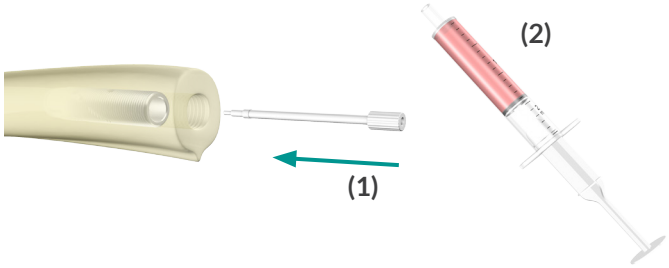


4. Screw the ***Fixture*** slowly into the bone to the 100 mm mark on the ***Fixture Holder G***.



5. Remove the ***Fixture Holder Screw G*** and F***ixture Holder G*** by using the 2.5 mm ***Allen Key***.

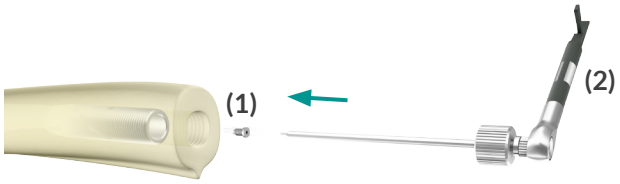
MARROW BLOOD INJECTION



1. (1) Mount the ***Marrow Blood introducer***.

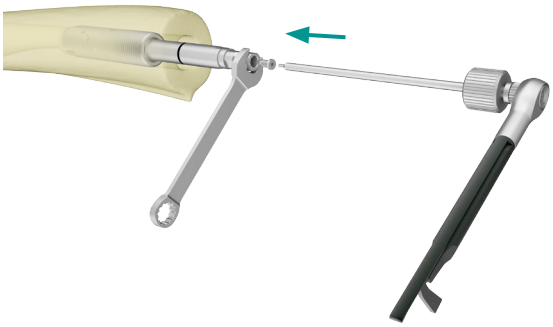
   (2) Inject approximately 2 ml of marrow blood.

CENTRAL SCREW MOUNTING



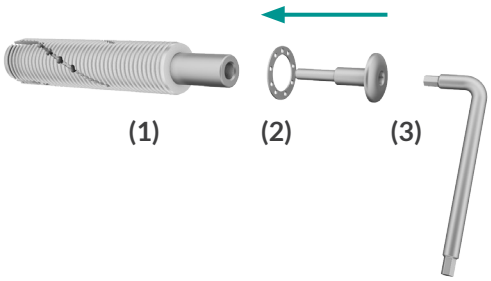
1. (1) Put the ***Central Screw*** on the ***Central Screw Driver*** and attach the ***Torque Wrench***.

   (2) Screw the ***Central Screw*** into the ***Fixture*** with a torque of 80 Ncm.



2. Optionally, if the ***Fixture*** has insufficient primary stability, tighten the central screw to 80 Ncm by using the ***Fixture Holder G*** and the 8 mm ***Spanner*** to stop rotation of the ***Fixture***.

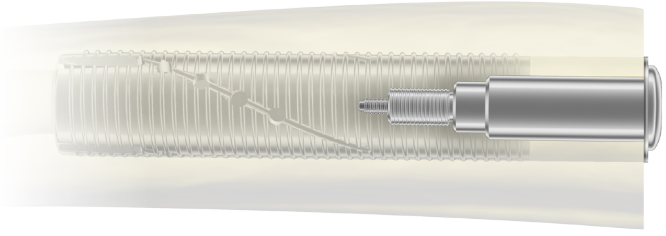
MOUNTING HEALING COMPONENTS



1. (1) Put the ***Healing Cylinder*** in the ***Fixture*** using the 3,5 mm ***Allen Key***.

   (2) If needed, use a ***Washer*** to keep the bone graft in place. There are different sizes of washer depending on skeletal anatomy.

   (3) Close with the ***Graft Screw*** using the 3.5 mm ***Allen Key***.



2. Schematic illustration of the S1 components in place.

SOFT-TISSUE CLOSURE AND DRESSING

Close the soft tissues over the distal bone in layers using resorbable sutures (e.g. Vicryl 2-0), with standard techniques for amputations including distal myoplasty. We do not recommend performing a myodesis with osteosutures as these might interfere with the healing of the distal bone graft. Close the skin with sutures/staples. Use standard dressings for conventional amputations.

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OPRA™ STAGE 2
FEMUR SURGICAL TECHNIQUE

Implant System for Direct Skeletal Anchorage of Amputation Prostheses

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- Pain
- A short stump preventing the use of socket prosthesis
- Volume fluctuation in the stump
- Soft tissue scarring
- Extensive area of skin grafting
- Socket retention problems due to excessive perspiration
- Restricted mobility

This manual contains stepwise instructions on the surgical procedure for Stage 2 of the OPRA™ Implant System. In this procedure, the temporary healing components for healing are removed, and the Abutment and Abutment Screw are installed.

Instructions for S1 are available in OPRA™ Stage 1 - Surgical Technique.

Please note that this is a short protocol. For further information, including pre- and postoperative management, see the OPRA™ Implant System - Instructions for Use.

A checklist for the OPRA™ Surgical Instrument Kit is provided separately.

GENERAL DESCRIPTION OF THE SURGERY

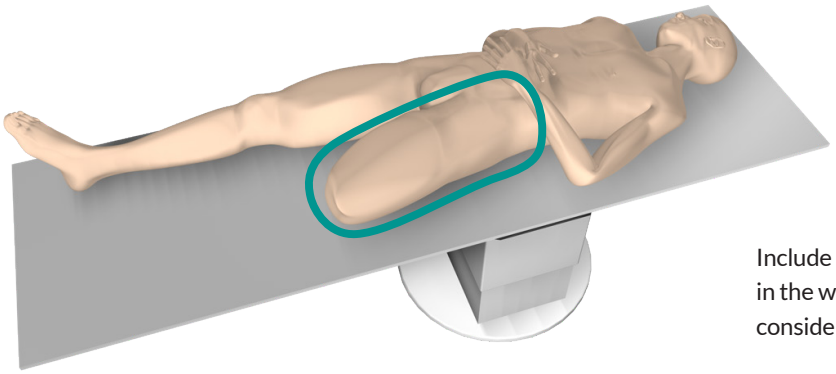
The surgery consists of the following main steps:

1. Preoperative setup
2. Removal of healing components
3. Soft tissue reconstruction
4. Installation of Abutment and Abutment Screw

The steps above are described with stepwise instructions and pictures in this manual.

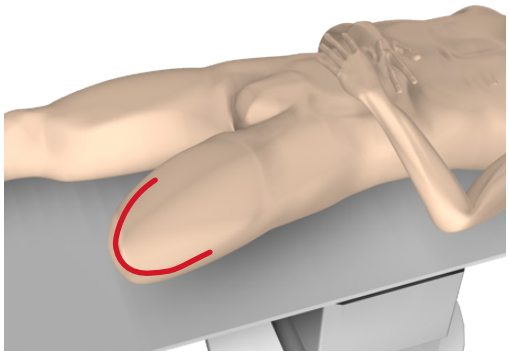
PREOPERATIVE SETUP

Position the patient on the operating table according to the hospital's current practices. Fluoroscopy is usually not needed at Stage 2 surgery.

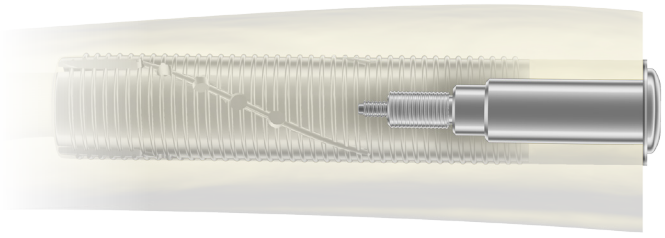


Include the hip joint and the ipsilateral iliac crest in the washing/dressing area if bone grafting is considered.

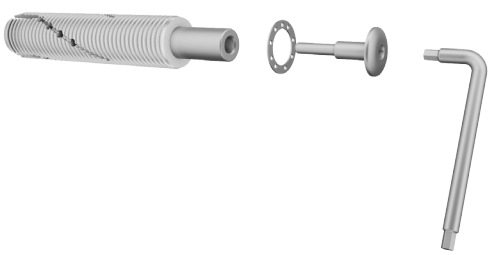
INCISION AND EXPOSURE



RECOMMENDED INCISION LINE



Identify the ***Healing Components*** and make sure that the head of the ***Graft Screw*** is cleaned from soft tissues.

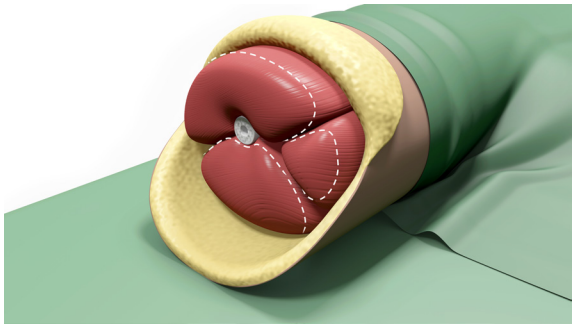


Use the 3.5 mm ***Allen Key*** to unscrew the ***Healing Components.***

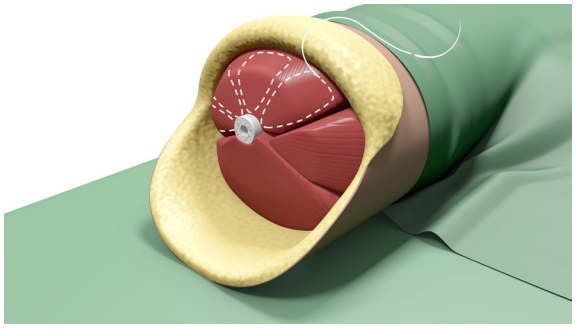
SOFT TISSUE RECONSTRUCTION

Before the Abutment and Abutment Screw are inserted, it is recommended to perform soft tissue reconstruction in accordance with the following instructions:

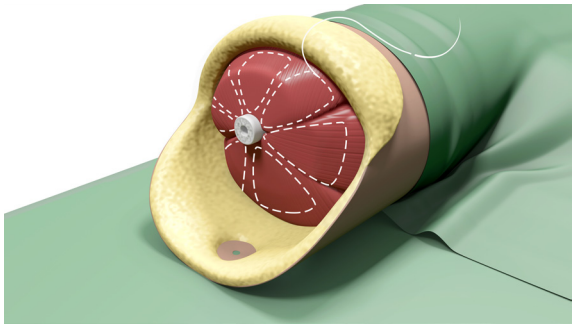
ALL PICTURES REFER TO THE RIGHT LEG



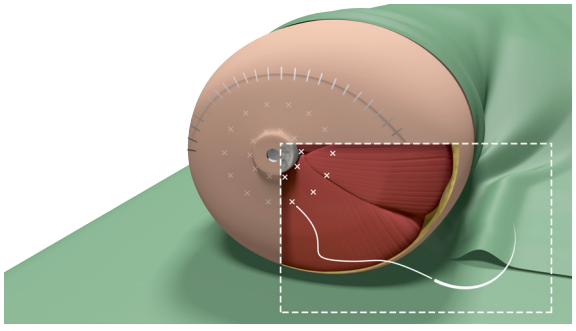
1. Make a guillotine amputation of the remaining muscles at the level of the distal end of the skeleton (see dashed line in picture).



2. Suture the muscles to the periosteum so that 10 mm of the distal end of the bone is protruding. Use resorbable sutures (e.g. Vicryl 0). Make sure that there is no soft tissue or periosteum left on the distal surface of the bone. If the distal bone surface is sclerotic, it is recommended to roughen it or even make small drill holes with a spiral drill of diameter 2 mm, 2-3 mm deep for instance, to have a bleeding bone surface.



3. Mark for the skin penetration: optionally, use a needle. Make a circular hole with a diameter of 11 mm in the central part of the trimmed skin area. Make sure that this hole is placed over the bone canal. Remove all subcutaneous tissue from the inside of the flap down to the rete arteriosum over a surface with a diameter of approximately 30 mm. Optionally, reduce the thickness of the flap to a subcutaneous thickness of approximately 10 mm.



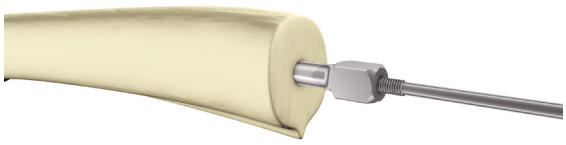
4. Put the dorsal flap over the distal end with minimal tension. Excise excessive soft-tissues and skin. Do not leave any bulging soft-tissue masses. Suture the flap starting from the dorsal part with numerous resorbable sutures (e.g. Vicryl 2-0) to support the flap and around the distal end of the bone. If possible, put napping resorbable sutures all around the distal circumference.

INSTALLATION OF ABUTMENT AND ABUTMENT SCREW

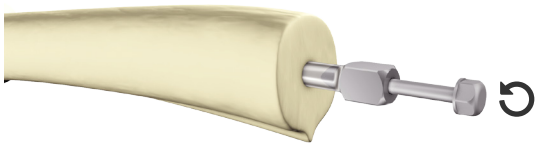
1. Insert the ***Pressure Peg Hex*** into the corresponding thread in the fixture and tighten very lightly with the 5 mm ***T-handle***.

2. Insert the ***Abutment*** over the ***Pressure Peg Hex***.

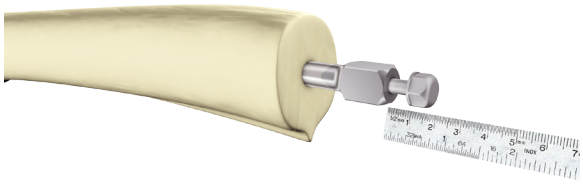
NOTE: Make sure the ***Abutment*** is engaging in the hex part of the ***Fixture***. See also step 5 below.



3. Remove the ***Pressure Peg Hex***.



4. Insert the ***Abutment Screw.*** Turn the screw anti-clockwise until the screw is standing on the top of the thread.



5. Use the ***Ruler*** to measure that the ***Abutment*** is engaging in the hex part of the ***Fixture***.

   The distance between the distal end of the ***Abutment*** and the proximal end of the ***Abutment Screw*** head should be at least 1.5 mm.

6. Tighten the ***Abutment Screw*** in the clockwise direction. Use 14 mm ***Spanner*** for the ***Abutment*** and 10 mm ***Spanner*** for the ***Abutment Screw***. Make sure that the ***Abutment*** is fully seated. Tighten to 12 Nm using a torque wrench.

   For further details on re-tightening the Abutment Screw, please see the OPRA™ Implant System - Instructions for Use.

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CARE, MAINTENANCE, CLEANING AND STERILIZATION INSTRUCTIONS

Integrum Manual Reusable Surgical Instruments

Integrum

TABLE OF CONTENTS

SCOPE

This manual provides information on the care, maintenance, cleaning, and sterilization of reusable manual surgical instruments manufactured by Integrum. These instructions should be directly followed. The instructions outlined in this document were developed using standard equipment and practices common to health care facilities. Any questions concerning the care, maintenance, cleaning or sterilization of these instruments should be directed to the following:

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DEFINITIONS

REUSABLE MEDICAL DEVICE: Device intended for repeated use on different patients, with appropriate cleaning and decontamination in between each use.

CONTAMINATION: Soil or debris (e.g., human blood, protein substances, bone chips, tissue).

CLEANING: Removal of contamination (e.g., blood, protein substances or other debris) from medical devices by a manual or mechanical process. Cleaning primarily removes rather than kills microorganisms. Cleaning removes the soil/debris to the extent necessary for further processing.

DECONTAMINATION: According to OSHA, “the use of physical or chemical means to remove, inactivate, or destroy blood-borne pathogens on a surface or item to the point where they are no longer capable of transmitting infectious particles and the surface or item is rendered safe for handling, use, or disposal.” [29 CFR 1910.1030]

PERSONAL PROTECTIVE EQUIPMENT (PPE): Refers to protective clothing, goggles, or other garments or equipment designed to protect the wearer's body from injury due to know hazards (e.g., physical, biohazards, and airborne particulate matter).

UNIVERSAL PRECAUTIONS: Refers to the practice, of avoiding contact with patients' bodily fluids, by means of the wearing of nonporous personal protective equipment (PPE) articles such as medical gloves, goggles, and face shields.

CONTAINMENT DEVICE: A reusable rigid sterilization container, instrument case, cassette, or organizing tray for use in healthcare facilities for the purpose of containing reusable medical devices for sterilization.

STERILIZATION: Validated process used to render a device free from viable microorganisms.

STEAM STERILIZATION: Process that utilizes saturated steam under pressure, for a specific time and temperature to sterilize a product.

WARNINGS

During orthopedic surgery, medical device instruments become contaminated from bone marrow and chips, blood, and tissue. Infection control requires that all contaminated devices be safely and correctly handled by health care workers. It is extremely important that reusable devices are adequately processed according to the instructions outlined in the following sections. The hospital must assume the responsibility for decontamination, cleaning, and sterilization of the reusable instruments.

LIMITATIONS OF REPROCESSING

Repeated reprocessing of reusable medical devices has minimal effect on the instruments. End of life is normally determined by wear and damage due to use.

GENERAL CONSIDERATIONS

SAFETY PRECAUTIONS

Personnel working in the decontamination area must wear personal protective equipment (PPE) designed to protect the worker from hazards related to cleaning contaminated instruments. Follow Occupational Safety & Health Administration (OSHA) and Joint Commission on Accreditation of Healthcare Organizations (JCAHO) recommendations regarding the use PPE (e.g., gloves, gown, face shield, mask, eye protection).

CLEANING

Careful cleaning is a critical process since it removes most contamination and helps to ensure the effectiveness of any microbicidal process that follows. It is critical that all instruments are thoroughly cleaned. If the instruments are not thoroughly cleaned, the device may not be adequately sterilized.

CLEANING AND DISINFECTING SUPPLIES

DETERGENTS

The choice of detergent is important to the cleaning process. The cleaning agent should be a pH neutral enzymatic detergent which is nonabrasive, low foaming and free rinsing. The detergent should be mixed according to the detergent manufacturer's instructions. Some detergents can form precipitates in the presence of hard water, in which case hard-water tolerant cleaning formulations should be used instead (AAMI TIR 12). It is important for the health care facility to choose a detergent that will thoroughly clean the instruments.

ENZYME DETERGENTS

Enzyme detergents are regularly used for difficult to clean orthopedic instruments. If enzyme detergents are used, it is critical that the instruments be thoroughly pre cleaned and that the detergent is used with sufficient water. If the debris is dried on the device, the debris must be rehydrated before the enzymes can be effective.

Each enzyme detergent has an optimal condition in which they must be used and stored. Therefore, cleaning agents should be used and stored according to the detergent manufacturer's instructions.

NON-ENZYME DETERGENTS

Non-enzyme detergents are also used from cleaning medical devices. When choosing a non-enzyme detergent, the composition, pH and manufacturer's directions must be considered. As with enzyme detergents, the cleaning agents should be used according to the detergent manufacturer's instructions.

DETERGENT-DISINFECTANTS

Detergent-disinfectants include both a detergent-type cleaning agent and a chemical disinfectant. This process is usually a multi-step process. While the process does include a disinfectant step, it does not replace the disinfection step in reprocessing. Detergent-disinfectants that include chlorine or chloride as the active ingredient are corrosive to stainless steel and must not be used.

WATER QUALITY FOR CLEANING

The water quality for cleaning should be carefully considered as the quality can influence the effectiveness of the cleaning and the detergent. Salt deposits can form when hard water used during the cleaning process. These deposits can be difficult to remove and may require a specific detergent formulation.

DECONTAMINATION INSTRUCTIONS

POINT OF USE PROCEDURES

Reprocessing of surgical instruments begins at the point of use. After the surgery is completed, contaminated instruments should be separated from waste. Soil should be wiped from the instruments with a towel or sponge moistened with water. Saline solution has a corrosive effect on stainless steel and should not be used. Devices with lumens should be flushed immediately after use to prevent drying of debris. Instruments should be kept moist after use to prevent soil from drying. This may be accomplished by placing the instruments in a basket covered with a towel moistened with water.

TRANSPORTATION TO WORK AREAS

Universal Precautions and hospital policies for handling, containing, and transporting contaminated instruments should be followed while handling and transporting the instruments to the cleaning area. Soiled instruments should not be hand carried to cleaning area. Instruments should be transported in closed containers, covered carts or impermeable bags. If the instruments have sharp edges, a puncture-resistant container should be used.

PREPARATION FOR DECONTAMINATION

Once the contaminated instruments arrive in the cleaning area, they should be removed from the container, sorted, and prepared for cleaning. Instruments should be sorted according to the recommended cleaning procedure into groups as follows:

- One piece or uncomplicated two piece instruments (e.g., Axial Rod, Small T- handle, Clamps)
- Multi-component or instruments that have hard to reach locations (e.g., Large T- Handle, Torque Wrench, Drill Rod, Drills, Thread Taps)

Once sorted, and where applicable, instruments with more than one component should be disassembled in reverse of the assembly instructions outlined in the surgical technique, prior to cleaning.

The following instruments should be disassembled and should be kept together to prevent loss:

- Main Body
- Clamp
- Vertical Rod
- Central Screw Driver
- T-Handles

CLEANING/DISINFECTION/DRYING PROCEDURES

Cleaning instructions are provided in the following table. Both pre-cleaning and the automated cleaning should be performed.

STEP	DESCRIPTION
Pre-Cleaning: Required for instruments with dried-on soil	
Step 1:	Position the instrument under running tap water (<35°C, 113°F) for a minimum of 1 minute. This can be done with a shower gun in a deep sink designed for this purpose. Many proteins cannot be removed with hot water. Therefore, it is critical that the water temperature not exceed 34°C (93°F) (AAMI TIR34).
Step 2:	Remove all visible soil with a clean, soft bristled brush while the instrument is still immersed in water. Manipulate and actuate instruments and all moveable parts while the instrument is under the running water. Flush challenging areas, with minimum 60mL, such as lumens and mating surfaces, with syringe and use a lumen brush to remove soil. Ensure that running water passes through the cannulation and that holes are filled and emptied.
Step 3:	Transfer instrument to washer for processing. When placing instrument in washer, ensure that all devices/features are accessible to cleaning.
Automatic Washing Cycle	
Step 4:	Run automatic wash cycle, set to high, with minimum cycle parameters as follows. • Cold tap water prewash for 2 minutes • Hot tap water enzyme wash for 1 minute • Detergent wash at 66°C (151°F) for 2 minutes • Rinse at 60°C (140°F) for 30 seconds • Critical Water (per AAMI TIR34) Rinse at 66°C (151°F) for 30 seconds
Step 5:	Remove instruments from washer and dry with a clean, lint-free cloth.
Step 6:	Visually inspect instruments to ensure that all visible soil has been removed. If soil is visible, repeat cleaning procedure.

INSPECTION, TESTING AND MAINTENANCE

After cleaning, the instrument should be inspected for damage (e.g., pitting, corrosion, major deformation), wear and functionality. Locking mechanisms and mating parts should be checked to ensure fit and function. Instruments with cutting elements should be examined for large nicks or distortion of edges. The instrument should be disposed of and replaced if they do not lock/mate correctly, or if there any corrosion, discoloration, deep cracks or notches are noted.

STERILIZATION PROCEDURES

WARNINGS

It is the responsibility of the health care facility to ensure that the recommended sterilization process is followed correctly and to verify the sterilization equipment achieves the recommended parameters.

PREPARATION FOR STERILIZATION

Prior to sterilization of the device, all original packaging and labelling inserts should be removed. Reusable instruments should be placed in suitable FDA-cleared packaging for the sterilization process (e.g., pouch, tray) and sterilized prior to surgical use. Containment trays should be wrapped with an FDA-cleared wrap or placed in an FDA-cleared reusable rigid container for sterilization. All sterilization wraps may not be cleared for all cycle types. Check with the wrap manufacturer for information on which cycles the wrap can be used with.

RECOMMENDED STERILIZATION PARAMETERS

The reusable instruments should be placed in a sterilization container using single use filters and sterilized using the following recommended dynamic-air-removal (pre-vacuum) sterilization cycle times and parameters:

- Temperature: 132°C (270°F)
- Exposure Time: 4 minutes
- Drying Time: 20 minutes

REASSEMBLY

Instruments that were disassembled should not be reassembled until the time of surgery.

STORAGE

Instruments should be stored appropriately to eliminate recontamination before reuse.

REFERENCES

AAMI TIR 12:2010, *"Designing, testing, and labeling reusable medical devices for reprocessing in health care facilities: A guide for medical device manufacturers."*

AAMI TIR 30: 2003, *"A compendium of processes, materials, test methods, and acceptance criteria for cleaning reusable medical devices."*

ANSI/AAMI ST79: 2010 and A1:2010, *"Comprehensive guide to steam sterilization and sterility assurance in health care facilities."*

AAMI TIR34:2014/(R)2017, *"Water for the reprocessing of medical devices."*

ISO 17664: 2004, *"Sterilization of medical devices —Information to be provided by the manufacturer for the processing of resterilizable medical devices."*

FDA 1996 Guidance, *"Labeling Reusable Medical Devices for Reprocessing in Health Care Facilities: FDA Reviewer Guidance."*

CONTACT INFORMATION

Please contact Integrum at the following phone number to request additional information on the device, including questions on infection control procedures, if needed.

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