Clinical Investigation Plan

Title:	A prospective, non-randomized, consecutive series, multicentre, observational study to evaluate the clinical outcome of ceramic-on-ceramic hip resurfacing arthroplasty using the ceramic, non-porous, non-cemented H1 Hip Resurfacing Arthroplasty
Short title:	H1 Hip Resurfacing Arthroplasty
Investigational device:	H1 Hip Resurfacing Arthroplasty
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Ethics approval date:	12th September 2017
Ethics reference number:	17/EE/0330

Sponsor:

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This Clinical Investigation is financed by Embody Orthopaedic Limited and managed by Imperial College London. The relationship between the parties is governed by the agreement dated 25 September 2017.

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Insurance Details

Type: Clinical Trials Insurance
Insurance Provider: Chubb European Group Limited
Policy Number: UKLSCD01988

Use of this Protocol

This protocol describes the H1 Hip Resurfacing study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version.

Problems relating to this trial should be referred, in the first instance, to the Investigation Manager.

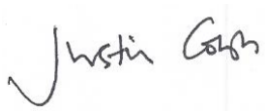
Statement of Compliance

This clinical investigation complies to EN ISO 14155:2011 [1] and shall adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.

This clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki [2] and local regulations of participating countries.

This clinical investigation shall not commence until Ethics Committee and MHRA approval of the protocol and informed consent have been obtained. Any additional requirements imposed by the Ethics Committee or MHRA shall be followed.

Study risks will be covered by a no-fault insurance policy taken out by the sponsor, Embody Orthopaedic Limited.

Role	***Name***	***Date***	***Signature***
Chief Investigator	Prof Justin Cobb	02 October 2020	

Contents

1 Clinical Investigation Synopsis

Investigation type

Premarket study to receive a CE marking, followed by post-marketing surveillance follow-up

Investigation design

Multi-centre, prospective, non-randomized, observational study

Investigation objectives

The *primary objective* is to confirm the **safety** and **efficacy** of the H1 hip resurfacing prosthesis by demonstrating non-inferiority of the cumulative percent success in subjects implanted with the H1 hip resurfacing compared to a literature reference rate of the Birmingham hip resurfacing (BHR).

The *secondary objective* is to demonstrate superiority of the ceramic-on-ceramic H1 hip resurfacing prosthesis with its metal-free articulation compared to MoM hip resurfacing in the absence of metal ion release. Additional goals are to demonstrate non-inferiority of the ceramic-on-ceramic H1 hip resurfacing prosthesis compared to hip resurfacing with regard to patient reported outcome measures, objective clinical and functional outcomes, and radiological assessment.

Primary Endpoint

- Revision for any reason

Secondary Endpoints

- Complication rate (adverse events and revisions)
- Toxicology (blood metal ion measurements)
- CT assessment (Implant migration)
- Patient Reported Outcome Measures (PROMs)
- Objective clinical and functional outcomes (Harris Hip Score, Gait Analysis)
- Radiological assessment (implant orientation, osseointegration)

Inclusion criteria

- Patient requires primary hip arthroplasty due to degenerative joint disease (primary osteoarthritis, posttraumatic osteoarthritis, avascular necrosis, developmental hip dysplasia)
- Patients femoral bone stock is adequate for hip resurfacing on plain radiographs
- Patient is between 18 and 70 years old
- Patient willing to comply with study requirements
- Patient plans to be available through ten (10) years postoperative follow-up
- Patient is able to understand the native language of the country where their procedure is taking place

Exclusion Criteria

- Patient has a BMI greater than 40
- Patient suffers from an active inflammatory joint disorder
- Patient has an active infection or sepsis (treated or untreated)
- Patient has insufficient bone stock at the hip (>1/3 necrosis of the femoral head)
- Patient has severe osteopenia or osteoporosis, defined using DXA by T-score of <-2.5 (if T-score does not meet the criteria, please confirm with coordinating site (ICL) for participant eligibility)
- Patient has large and multiple cysts in the femoral head (patients with cysts to be reviewed by coordinating site (ICL) for participant eligibility)
- At the time of enrolment, patient has one or more of the following arthroplasties that have been implanted less than 6 months before the current hip arthroplasty:
    - Contralateral primary total hip arthroplasty or hip resurfacing arthroplasty
    - Ipsilateral or contralateral primary total knee or unicondylar knee arthroplasty
- Patient takes medications which potentially affect the bone such as corticosteroids and antimitotic medications.
- Patient has a condition that may interfere with the hip arthroplasty survival or outcome (i.e., Paget's or Charcot's disease, vascular insufficiency, muscular atrophy, uncontrolled diabetes, moderate to severe renal insufficiency or neuromuscular disease)
- Patient has a known alcohol or drug abuse
- Patient has an immunosuppressive disorder
- Patient has a malignant tumour, metastatic, or neoplastic disease
- Patient has severe comorbidities or a limited life expectancy
- Patient lacks capacity to consent
- Patient has an emotional or neurological condition that would pre-empt his/her ability or willingness to participate in the study
- Patient is not willing or able to sign an informed consent form
- Patient pregnant or breast feeding
- Patient is not able or willing to come to follow-up visits
- Any other clinical reason, which the investigator considers would make the patient unsuitable for the trial
- Implant size unavailable

Length of investigation

10 years from the date of surgery.

Investigation population

250 cases

2 Data Collection Overview

Please refer to Figure 1 to Figure 3 for a flow diagram explanations of the clinical investigation plan for Cohort 1A, Cohort 1B and Cohort 2.

Figure 1. Clinical Investigation Flow diagram Cohort 1A

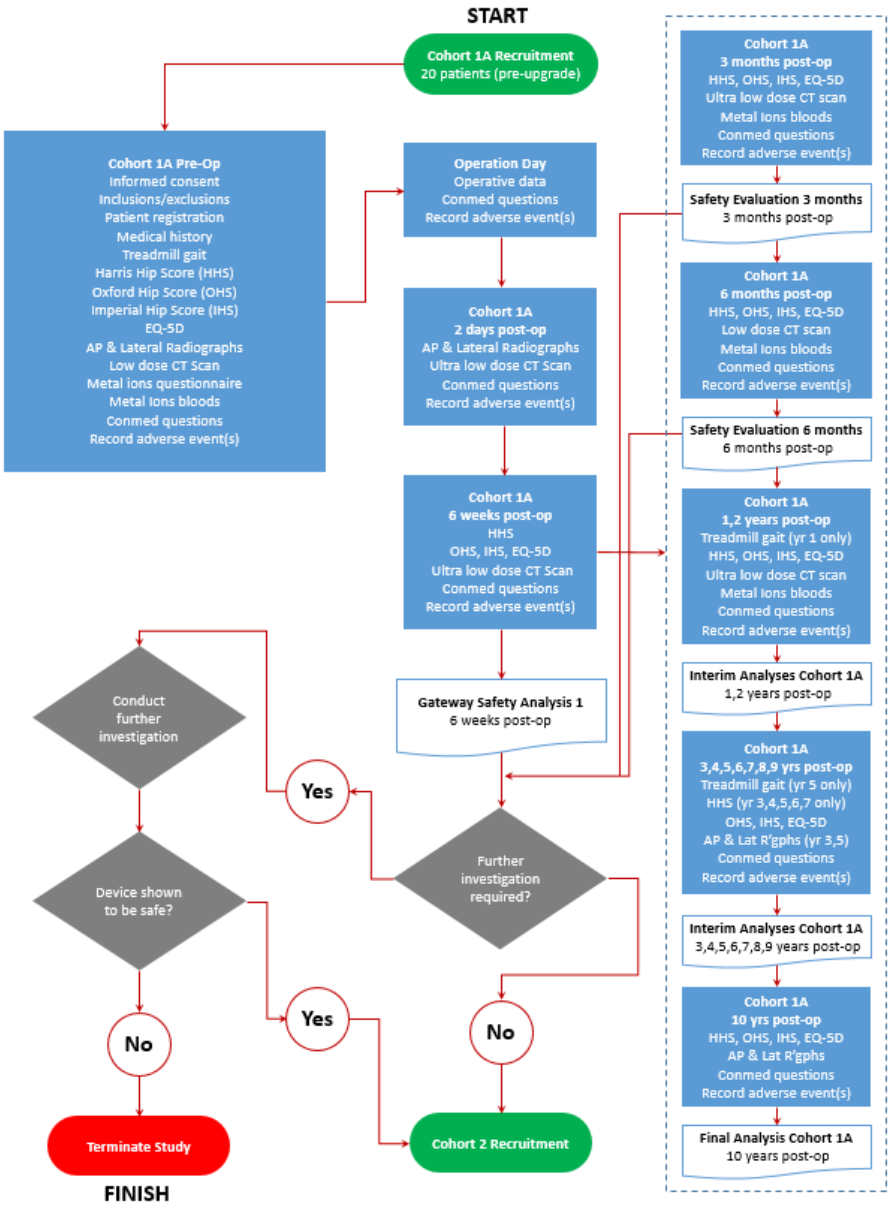


Figure 2. Clinical Investigation Flow diagram Cohort 1B

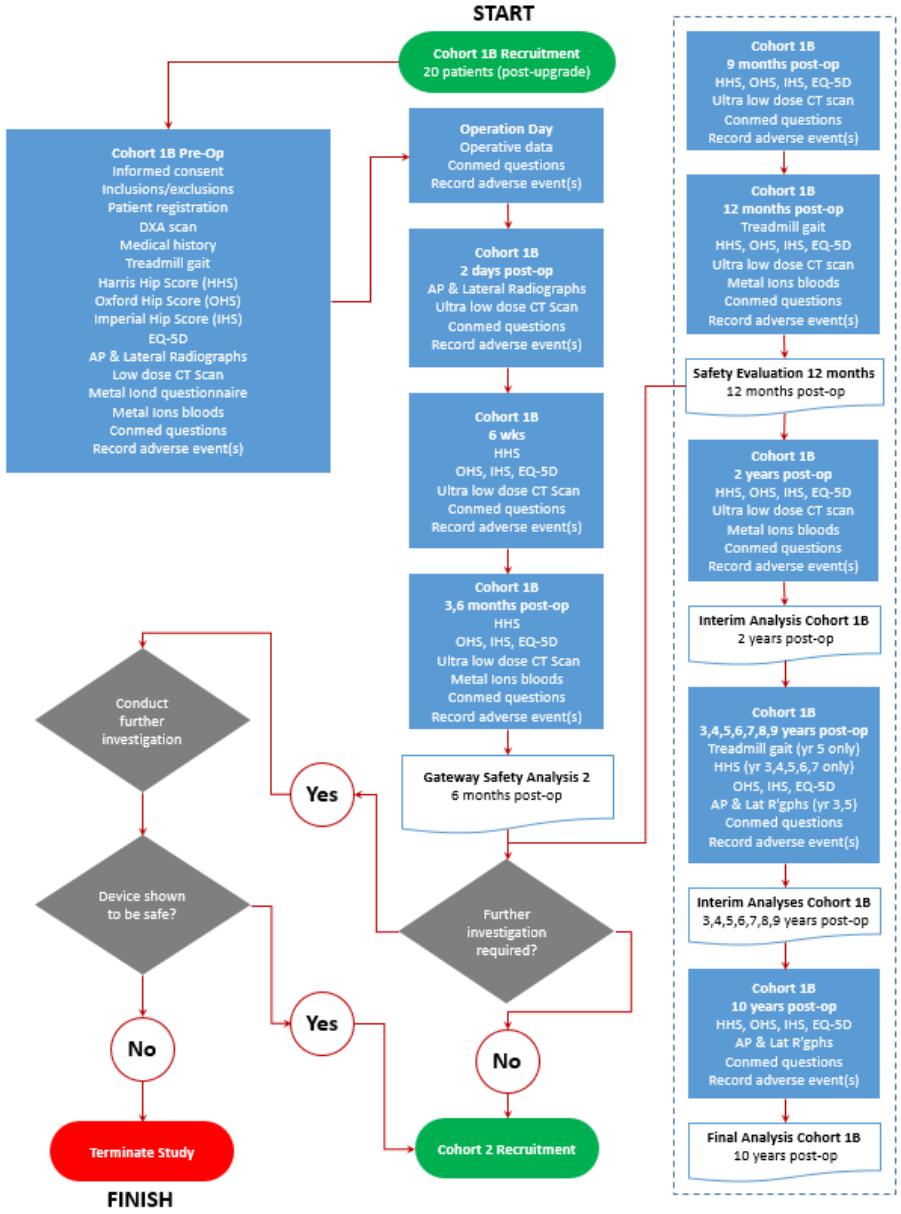
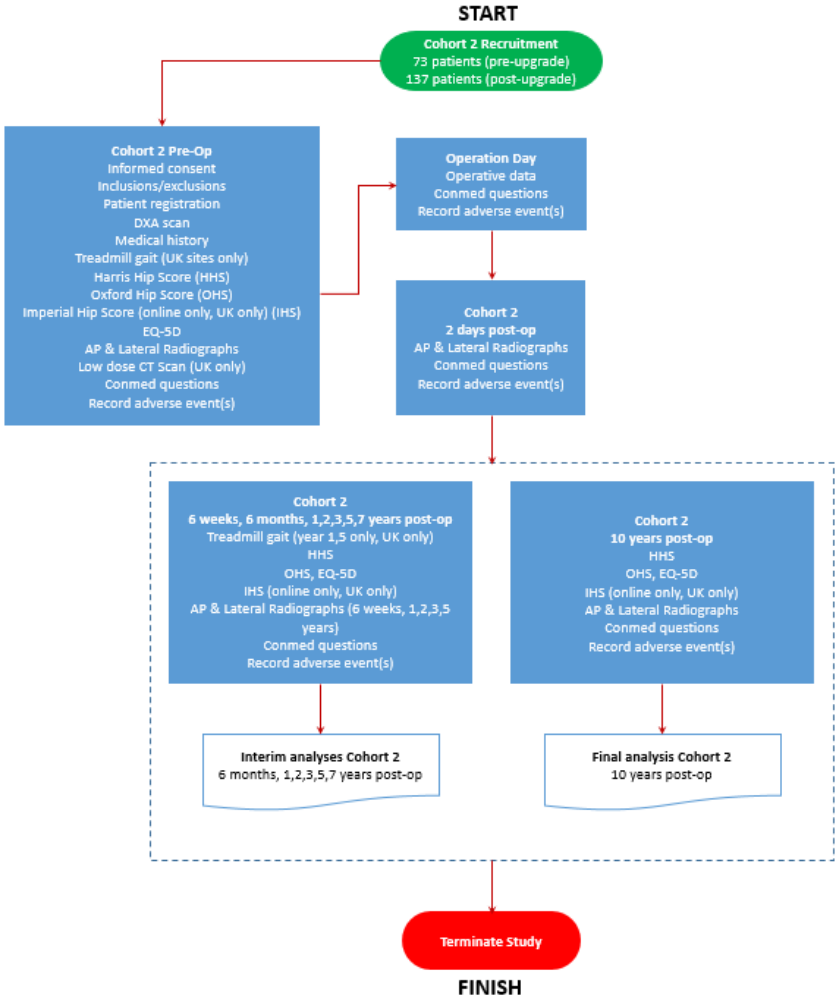


Figure 3. Clinical Investigation Flow diagram Cohort 2



PART A: THE DEVICE

3 Introduction and Purpose

Total Hip Arthroplasty (THA) is one of the most successful surgical interventions. Replacement of an arthritic hip joint provides significant pain relief and improvement of hip function and mobility [4]. Patients, even elderly people, are more active, have a better quality of life, less comorbidities and a longer life expectancy [5]. The World Health Organisation (WHO) has declared THA the second best intervention, only preceded by cataract surgery, regarding cost effectiveness and quality of outcome [4]. In patients older than 70 years, the overall survivorship of THA is more than 90% at 10 years and the best clinical results are obtained for THA as a treatment for osteoarthritis (OA). In this patient population, THA can thus be considered a lifelong solution. However, both survivorship and clinical results are much worse in young and active people [6]. The reasons for this worse outcome are multiple. First of all, younger people usually have a more active lifestyle regarding work and sports [7]. Secondly, the hip disorders leading to THA in a younger patient population are more difficult to treat. Congenital hip dysplasia is frequently associated with gross hip deformities, as may be the case in secondary traumatic OA. Bone stock may be jeopardised in cases of avascular necrosis of the femoral head (AVN) and rheumatoid arthritis (RA). Thirdly, a faster bone metabolism may play a role, but this remains to be elucidated[3].

Modern hip resurfacing arthroplasty (HRA) was introduced to address the inferior survivorship and unsatisfactory clinical results with THA in young and active patients [5, 7]. The anatomical reconstruction of the joint has the potential to provide a better function and higher activity levels compared to THA [7]. Hip resurfacings are inherently higher performing than total hip replacements because they preserve the flexibility of native femoral head and neck. Metal-on-Metal (MoM) hip resurfacings have been shown to be safe and effective in many patients [8-11]. These patients have superior clinical function over patients with total hip replacements, with little or no wear at the bearing surface in comparison to hard on soft bearings [12]. The two most serious complications following hip surgery are death and infection. Both of these are substantially rarer after hip resurfacing when compared to patients with a cemented total hip arthroplasty [13, 14], which is often presented as the gold standard of hip replacement [15]. However, patients with poorly positioned hip resurfacing implants, poorly designed implants and smaller sizes especially in females have reported progressive pain leading to early revision [3, 16, 17]. This pain is commonly caused by one of two problems: either metal ion particles generated by excessive wear associated with adverse soft tissue reactions to metal debris [18] or soft tissue impingement on the hard metal edges of the components. Despite these two problems, hip registries continue to show superior survivorship of hip resurfacing using a well-designed device in young and active males when compared to total hip arthroplasty [15, 19].

Higher metal ion levels have been found in whole blood, serum and urine of patients with MoM hip arthroplasties (THA and HRA) compared to preoperative values, and to THA with other bearing surfaces (metal-on-polyethylene, ceramic-on-polyethylene, ceramic-on-ceramic) [20]. Although MoM hip arthroplasty has been shown to produce less volumetric wear compared to metal-on-polyethylene, the wear debris consists of more numerous, small, nanometre size particles, which are ingested by macrophages [21]. Contrary to polyethylene, metal particles and ions are not chemically inert but may have directly toxic, biological effects and may elicit hypersensitivity reactions in addition to the macrophage-driven, innate, foreign-body immune responses to particulate debris of any material. Consequently, concerns have been raised about the physiological consequences of metal release from MoM hip prostheses into the peri-prosthetic tissue and systemic circulation [7].

By exchanging the metal material of the bearing with BIOLOX®*delta* ceramic, a better wearing and more inert material [22], the positive clinical performance aspects of MoM hip resurfacings are retained, while the main cause of early revision is removed. The anatomic shape of the contours of the devices may go some way to reducing the pain caused by soft tissue erosion, Thus, the H1 ceramic-on-ceramic hip resurfacing could be used for wider indications than the currently restricted group of large men. Patients with smaller head sizes, females and patients with metal sensitivity may all be candidates, enabling them the option to have a more conservative operation if appropriate.

The H1 hip resurfacing design is innovative both in its anatomical shape and in the bearing couple materials as there is currently no all-ceramic bearing hip resurfacing implant in clinical use. Ceramic-on-ceramic THA has a proven track record with excellent survivorship results in the arthroplasty registries [19, 23] as well as low complication

rates and good functional results from large clinical series [24]. The materials have been thoroughly tested regarding biocompatibility, biomechanical and tribological characteristics [22], and have been used in over one million clinical cases over the last 11 years, confirming safety of the material [19, 23]. However, a mono-block ceramic acetabular component without a metal shell such as the H1 hip has not yet been used clinically. The concept requires investigation before it can be CE marked and marketed in Europe.

The anatomical contoured edge of both the cup and the head may reduce the incidence of psoas impingement. The psoas (or iliopsoas to give its full name) tendon is stretched over the femoral head when the hip is extended. In the normal hip, the tendon runs over the front edge of the acetabulum, and femoral head, which it uses as a fulcrum giving some leverage advantage as the muscle contracts to lift the leg up when bringing the leg up into the bath or into a high car for instance. When the femoral head is resurfaced, the tendon may rub over the hard edge of the resurfacing device. Until now, femoral resurfacing devices have had a symmetric rim, which tends to extend beyond the normal limits of a femoral head, particularly in female hips. This overhang can cause painful abrasion of the tendon. Most acetabular components are also symmetric in shape, unlike the natural acetabular rim contour, which has a recess where the tendon runs. The rim of the acetabular shell can also be a cause of tendon irritation.

BIOLOX®*delta* is a zirconia toughened alumina (ZTA). Along with alumina (Al) and zirconia (Zr), this material also contains traces of chromium (Cr), strontium (Sr) and very low amounts of yttrium (Y). This ceramic has an 11-year history of worldwide use in hip arthroplasty, with an excellent track record. Ceramic-on-ceramic bearings consist of the hardest material with the lowest wear rate of all bearing couples used in hip arthroplasty [22]. The very low volume of inert ceramic nanoparticles and the absence of elevated Cobalt (Co) and Cr ion levels in the bloodstream [20] virtually abolishes the risk of adverse local tissue reactions (ALTR), allergic reactions and systemic cobalt toxicity which can complicate some MoM Hip replacements. BIOLOX®*delta* contains very small amounts of Cr, but Cr release from the material remains below the detection limit in the blood [25]. Strontium ions are found in the blood of control patients without any implant and remain at similar background level in patients with BIOLOX®*delta* ceramic implants [25], Yttrium ions are not detected [25].

BIOLOX®*delta* is a zirconia-toughened alumina ceramic with increased fracture strengths. The use of BIOLOX®*delta* has virtually eliminated the already low fracture risk of the older ceramic implants [19, 22, 23]. The fracture risk in the arthroplasty registries and as assessed by the manufacturer CeramTec is now estimated at < 0.001%.

Besides a significantly lower risk of mortality with hip resurfacing compared to conventional cemented total hip arthroplasty (THA), the use of BIOLOX®*delta* ceramic on ceramic bearings further reduces the risk of the most devastating complication associated with THA, i.e. periprosthetic infection . Because of a significant reduction in biofilm formation and adherence to ceramic surfaces (69%) compared to metal (92%) and highly cross-linked polyethylene (HXL PE) (100%), the risk of periprosthetic infection is significantly reduced, to <0.5% at 10 years compared to >1% with polyethylene bearings including HXL PE [19, 23, 26].

The uncemented fixation of the H1 hip resurfacing is not novel. The rough coating of plasma sprayed titanium and hydroxyapatite has been applied by a leading implant coating specialist (Medicoat AG, Mägenwil, Switzerland). Acetabular cups using these coatings are now standard products with more than 15 years of experience [19, 23]. Several metal-on-metal hip resurfacing designs for non-cemented use, have successfully been implanted in large series of patients [27, 28]. Ti ions may be released as part of the bone ongrowth process of the non-cemented hip of knee prosthesis [29], but Ti_ions from Titanium dioxide (TiO_2) coatings or Titanium-aluminum-vanadium (TiAlV) hip or knee arthroplasty components are not associated with toxic, teratogenic or carcinogenic reactions [30].

3.1 Femoral Crush Fractures

A high prevalence of femoral crush-fractures were observed in Cohorts 1A and 2. Cohort 1A was followed up as per Figure 1 and recruitment of Cohort 2 commenced after the gateway safety analysis. The gateway safety analysis did not indicate any safety issues, but the 6 month safety data showed unexplained movement of the femoral head. As per procedure, recruitment for Cohort 2 was suspended and an investigation was launched in to the observed movement. The movement was found to be as a result of a femoral crush fracture. A thorough investigation was undertaken which concluded that

the root cause of the fracture was surgical technique, in particular post-operative femoral head centre. Upgrades have been made to the instrumented technique to eliminate these errors and the contoured rim of the implant has been modified to be more forgiving to implant placement error. A full report of the investigation is available on request.

4 Investigational Device Information

4.1 Manufacturer

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4.2 Name of the device

H1 Hip Resurfacing Arthroplasty (HRA)

4.3 Summary

The H1 HRA is a monoblock ceramic hip resurfacing device with a rough titanium and hydroxyapatite (HA) coating (Figure 4). The ceramic is BIOLOX®*delta*. Both the ceramic and coatings are known to be clinically safe and perform well within the body. A range of non-clinical tests has been conducted in preparation for clinical investigation of the H1. The test results demonstrate that the H1 meets its design requirements and is compliant with the relevant standards.

There are four features of the H1 that have been evaluated for clinical precedence (see the Clinical Evaluation for full details [31]):

1. Bone conserving hip resurfacing concept;
2. Ceramic-on-ceramic bearing;
3. Rough fixation surface;
4. Contoured edge profile.

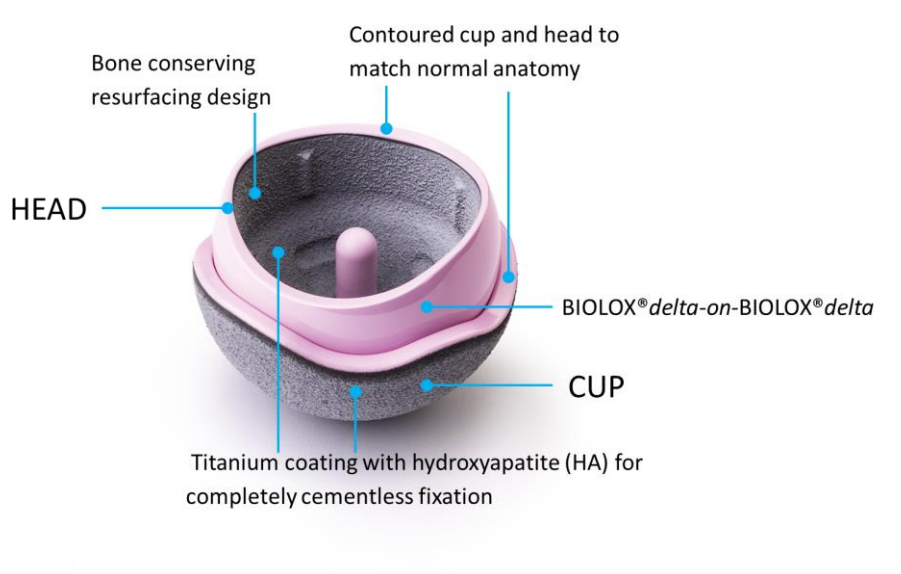

Figure 4. The H1

Each of these features is supported by clinical data, but the novelty of the H1 is that all four features are incorporated into a single device.

Full details of the device, including its manufacturing processes, pre-clinical testing results and biological evaluation summary can be found in the Investigator Brochure [32].

4.4 Traceability

Throughout the clinical investigation and beyond into general use, the product will be fully traceable via unique batch and LOT codes, specific to the trial, which will be laser engraved onto each component. Stickers from each product label will be removed during surgery and affixed to each patient's case report form (CRF) so that there is traceability between each patient and their device's manufacturing route.

4.5 Purpose of the device and intended population

The H1 HRA is a sterile implantable artificial substitute for a disease-damaged hip joint intended to replace the articulating surfaces of the hip while preserving the natural femoral head and neck. It consists of a cementless ceramic femoral head component, that is placed over (resurfaces) a surgically prepared femoral head, and a cementless ceramic acetabular component that is placed into a surgically prepared acetabulum. This device is typically used to replace parts of the hip damaged by degenerative joint diseases (e.g., arthritis, avascular necrosis) and is commonly used for younger/active patients to avoid total hip replacements.

4.6 Materials

The H1 resurfacing implant comprises the following materials:

- BIOLOX®*delta* – ceramic head and cup
- Rough titanium coating – primary coating on ceramic
- Hydroxyapatite coating – secondary coating for implant-bone interface

For full details of the materials characterisation, please refer to the Investigator Brochure [32].

4.7 Surgeon Training

Surgeons selected to participate in this clinical investigation have longstanding experience with hip resurfacing implants and their implantation. Only surgeons who have received appropriate training and are familiar with the implant components, instruments, procedure, clinical applications, adverse events, and risks associated with the H1 Hip Resurfacing will implant this device.

4.8 Surgical Technique

All study related hip replacement procedures for the H1 hip resurfacing will be performed according to state-of-the art hip resurfacing surgical technique as performed by experienced hip resurfacing surgeons, who will be the investigators in this study. The full surgical technique can be found in document *HRAinst-TD-00023 H1 Surgical Technique*. Cohort 1A and Cohort 1B will have tantalum markers implanted in the surrounding bone.

5 Justification for Clinical Investigation

5.1 Pre-clinical assessment

A risk-based approach was taken to define design and manufacturing requirements of the H1 by identifying and mitigating the unacceptable risks. The test plan was developed and conducted to verify the design and manufacturing requirements. Where possible, standardised tests were used. Where no standard tests were available, literature-supported protocols and in-house developed test methods were used.

Test results are provided in support of the H1 in the Investigator Brochure [32], including information relating to integrity, wear and bearing friction, coating adhesion and characterisation, stability, sterilisation and shelf life. The test results demonstrate that the H1 system meets its user and technical requirement specifications and conforms to the Essential Requirements of the Medical Devices Directive.

5.2 Clinical data evaluation

The intended application of the H1 resurfacing device is to replace the diseased areas of the articular surface and restore joint function. To this end, the H1 resurfacing device must not be inferior in overall safety or performance to an existing joint replacement options, these being:

- Conventional total hip replacement
- Hip resurfacing (Birmingham Hip Replacement (BHR) – a device with a 10A ODEP rating).

Clinical safety and performance in relation to the above devices were analysed through appraisal of literature data pertaining to the following device characteristics:

- Hip resurfacing implant configuration
- Ceramic-on-ceramic (CoC) bearing
- Non-planar rim profiles
- Cementless vacuum-plasma sprayed (VPS) coatings

Clinical evidence supports conformity with the essential requirements and establishes both the performance and safety of the design of the H1 Hip Resurfacing. The strength of evidence, however, requires further consideration. Clinical evidence is considered stronger when there is either a relationship between all varying implant types within a category, which could easily be extended to include the H1 (e.g. reduced risk of dislocation in hip resurfacing) or when an exact match is provided (e.g. clinically proven Biolox®*delta*).

6 Risks and benefits

The development of the H1 HRA has been carried out under the risk management process described by ISO 14971 [33].

6.1 Anticipated clinical benefits

6.1.1 Advantages of hip resurfacing in contrast to THR

Total hip replacement (THR) is the gold standard for treatment of arthritis of the hip joint and has been described as "the operation of the century". THR is not always successful, however, and there are potential benefits an all-ceramic hip resurfacing procedure offers over the total procedure:

- Lower risk of dislocation
- No femoral canal invasion
- Conservation of bone stock
- Reduced stress shielding
- Higher activity levels
- Potentially Higher ROM
- Treatment of peri-prosthetic fracture
- No risk of liner fracture
- Potentially lower rate of infection
- Lower wear

6.1.2 Advantages of the H1 in contrast to the Birmingham Hip Resurfacing

The 'safe use' of the Birmingham Hip Resurfacing (BHR) was chosen as a comparator for the H1 device. In a certain cohort of patients (relatively younger, more active men with larger diameter femoral heads), the BHR has performed well and presents a suitable clinical benchmark for the H1 device. The H1 presents the following potential benefits over the BHR:

- Fully cementless
- Metal free articulation
- Lower femoral stress-shielding
- Lower risk of dislocation
- Lower risk of infection
- Reduced psoas impingement
- Easier revision
- Better follow-up imaging

For a full description of these benefits, please refer to the Risk Management Report [34].

6.1.3 Participation in the clinical investigation

There is no additional clinical benefit associated with participating in this study. However, the information gained from this study may help improve the treatment of people who require hip surgery in the future. Although as yet unproven, it is anticipated that non-cemented H1 hip resurfacing arthroplasty will be associated with less surgery, fewer device-related adverse events and improved mortality in comparison to cemented total hip arthroplasty [12].

6.2 Residual risks identified

Risk control measures have been put into place for every risk that was identified during the risk assessment process. All residual risks are considered and are reported in the Instructions for Use [35]. All residual risks are below the clinical benchmark derived in the Risk Management Plan [36]. It is essential, however, to control risks as far as possible, beyond the benchmark if feasible. As such the highest residual risks which are reported in the Clinical Evaluation Report [31] are analysed to see if further control is possible.

6.2.1 Anticipated adverse device effects

Anticipated adverse device effects are those associated with surgical implantation. The H1 hip resurfacing has been designed and manufactured to comply with the Essential Requirements of the Medical Devices Directive. The H1 device will be implanted by experienced surgeons with a device specific instrument set. Nevertheless, possible risks remain. Adverse device effects include:

- Pain
- Reduced Function (including squeaking)
- Fracture (Implant fracture, femoral fracture, explantation related fracture)
- Implant loosening

These risk categories also reflect the clinically highlighted safety risks from the clinical evaluation report. The clinical outcomes, which do not feature on these risk categories, are:

- Dislocation: the probability of occurrence of dislocation is extremely low
- Metallosis: the probability of occurrence of metallosis is extremely low

6.2.2 Risks associated with participation in the clinical investigation

As the surgery undertaken in this study is the same as that which a patient not partaking in this study would receive, the risks of participation are those associated with hip replacement surgery and anaesthesia:

- Adverse events associated with anaesthesia (cardiac, pulmonary, neurological, gastrointestinal, urinary)
- Bleeding, haematoma, wound suture dehiscence
- Superficial or deep infection of the wound or hip joint
- Deep vein thrombosis
- Transient nerve palsy
- Mortality

6.2.2.1 Possible interactions with concomitant medical treatments

There are no foreseen possible interactions with concomitant medical treatments.

6.3 Risk mitigation

Risk control measures have been verified through pre-clinical testing of the H1 device and risks have been reduced as far as possible, using the following techniques in the order in which they are presented:

1. Inherent safety by design;
2. Protective measures in the medical device itself or in the manufacturing process;
3. Information for safety (labelling, instructions for use (IFU), etc.);

Wherever possible risks have been mitigated through the design of the device.

6.4 Overall risk benefit profile of the H1 device

The H1 device has been designed for reducing pain and restoring function to patients with arthritis of the hip. The potential benefits of the H1 device in comparison to the THR and the gold standard metal-on-metal hip resurfacing (The Birmingham Hip Resurfacing – BHR) clearly out-weigh the residual risks in quantity. There are no 'high' residual risks, which have not been accounted for in the clinical evaluation. By weighing the clinically evidenced risks against the clinically evidenced benefits, it is clear that the H1 has the potential to provide a superior solution to both THR and BHR, assuming that the patient indications are correct. The risk benefit profile of the H1 HRA has been presented based on clinical evaluation and design verification. Further clinical data may be required to fully verify the design. In its current status the benefits of the H1 hip resurfacing outweigh the risks.

For the full risk management process, and a deeper discussion of the risk-benefit analysis, please refer to the Risk Management Plan and the Risk Management Report [34, 36].

PART B: INVESTIGATION DESIGN

7 Investigation Objectives and Hypotheses

7.1 Objectives

The investigational device – the H1 HRA – is a cementless ceramic-on-ceramic hip resurfacing arthroplasty. It meets all the Essential Requirements of the Medical Devices Directive, with the exception of clinical data to support its design. The principles of ceramic-on-ceramic hip replacement, hip resurfacing and cementless fixation in joint replacement have been proven in many long-term studies.

Therefore, this clinical investigation is being conducted to verify the short-, mid- and long-term **safety** and **efficacy** of the H1 HRA, in relation to its design features.

7.1.1 Primary Objective – Safety and Efficacy Study

The *primary objective* is to confirm the **safety** and **efficacy** of the H1 hip resurfacing prosthesis by demonstrating non-inferiority of the cumulative percent success in subjects implanted with the H1 hip resurfacing compared to a literature reference rate of 98.6% cumulative survivorship without revision for any reason of the Birmingham hip resurfacing (BHR) at 1 year, 97.6% survivorship at 3 years, 96.5% survivorship at 5 years and 93% cumulative survivorship at 10 years (Australian Joint Registry AOAAJR annual report 2015)[19].

7.1.2 Secondary Objectives

Preliminary Safety Study

In the first cohort of 20 patients (Cohort 1A), the **safety** of the H1 device will be determined via assessment of complication rate, toxicology and CT assessment. The *secondary objective* is to demonstrate superiority of the ceramic-on-ceramic H1 hip resurfacing prosthesis with its metal-free articulation compared to MoM hip resurfacing in the absence of metal ion release.

Second Safety Study

In a second cohort of 46 patients (Cohort 1B), the **safety** of the H1 device will be determined via assessment of complication rate, toxicology (first 14 patients only) and CT assessment. The *secondary objective* is to demonstrate superiority of the ceramic-on-ceramic H1 hip resurfacing prosthesis with its metal-free articulation compared to MoM hip resurfacing in the absence of metal ion release.

Safety and Efficacy Study

Additional goals are to demonstrate non-inferiority of the ceramic-on-ceramic H1 hip resurfacing prosthesis compared to hip resurfacing and total hip arthroplasty with regard to patient reported outcome measures, objective clinical and functional outcomes, and radiological assessment at each follow up visit.

Data collected during this study may also be used for other orthopaedic research into the genesis of disease and the effectiveness of treatment in the MSk Lab at Imperial College London. The investigation subjects will be split into two cohorts.

7.2 Hypotheses

It is hypothesised that:

1. The H1 will demonstrate non-inferiority in terms of survivorship compared to the BHR
2. The H1 will be demonstrated to be superior in terms of toxicology compared to the BHR

Please refer to Section 10 for more details regarding the null hypotheses and sample size calculations.

7.3 Outcome Measures

7.3.1 Preliminary Safety Study Outcome Measures (Cohort 1A)

- Complication rate (adverse events and revisions)
- Toxicology (blood metal ion measurements)
- CT assessment (Implant migration, osseointegration)

7.3.2 Second Safety Study Outcome Measures (Cohort 1B)

- Complication rate (adverse events and revisions)
- Toxicology (blood metal ion measurements)
- CT assessment (Implant migration, osseointegration)

7.3.3 Safety and Efficacy Study Outcome Measures (Cohort 1A, 1B, 2)

- Implant survivorship
- Patient Reported Outcome Measures (PROMs)
- Objective clinical and functional outcomes (Harris Hip Score, Gait Analysis)
- Radiological assessment (implant orientation, osseointegration)

8 Investigation Design and Endpoints

8.1 General

8.1.1 Type of investigation

This is a multi-centre, prospective, non-randomized, observational study to evaluate the clinical outcome of the H1 hip resurfacing implant.

In order to evaluate the safety of the new device, the study will be subdivided in a short-term safety study and a long-term safety and efficacy study. The safety study (Cohort 1A – 20 patients) will record complication rate, toxicology and radiological assessment. Cohort 2 will consist of the remaining patients due to undergo a primary hip arthroplasty. Owing to the observation of femoral crush fractures in the first cases undertaken, a second safety cohort will be undertaken - Cohort 1B. Cohort 1B will consist of a further 46 patients.

The data from the study will also be used to compile a report for submission to the manufacturer's notified body in order to obtain a CE marking for the H1 HRA. If the H1 receives a CE mark at this stage, an amendment will be placed to the main REC and the competent authority in order to continue with the study as a post-market surveillance of a CE Marked device as per assessments listed in the schedule of procedures. If the CE marking is not obtained at that point, the study will continue as per protocol.

See the flow diagrams in Figure 1 to Figure 3 for a graphical explanation of the investigation plan.

8.1.2 Investigation bias

Improper Influence

The sponsor and all investigators shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation.

Patient recruitment and screening

To eliminate the potential for selection bias, investigators will consecutively screen all their patients who could be eligible for an H1 HRA. Patients meeting the eligibility criteria will be approached for informed consent and subsequent enrolment in the investigation. Screening efforts must be documented on a screening and enrolment log, on which reasons for exclusion from or denial to participate should be noted.

Participants suitable for hip resurfacing arthroplasty will be identified from the clinic list and theatre waiting list. Those patients meeting the inclusion/exclusion criteria will be given the option to take part. All participants will be given both verbal and written explanation of the study by an appropriately experienced and informed clinician. No pressure will be placed on participants, nor time pressure imposed to make a quick decision. A minimum of twenty-four-hours will be required before decision to participate will be accepted. The patient will be given the opportunity to ask questions and highlight any concerns they may have. Patients will be told they are free withdraw at any time. If participants wish to take part, they will be asked to sign the study informed consent form.

Women of child-bearing age will be asked about their method of anticonception, which will be noted in the Conmed section prior to inclusion in the study and prior to every imaging (X-ray or CT scan) as usual. If a female participant does become pregnant during the study, imaging will be postponed until after the childbirth but questionnaires will be performed as planned.

Independent assessor

At each participating site, an independent assessor will be assigned for the study-related clinical and radiological follow-up of the patients included into the study to avoid bias. The independent assessor should not be the surgeon who performed the total hip arthroplasty but another surgeon, physician, research nurse or research assistant properly trained in the clinical follow-up of the patients and the correct completion of the Case Report Forms. The official independent assessor will be assigned on the delegation log at each study site.

Safety analysis of Cohort 1A and Cohort 1B (first 14 patients only) will be reviewed by independent assessors from the Karolinska Institute in Stockholm, Sweden, who are experts in assessing safety and performance of hip replacement including implant migration. At a later stage those independent assessors will also evaluate the anonymised clinical and radiographic outcome of Cohort 1A, Cohort 1B and Cohort 2 until the 2 year postoperative time point.

8.1.3 Endpoints

Primary Endpoint

- Revision for any reason

Secondary Endpoints

- Complication rate (adverse events and revisions)
- Toxicology (blood metal ion measurements)
- CT assessment (Implant migration)
- Patient Reported Outcome Measures (PROMs)
- Objective clinical and functional outcomes (Harris Hip Score, Gait Analysis)
- Radiological assessment (implant orientation, osseointegration)

The primary endpoint will be revision of the H1 prosthesis for any reason. However, since hip resurfacing components are considered to be easy to revise, the threshold for revision may be lower than for a total hip arthroplasty. Therefore, the secondary endpoints of the H1 ceramic-on-ceramic and comparison with Metal-on-metal hip resurfacing and with conventional Total Hip Arthroplasties is considered to be a very important discriminating factor as well. Secondary endpoints will investigate the short- (6 months, 1 year, 2 years, 3 years), mid- (5, 7 years) and long-term (10 years) safety and efficacy of the H1 hip resurfacing prosthesis for the whole patient cohort.

In the Cohort 1A and 1B, cementless acetabular and femoral component migration, and bone ongrowth will be assessed on low-dose CT scans. Absence of generation of metal wear debris potentially leading to local adverse tissue reactions and systemic toxicity will also be assessed by measuring metal ions (cobalt, chromium) in whole blood. Metal ion blood levels will be compared to historical metal ion measurements from MoM hip resurfacings and publications in the orthopaedic literature.

8.2 Data Collection

The assessments and data collection are detailed in Part C, Procedures.

8.2.1 All participants (Cohort 1A, Cohort 1B, Cohort 2)

Baseline Data

Baseline data collection will include imaging, clinical questionnaires, demographical data, medical history and data related to the surgery and the implant used. All patients in the study will undergo hip resurfacing with the H1 hip implant. Operative data will be collected along with discharge information.

Patient Reported Outcome Measures and objective clinical and functional outcomes

Data that will be collected as part of the clinical follow-up will include x-rays and subjective hip and general health clinical evaluation including PROMs (Harris Hip Score (HHS) and the Oxford Hip Score (OHS) [39]). The patients' opinion about their state of health, according to a visual analogue scale and 5 dimensions - mobility, self-care, usual activities, pain/discomfort and anxiety/depression, (each dimension having 5 levels: no problems, slight problems, moderate problems, severe problems and extremely) - will be assessed with the EQ-5D questionnaire [40]. Patient satisfaction, expectations and a self-assessment of the physical outcome will also be done according to the new Imperial Score evaluating pain, function and fulfilment of preoperative aspirations after hip arthroplasty. The Imperial Score can only be collected online.

Radiological Assessment

Radiological evaluation at the scheduled follow-up intervals (see flow diagram in Figure 1 to Figure 3 and Schedule of procedures in Table 2 to Table 8) will include standard anteroposterior (AP) pelvis and lateral hip radiographs, or 3D CT-series where available.

Complication Rate

Adverse Events (AE), Serious Adverse Events (SAE), complications and revisions and causal relation of the complication to the implant and/or surgery will be recorded whenever applicable. The sponsor and manufacturing company (both Embody Orthopaedic Ltd), the Ethics committees, regulatory authorities will be notified of any device related adverse events and of all SAE, device related or not device related as further outlined in Section 16.

In the unlikely event of an early failure and revision, thorough tissue, fluid and implant retrieval analysis will be performed in order to detect the exact cause of failure. Steps will be put in place to monitor patients on the study, please see Section 15.1.

8.2.2 Cohort 1A Only

CT Assessment

Cohort 1A (first 20 patients) will undergo a low dose CT scan preoperatively and post-operatively at 6 months and an ultra-low dose CT scan at the following time points: immediately postoperatively (2days), 6 weeks, 3 months, 1 year and 2 years. This will be used to evaluate the interfaces between implants and bone to assess possible migration of the acetabular and femoral components based on tantalum markers.

Toxicology

Metal ion exposure questionnaires will be collected pre-operatively only. Metal ion testing (whole blood Co, Cr, and Ti, concentrations) will be performed in all Cohort 1A patients. Co ion testing is performed as a confirmation of the absence of Co as opposed to the standard metal-on-metal hip resurfacings. Cr ions are expected to remain below the detection limit as outlined above. Ti ions may be present as part of the bone ongrowth process of the non-cemented components, but are not associated with toxic reactions as outlined in section 1. Since previous studies have demonstrated that ceramic-on-ceramic bearings are not associated with adverse metal ion release it is not deemed necessary to subject all patients to metal ion testing provided the results from the Cohort 1A patients confirm the absence of metal ions release at 3, 6, 12 and 24 months postoperatively. With well-functioning metal-on-metal hip resurfacing a characteristic 9-12 months run-in phase of metal ion release is followed by a steady-state phase of much lower and decreasing metal ion release.

8.2.3 Cohort 1B Only

CT Assessment

Cohort 1B (46 patients) will undergo a low dose CT scan preoperatively and an ultra-low dose CT scan at the following time points: immediately postoperatively (2days), 6 weeks, 3 months, 6 months, 9 months, 1 year and 2 years. This will be used to evaluate the interfaces between implants and bone to assess possible migration of the acetabular and femoral components based on tantalum markers.

Toxicology

Metal ion exposure questionnaires will be collected pre-operatively only. Metal ion testing (whole blood Co, Cr, and Ti, concentrations) will be performed in the first 14Cohort 1B patients. Co ion testing is performed as a confirmation of the absence of Co as opposed to the standard metal-on-metal hip resurfacings. Cr ions are expected to remain below the detection limit as outlined above. Ti ions may be present as part of the bone ongrowth process of the non-cemented components, but are not associated with toxic reactions as outlined in section 1. Since previous studies have demonstrated that ceramic-on-ceramic bearings are not associated with adverse metal ion release it is not deemed necessary to subject all patients to metal ion testing provided the results from the Cohort 1B patients confirm the absence of metal ions release at 3, 6, 12 and 24 months postoperatively. With well-functioning metal-on-metal hip resurfacing a characteristic 9-12 months run-in phase of metal ion release is followed by a steady-state phase of much lower and decreasing metal ion release.

8.3 Data Analysis

8.3.1 Cohort 1A Only

Short-term safety evaluation will be performed in the first 20 patients recruited into the study, which will include data analysis at 2 days, 6 weeks 3 months and 6 months. This short-term analysis will include: complication rate and radiological assessment at 2 days; complication rate, functional assessment and radiological assessment at the 6-week interval; and complication rate, CT assessment, functional assessment and toxicology at the 3 month and 6 month intervals. Metal ion blood levels will be compared to historical metal ion measurements from MoM hip resurfacings and publications in the orthopaedic literature. The safety evaluations shall be independently reviewed by the Karolinska Institute in Stockholm, Sweden.

If the safety analysis at 2 days shows no impact on patient safety (no unanticipated intraoperative or postoperative complications, no issues regarding implant seating) recruitment will commence for Cohort 2. At 3 months, a second evaluation will include a toxicological report (metal ion measurements) which is expected to confirm the safety since the material does not contain toxic elements (no Cobalt, very low amount of non-toxic Chromium 3+) and CT-scans evaluating migration of the non-cemented components.

If the safety analyses of Cohort 1A suggest further investigation, the study will be put on hold until the results of the investigation have been obtained. If those suggest the implant is not safe, the study will be terminated. If the investigation supports the safety of the implant, the study will proceed.

CT analyses will evaluate migration at 6 weeks, 3 months, 6 months, 1 year and 2 years whilst yearly follow-up will be performed until 10 years, and radiographs at 3, 5, and 10 years.

8.3.2 Cohort 1B Only

Safety evaluations will be performed on a second set of 46 patients at 6 and 12 months. These analyses will include complication rate, toxicology, CT assessment and functional assessment. The safety evaluations shall be independently reviewed by the Karolinska Institute in Stockholm, Sweden.

If the safety analysis at 6 months shows no impact on patient safety (no unanticipated intraoperative or postoperative complications, no issues regarding femoral crush fractures) recruitment will resume for Cohort 2.

CT analyses will evaluate migration at 6 weeks. 3 months, 6 months, 9 months, 1 year and 2 years.

8.3.3 All participants (Cohort 1A, Cohort 1B, Cohort 2)

In the safety and efficacy study the clinical and functional assessments will be done at 6 months and 7 years; and at 1, 2, 3, 5 and 10 years assessment of the clinical, functional and radiographic performance.

An interim analysis describing the safety and efficacy parameters is planned at 6 months and annually, and a final analysis will be done at 10 years. The interim analysis will consider the overall study population as well as the following pre-defined subgroups:

- Female Resurfacing Patients
- Patients implanted with a small femoral head diameter (Size 46 and below)
- Patients operated on pre- and post- the design upgrade

The interim analyses shall be independently reviewed by the Karolinska Institute in Stockholm, Sweden up to the 2 year interval.

8.3.4 Analysis reporting time-points

Table 1 Reporting time-points

Report Title	Time point	Cohort(s)	Independent Review?	Data
Gateway Safety Analysis 1	2 days	1A	Yes	Complication rate, Radiological Assessment
Safety Evaluation 6 weeks	6 weeks	1A	Yes	Complication rate, Functional Outcomes, Radiological Assessment
Safety Evaluation 3 months	3 months	1A	Yes	Complication rate, Functional Outcomes, CT Assessment, Toxicology
Safety Evaluation 6 months	6 months	1A	Yes	Complication rate, Functional Outcomes, CT Assessment, Toxicology
Gateway Safety Analysis 2	6 months	1B	Yes	Complication rate, Functional Outcomes, CT Assessment, Toxicology
Interim Analysis 6 months	6 months	1A,1B,2	Yes	Complication rate, Functional Outcomes, CT Assessment (Cohort 1A and 1B only), Toxicology (Cohort 1A only), PROMS, Survivorship
Safety Evaluation 1 year	1 year	1B	Yes	Complication rate, Functional Outcomes, CT Assessment, Toxicology
Interim Analysis 1 year	1 year	1A,2	Yes	Complication rate, Radiological Assessment, Functional Outcomes, CT Assessment (Cohort 1A and 1B only), Toxicology (Cohort 1A only), PROMS, Survivorship
Interim Analysis 2 years	2 years	1A,1B,2	Yes	Complication rate, Radiological Assessment, Functional Outcomes, CT Assessment (Cohort 1A and 1B only), Toxicology (Cohort 1A only), PROMS, Survivorship
Interim Analysis 3 years	3 years	1A,1B,2	No	Complication rate, Radiological Assessment, Functional Outcomes, PROMS, Survivorship
Interim Analysis 4 years	4 years	1A,1B	No	Complication rate, PROMS, Survivorship
Interim Analysis 5 years	5 years	1A,1B,2	No	Complication rate, Radiological Assessment, Functional Outcomes, PROMS, Survivorship
Interim Analysis 6 years	6 years	1A,1B	No	Complication rate, PROMS, Survivorship
Interim Analysis 7 years	7 years	1A,1B,2	No	Complication rate, Functional Outcomes, PROMS, Survivorship
Interim Analysis 8 years	8 years	1A,1B	No	Complication rate, PROMS, Survivorship
Interim Analysis 9 years	9 years	1A,1B	No	Complication rate, PROMS, Survivorship
Final Analysis 10 years	10 years	1A,1B,2	No	Complication rate, Radiological Assessment, Functional Outcomes, PROMS, Survivorship

9 Investigation Population

9.1 Indications for H1 hip resurfacing arthroplasty

Indications for use of the H1 HRA in this investigation will be patients with end-stage hip disease who are candidates for primary hip arthroplasty using either a metal-on-metal hip resurfacing or a ceramic-on-ceramic THR. Typically they will be younger (<70 years) and active males and females with end-stage hip osteoarthritis, avascular necrosis of the femoral head, post-traumatic osteoarthritis or developmental dysplasia of the hip (DDH). Patients recruited in cohort 2 that require a bilateral HRA will be able to undergo simultaneous bilateral hip resurfacing with the H1 implant.

9.2 Bilateral H1 Hip Resurfacing patients

9.2.1 Simultaneous Bilateral HRA (Cohort 2 only)

Patients who require a simultaneous bilateral hip resurfacing with the H1 implant will undergo all assessments as detailed in Table 5. These patients will undergo additional Lateral radiographs and will be required to complete the following questionnaires for the contralateral hip: Oxford Hip Score, EQ5D-5L, Harris Hip Score and Imperial Score (online only).

9.2.2 Staggered Bilateral HRA

Patients who are enrolled into the study as part of Cohort 1A, Cohort 1B or 2 can undergo a HRA with a H1 implant on the contralateral side if they meet the inclusion/exclusion criteria, and pass the screening assessments. All staggered bilateral patients recruitment must be re-consented for the additional assessments before taking part in the study for their contralateral hip. At point of re-consent these patients will be registered again with the coordinating site for a unique identification number for their contralateral second hip.

Patients recruited in cohort 1A who opt to undergo HRA for the contralateral hip will follow the assessments as detailed in Table 6. Those patients in cohort 2 who opt to undergo HRA for the contralateral hip will follow assessments as detailed in Table 7. Patients recruited in cohort 1B will follow the assessments as detailed in Table 8. These patients will undergo additional AP and Lateral radiographs and will be required to complete the following questionnaires for the contralateral second hip: Oxford Hip Score, EQ5D-5L, Harris Hip Score and Imperial Score (online only).

Bilateral and staggered bilateral patients can be recruited from all sites participating in the trial, however the total number of bilateral implants cannot exceed 20% of the total study sample size (250). Therefore only 25 patients (50 hips) can be recruited as a bilateral or staggered bilateral patient, once this number has been reached, recruitment for the contralateral hip will cease and recruitment will continue for uni-lateral hips only. Bilateral patients and those recruited for the contralateral hip as staggered bilateral patients will be registered as a separate patient for each hip with a unique trial identification number for both hips. Case Report Forms will be completed for each hip.

9.3 Inclusion criteria for subject selection

- Patient requires primary hip arthroplasty due to degenerative joint disease (primary osteoarthritis, posttraumatic osteoarthritis, avascular necrosis, developmental hip dysplasia)
- Patients femoral bone stock is adequate for hip resurfacing on plain radiographs
- Patient is between 18 and 70 years old
- Patient willing to comply with study requirements
- Patient plans to be available through ten (10) years postoperative follow-up
- Patient is able to understand the native language of the country where their procedure is taking place

9.4 Exclusion criteria for subject selection

- Patient has a BMI greater than 40
- Patient suffers from an active inflammatory joint disorder
- Patient has an active infection or sepsis (treated or untreated)
- Patient has insufficient bone stock at the hip (>1/3 necrosis of the femoral head)
- Patient has severe osteopenia or osteoporosis, defined using DXA by T-score of <-2.5 (if T-score does not meet the criteria, please confirm with coordinating site (ICL) for participant eligibility)
- Patient has large and multiple cysts in the femoral head (patients with cysts to be reviewed by coordinating site (ICL) for participant eligibility)
- At the time of enrolment, patient has one or more of the following arthroplasties that have been implanted less than 6 months before the current hip arthroplasty:
    - Contralateral primary total hip arthroplasty or hip resurfacing arthroplasty
    - Ipsilateral or contralateral primary total knee or unicondylar knee arthroplasty
- Patient takes medications which potentially affect the bone such as corticosteroids and antimitotic medications.
- Patient has a condition that may interfere with the hip arthroplasty survival or outcome (i.e., Paget's or Charcot's disease, vascular insufficiency, muscular atrophy, uncontrolled diabetes, moderate to severe renal insufficiency or neuromuscular disease)
- Patient has a known alcohol or drug abuse
- Patient has an immunosuppressive disorder
- Patient has a malignant tumour, metastatic, or neoplastic disease
- Patient has severe comorbidities or a limited life expectancy
- Patient lacks capacity to consent
- Patient has an emotional or neurological condition that would pre-empt his/her ability or willingness to participate in the study
- Patient is not willing or able to sign an informed consent form
- Patient pregnant or breast feeding
- Patient is not able or willing to come to follow-up visits
- Any other clinical reason, which the investigator considers would make the patient unsuitable for the trial
- Implant size unavailable

In addition, the following exclusion criteria are applied to the patients in the safety study in whom metal ion measurements will be performed, since those conditions may be associated with elevated metal ion levels and could complicate the interpretation of the metal ion results [41]:

- Patients who already received another joint replacement, hip, knee, shoulder, ankle
- Workers in the paint, diamond, leather or other industries producing Co or Cr dust
- Patients taking medication, vitamins or food supplements containing Co or Cr and not able or willing to discontinue those.

9.5 Subject withdrawal

All reasonable efforts should be made to retain the patients for the 10-year duration of the investigation. However, participation is voluntary and patients may withdraw at any point. A final evaluation including questionnaires will be completed for all patients who do withdraw, and the reason for the withdrawal will be documented on the enrolment and withdrawal form. After a patient withdraws from the study, he or she will be further followed outside the study preferably by the surgeon who performed the hip arthroplasty. Any patients withdrawn due to an adverse event will be followed-up by the Chief Investigator until the adverse event has been resolved or stabilised.

The investigator may also discontinue patients due to non-compliance with visits and assessments or if the patient is simply lost to follow-up.

9.6 Point of enrolment

Once patient has consented to take part in the study, they will be assigned a unique patient identification number via online platform Castor EDC (Ciwit B.V.), an electronic data capture system. All participants will be anonymised when registered onto Castor. The patient identification number is comprised of a five-digit number starting with a two-digit site number assigned by the co-ordinating centre, followed by a three-digit patient number, assigned chronologically for the entire study. For example, at site 01, the first patient enrolled will receive the number 01001. Each investigation site shall maintain a subject identification log of all the subjects enrolled in the clinical investigation. If the patient does not pass the screening assessments and is deemed ineligible to participate in the study, the patient will be considered a screening failure and is recorded as a screening failure in the subject identification and enrolment log. The patient identification numbers for screen failures are not to be re-used.

Once the patient has been consented to the study, the screening assessments as detailed in section 7.4.1 will be required to ensure patients eligibility:

9.7 Total expected duration of the clinical investigation

The investigation will last for 10 years from the date of surgery.

9.8 Subject duration and number

A total number of 250 cases will be recruited into the study for the duration of 10 years from date of surgery.

9.9 Enrolment Period

Cohort 1A will be recruited within 6 months of investigation start date.

Cohort 1B will be recruited within 6 months of investigation resumption date.

Cohort 2 (pre-upgrade) will be recruited within 1 year of local site approval.

Cohort 2 (post-upgrade) will be recruited within 1 year of local site approval or within 1 year of the clinical trial restart after design upgrade, whichever is longer.

10 Statistical Methods

10.1 Hypotheses and Sample Size

10.1.1 Primary Objective - Safety and Efficacy Study

A total of 250 cases will be enrolled into the study at the 9 investigation sites.

When 250 cases are enrolled from all sites, enrolment will be stopped, regardless of the number contributed from each site.

The sample size is calculated based on the non-inferiority of the study device; the following hypotheses will be tested to test the difference in success rate (defined in section 2) of the study device with the reference rate with non-inferiority margin, $\delta > 0$:

$$H_0: \pi_0 - \pi \geq \delta$$

$$H_a: \pi_0 - \pi < \delta$$

Where π is success rate of study device and π_0 is reference rate, respectively and $\delta = 5\%$. For these hypotheses, rejection of the null hypotheses will imply non-inferiority of the study device compared to the reference rate.

For the above hypotheses, the sample size for a specified α and power $(1 - \beta)$ is given by:

$$n = \frac{(z_a + z_b)^2(\pi(1-\mu))}{(\mu_0 - \mu - \delta)^2}$$

Where δ is the non-inferiority margin and non-negative number [43].

The success rate for the study device is unknown for this population but there is no reason to believe that it would be less than reference rate of 93% (95%CI: 92.4-93.6%) [19]. Therefore, a conservative success rate of 93% of the study device is used at 10 years study.

The non-inferiority margin δ of 0.05 is chosen in the study [43]. 225 subjects are required to achieve 100(1 – β) % = 80% power to detect non-inferiority at the Significance level of α = 0.05 (single-sided hypothesis). Based on the experience, allowing 10% of the patients lost to follow up by the end of 10 years, a sample size of 250 cases are needed in this study. Therefore, 250 cases will be enrolled in the study (20 cases minimum to be recruited at each site; in case one centre is not able to recruit the allocated target size of cases, numbers can be picked up by the other centres).

10.1.2 Secondary Objective - Safety Study

Regarding the safety analysis, the sample size is calculated based on the superiority of the ceramic-on-ceramic bearing couple compared to MoM hip resurfacings. Several studies [22] have demonstrated that ceramic bearings are not associated with metal ion release (levels below detection limits of most labs i.e. < 0.5 µg/L). Previous research [3] investigated metal ion measurements from well-functioning MoM unilateral hip resurfacings (n = 251) and found mean cobalt (Co) levels of 1.8 µg/L (median 1.5 µg/L – SD 1.2) and mean chromium levels of 2.0 µg/L (median 1.6 µg/L – SD 1.5). The Co and Cr levels of the ceramic-on-ceramic hips are expected to be < 0.5 µg/L. Thus 14 subjects in each group are required to achieve 100(1 – β) % = 80% power to detect a difference in the mean Co levels at the Significance level of α = 0.05 (NCSS statistical software).

In order to account for patients lost to follow-up, unavailability or loss of blood samples or laboratory problems with measurements, 20 patients will be included in the metal ions investigation.

10.2 Statistical Analysis

A non-inferiority test of the cumulative percent success (defined in section 2) in subjects implanted with the H1 hip resurfacing compared to a literature reference rate will be the primary test of efficacy in this study. The null hypothesis is H_0: $\pi_0 - \pi \geq 0.05$ and the alternative hypothesis is Ha: $\pi_0 - \pi < 0.05$.

Primary and secondary outcomes will be evaluated using listings and summary statistics. A confidence interval of 95% will be calculated for proportions and averages. Improvement in pain and function will be analysed using parametric (t-test) or non-parametric (Wilcoxon Rank tests) as appropriate. A Kaplan Meier survival estimate will be calculated in this study. For the survivorship analyses, revisions are defined as revision for any reason. Prognostic factors will be adjusted, if necessary, using parametric or non-parametric analyses (log Rank; Cox regression). All statistical analyses and calculation of confidence intervals will be performed using appropriate statistical software packages.

10.3 Missing data

In order to evaluate the potential impact of interim and final analyses, the reason of non-completed Patient Reported Outcome Measures Forms, or Radiographic Evaluation will be provided in the analysis reports. A complete accountability report, along with the explanation for lost-to-follow-up, death, revision, and withdrawn patients, is to be provided in the interim and final study analyses.

PART C: PROCEDURES

11 Investigation procedures

The investigation procedures are summarised in Table 2 to Table 8.

Key:

- Blue indicates data for patient enrolment
- Green indicates baseline data
- Purple indicates data for clinical and functional outcomes
- Red indicates patient reported outcome measures
- Grey indicates data for radiological assessment
- Yellow indicates data for CT assessment
- Pink indicates data for toxicology
- Orange indicates data for complication rate

Table 2. Schedule of procedures: Cohort 1A

Date		Pre-op	Op day	Post-op												
				2days	6 wks	3 mos	6 mos	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8,9 years	10 years
Deviation window		≤4mos prior	0	±1day	±2wks	±2wks	±2wks	±2wks	±4wks	±4wks	±3mos	±3mos	±3mos	±3mos	±3mos	±3mos
Assessment	Informed consent	✓														
	Inclusions/exclusions	✓														
	Patient registration	✓														
	Medical history	✓														
	Operative data		✓													
	Treadmill gait	✓						✓				✓				
	Harris Hip Score	✓			✓	✓	✓	✓	✓	✓		✓		✓		✓
	Oxford Hip score	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Imperial Hip Score	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	EQ-5D	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	AP & Lateral Radiographs	✓ ≤12 mos prior		✓						✓		✓				✓
	Low dose CT scan Ultralow dose CT scan	✓		✓	✓	✓	✓	✓	✓							
	Metal ions questionnaire	✓														
	Metal Ions bloods	✓				✓	✓	✓	✓							
	Conmed questions	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Record Adverse Event	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 3. Schedule of procedures: Cohort 1B

Date		Pre-op	Op day	Post-op													
				2days	6 wks	3 mos	6 mos	9 mos	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8,9 years	10 years
Deviation window		≤4mos prior	0	±1day	±2wks	±2wks	±2wks	±2wks	±2wks	±4wks	±4wks	±3mos	±3mos	±3mos	±3mos	±3mos	±3mos
Assessment	Informed consent	✓															
	Inclusions/exclusions	✓															
	Patient registration	✓															
	DXA scan	✓ ≤12 mos prior															
	Medical history	✓															
	Operative data		✓														
	Treadmill gait	✓							✓				✓				
	Harris Hip Score	✓			✓	✓	✓	✓	✓	✓	✓		✓		✓		✓
	Oxford Hip score	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Imperial Hip Score	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	EQ-5D	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	AP & Lateral Radiographs	✓ ≤12 mos prior		✓							✓		✓				✓
	Low dose CT scan Ultralow dose CT scan	✓		✓	✓	✓	✓	✓	✓	✓							
	Metal ions questionnaire*	✓															
	Metal Ions bloods*	✓				✓	✓		✓	✓							
	Conmed questions	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Record Adverse Event	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

*Metal ions questionnaire and bloods only taken for the first 14 patients in Cohort 1B

Table 4. Schedule of procedures: Cohort 2 All sites (except * which are UK sites only and ** which are online only)

	Date	Pre-op	Op day	Post-op								
				2 days	6 weeks	6 months	1 year	2 years	3 years	5 years	7 years	10 years
	Deviation window	**≤4 mos prior**	**0**	**±1 day**	**±2 weeks**	**±2 weeks**	**±2 weeks**	**±4 weeks**	**±4weeks**	**±3 months**	**±3 months**	**±3 months**
Assessment	Informed consent	✓										
	Inclusions/exclusions	✓										
	Patient registration	✓										
	DXA Scan	✓ ≤12 mos prior										
	Medical history	✓										
	Operative data		✓									
	Treadmill gait*	✓*					✓*			✓*		
	Harris Hip Score	✓			✓	✓	✓	✓	✓	✓	✓	✓
	Oxford Hip score	✓			✓	✓	✓	✓	✓	✓	✓	✓
	Imperial Hip Score**	✓**			✓**	✓**	✓**	✓**	✓**	✓**	✓**	✓**
	EQ-5D	✓			✓	✓	✓	✓	✓	✓	✓	✓
	AP & Lateral Radiographs Low dose CT scan*	✓ ✓* ≤12 mos prior		✓	✓		✓	✓	✓	✓		✓
	Conmed questions	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Record Adverse Event(s)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 5. Schedule of procedures: Cohort 2 simultaneous bilateral patients – All sites (except * which are UK sites only and ** which are online only)

Date		Pre-op	Op day	Post-op								
				2 days	6 weeks	6 months	1 year	2 years	3 years	5 years	7 years	10 years
Deviation window		≤4 mos prior	0	±1 day	±2 weeks	±2 weeks	±2 weeks	±4 weeks	±4weeks	±3 months	±3 months	±3 months
Assessment	Informed consent	✓										
	Inclusions/exclusions	✓✓										
	Patient registration	✓✓										
	DXA Scan	✓ ≤12 mos prior										
	Medical history	✓✓										
	Operative data		✓✓									
	Treadmill gait*	✓*					✓*			✓*		
	Harris Hip Score	✓✓			✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓
	Oxford Hip score	✓✓			✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓
	Imperial Hip Score**	✓✓**			✓✓**	✓✓**	✓✓**	✓✓**	✓✓**	✓✓**	✓✓**	✓✓**
	EQ-5D	✓✓			✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓
	AP Radiographs	✓ ≤12 mos prior		✓	✓		✓	✓	✓	✓		✓
	Lateral Radiographs	✓✓ ≤12 mos prior		✓✓	✓✓		✓✓	✓✓	✓✓	✓✓		✓✓
	Low dose CT scan*	✓*^ ≤12 mos prior										
	Conmed questions	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓
	Record Adverse Event(s)	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓	✓✓

✓✓= Separate assessments to be taken for both hips

Table 6. Schedule of procedures: Staggered bilateral patient recruited from Cohort 1A into Cohort 2

First Study Hip (Cohort 1A)		**Pre-op**	**Op day**	**2D**	**6 wks**	**3 mos**	**6 mos**					**1 year**			**2 years**		**3 years**		**4 years**	**5 years**		**6 years**	**7 years**		**8,9 years**	**10 years**	
Contralateral Second Study Hip (Cohort 2)								**Pre-op**	**OP Day**	**2 D**	**6 wks**		**6 mos**	**1 year**		**2 years**		**3 years**				**5 years**			**7 years**			**10 years**
Assessment	Re-consent for contralateral Hip	Assessments done as per Table 2						✓																			
	Inclusion/exclusion							✓																			
	Patient registration							✓																			
	DXA Scan							✓^ ≤12 mos prior																			
	Medical History							✓																			
	Operative data								✓																		
	Treadmill gait							✓				✓		✓						✓	✓						
	Harris Hip Score							✓			✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓		✓	✓
	Oxford Hip score							✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Imperial Hip Score							✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	EQ-5D							✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	AP & Lateral Radiographs							✓ ≤12 mos prior		✓	✓			✓		✓	✓	✓		✓	✓					✓	✓
	Ultra low dose CT											✓			✓												
	Metal Ions bloods											✓			✓												
	Conmed questions							✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Record Adverse Event(s)							✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

✓ = First Study Hip ✓= Contralateral Second Hip ✓^= To be taken only if previously DXA scan not done

Table 7. Schedule of procedures: Staggered bilateral patients recruited from Cohort 2 into Cohort 2 – All sites (except * which are UK sites only and ** which are online only)

	First Study Hip (Cohort 2)	**Pre-op**	**Op day**	**2D**	**6 wks**	**6 mos**					**1 year**		**2 years**		**3 years**			**5 years**		**7 years**		**10 years**	
	Contralateral second study Hip (Cohort 2)						**Pre-op**	**Op day**	**2D**	**6 wks**		**6 mos**		**1 year**		**2 year**	**3 year**		**5 years**		**7 years**		**10 years**
Assessment	Re-consent for contralateral Hip	Assessments done as per Table 4					✓																
	Inclusions/exclusions						✓																
	Patient registration						✓																
	DXA Scan						✓^ ≤12 mos prior																
	Medical History						✓																
	Operative data							✓															
	Treadmill gait*						✓*				✓*			✓*				✓*	✓*				
	Harris Hip Score						✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Oxford Hip score						✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Imperial Hip Score**						✓**			✓**	✓**	✓**	✓**	✓**	✓**	✓**	✓**	✓**	✓**	✓**	✓**	✓**	✓**
	EQ-5D						✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	AP & lateral Radiographs						✓ ≤12 mos prior		✓	✓	✓		✓	✓	✓	✓	✓	✓	✓			✓	✓
	Low dose CT scan*						✓* ≤12 mos prior																
	Conmed questions						✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Record Adverse Event(s)						✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

✓ = First Study Hip ✓= Contralateral Second Hip ✓^= To be taken only if previously DXA scan not done

Table 8. Schedule of procedures: Staggered bilateral patients recruited from Cohort 1B into Cohort 2 or vice versa

	Cohort 1B Study Hip	**Pre-op**	**Op day**	**2D**	**6 wks**	**3 mos**	**6 mos**	**9 mos**					**1 year**		**2 years**		**3 years**			**4 years**	**5 years**		**6 years**	**7 years**		**8,9 years**	**10 years**	
	Cohort 2 Study Hip								**Pre-op**	**Op day**	**2D**	**6 wks**		**6 mos**		**1 year**		**2 year**	**3 year**			**5 years**			**7 years**			**10 years**
Assessment	Informed consent	Assessments done as per Table 3							✓																			
	Inclusions/exclusions								✓																			
	Patient registration								✓																			
	DXA Scan								✓^ ≤12 mos prior																			
	Medical History								✓																			
	Operative data									✓																		
	Treadmill gait								✓				✓			✓					✓	✓							
	Harris Hip Score								✓			✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓		✓	✓	
	Oxford Hip score								✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
	Imperial Hip Score								✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
	EQ-5D								✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
	AP & lateral Radiographs								✓ ≤12 mos prior		✓	✓				✓	✓	✓	✓		✓	✓					✓	✓	
	Low dose CT scan								✓ ≤12 mos prior																			
	Ultra low dose CT												✓		✓													
	Conmed questions								✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
	Record Adverse Event(s)								✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

✓ = Cohort 1B Study Hip ✓= Cohort 2 Study Hip ✓^= To be taken only if previously DXA scan not done

Table 9. Schedule of procedures: Staggered bilateral patient recruitment from Cohort 1A into Cohort 1B

First Study Hip (Cohort 1A)		**Pre-op**	**Op day**	**2D**	**6 wks**	**3 mos**	**6 mos**						**1 year**				**2 years**		**3 years**		**4 years**		**5 years**		**6 years**		**7 years**		**8,9 years**		**10 years**	
Contralateral Second Study Hip (Cohort 1B)								**Pre-op**	**OP Day**	**2 D**	**6 wks**	**3 mos**		**6 mos**	**9 mos**	**1 year**		**2 years**		**3 years**		**4 years**		**5 years**		**6 years**		**7 years**		**8,9 years**		**10 years**
Assessment	Re-consent for contralateral Hip	Assessments done as per Table 2						✓																								
	Inclusion/exclusion							✓																								
	Patient registration							✓																								
	DXA Scan							✓^ ≤12 mos prior																								
	Medical History							✓																								
	Operative data								✓																							
	Treadmill gait							✓					✓			✓							✓	✓								
	Harris Hip Score							✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓	✓			✓	✓			✓	✓
	Oxford Hip score							✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Imperial Hip Score							✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	EQ-5D							✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	AP & Lateral Radiographs							✓ ≤12 mos prior		✓									✓	✓			✓	✓							✓	✓
	Ultra low dose CT									✓	✓	✓	✓	✓	✓	✓	✓	✓														
	Metal Ions bloods*							✓				✓	✓	✓		✓	✓	✓														
	Conmed questions							✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Record Adverse Event(s)							✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

✓ = First Study Hip ✓= Contralateral Second Hip ✓^= To be taken only if previously DXA scan not done *Metal ions questionnaire and bloods only taken for first 14 patients

11.1 Site Initiation and training

A site initiation visit for each participating investigation site shall be conducted and documented by the Investigation Manager at the beginning of the clinical investigation. A log shall be initiated and kept identifying names, initials, signatures, functions, and designated authorizations for the principal investigator and members of the investigation site team.

At the site initiation visit the Investigation Manager shall ensure that the principal investigator and investigation site team have received and understood the requirements and contents of all clinical trial documentation, have access to an adequate number of investigational devices, have been trained in the use of the investigational device, and are familiar with the responsibilities of the principal investigator.

11.2 Patient Enrolment

11.2.1 Informed Consent Process

Informed consent shall be obtained from all study participants according to ISO 14155 guidelines [44] and all applicable national regulations. Potential patients must be informed as to the purpose of the study and the potential risks and benefits known or that can be reasonably predicted or expected as described in the written consent form. The patient shall have sufficient opportunity to consider participation in the study; a patient cannot be led to believe that they are waiving their rights as a subject or the liability of the sponsor or investigator. Patients are then invited to sign and date the consent form, indicating their consent for enrolment. Once a patient has signed and dated the consent form, they are considered a participant of the study. The investigator will retain the original copy of the signed consent form in the study files. A duplicate copy shall be provided to the patient. Patients will be told they are free to withdraw at any time and they will be followed up by their healthcare team outside the study and if results throughout the 10 year study show to have an impact on patient safety, all patients will be notified and they will have the opportunity to see the consultant for further information.

The patient must sign and date the consent form in the presence of the investigator or the investigator's designee, who must sign and date the consent form in the presence of the patient.

11.2.2 Screening Assessment

Check patient meets inclusion and exclusion criteria:

- DXA bone density measured t-score $\leq$ -2.5 scan of those patients suspected to have osteopenia or osteoporosis.
- Analysis of femoral head cysts (to be undertaken at ICL)
- Calibrated X-ray used to template the implant size
- Confirmation of implant size availability from Sponsor
- If the patient is being consented for a bilateral or re-consented for the contralateral side, please check with the coordinating site (ICL) that the total number of bilateral implants inlcuded in the study will not exceed the 20% margin

11.3 Patient Visits

11.3.1 Preoperative Procedures

Demographic information will include:

- Age at surgery
- Height (in cm) and weight (in kg), measured at the preoperative assessment visit
- Gender

Medical history will be obtained and will include:

- Significant comorbidities (HEENT, respiratory, digestive, blood/lymphatic, cardiovascular, endocrine/metabolic, musculoskeletal, integumentary, genitourinary, other)
- Primary diagnosis prompting hip arthroplasty (primary osteoarthritis, post-traumatic arthritis, avascular necrosis, developmental dysplasia)
- Previous surgeries on the affected hip (none, fracture fixation, arthroscopy, AVN treatment)
- Joint involvement status of the contralateral hip and knee, and the ipsilateral knee (currently not symptomatic, currently symptomatic, previously replaced)
- Tobacco use (Never Smoked, Past Smoker, or Current Smoker.
- Alcoholic beverage intake (Never Drinks Alcohol, Occasional or Social Drinker, Only Drinks on Weekend, or Daily Drinker)

Clinical evaluation:

- Harris Hip Score
- Patient Reported Outcome Measures:
    - UK Sites – via JointPRO or paper based questionnaires (OHS, EQ5D)
    - Non UK sites – Paper based questionnaires (OHS, EQ5D)
- Radiographic data: preoperative standard AP pelvis and lateral hip radiographs, performed with a calibration to allow calculation of magnification, and size of implants required.
- Gait analysis on treadmill (UK Sites only, for further information see Section 11.4)
- Preoperative CT scan (UK sites)
- Bloods (metal ion testing) and Metal ion exposure questionnaires – Cohort 1A
- All Adverse Events and Serious Adverse Events must be reported.
- Concomitant medication recorded.

11.3.2 Operative Procedures

Operative information for each subject will include:

- Surgical time (time from skin open to skin closure, defined as the number of minutes between start and end of the surgery)
- Surgical approach (posterior, posterolateral, anterior, anterolateral, other)
- Acetabular and femoral component sizes
- Lot and catalogue numbers of the acetabular and femoral component
- Chart stickers on the device components used are to be adhered to a page within the record.

Please refer to the Case Report Form for full details.

11.3.3 Discharge Procedures

All operative complications, both intraoperative and postoperative through discharge will be collected. Any complication whether device-related, surgery related or otherwise will be collected and reported where applicable.

Post discharge information will include:

- Radiological Assessment (Section 11.6)
- Date of discharge
- Prophylactic antibiotics (yes, no)
- DVT prophylaxis (yes, no)
- Blood transfusion (yes, no; if yes specify amount in Packed RBC units)
- In case of clinical symptoms an AE form should be completed

11.3.4 Follow-up Procedures – clinical visits

All patients will be seen immediately postoperatively (2days), at 6 weeks (standard postoperative visits), 6 months, 1, 2, 3, 5, 7 and 10 years following surgery. Cohort 1A will be seen additionally at 3 months, 4, 6, 8 and 9 years. Cohort 1B will be seen additionally at 3, 9 months, 4, 6, 8 and 9 years.

The following data points will be collected at the scheduled postoperative visits (see Table 2 to Table 8).

- All Adverse Events and Serious Adverse Events.
- Concomitant medication.
- Harris Hip Score (see Section 11.4).
- Patient Reported Outcome Measures (see Section 11.5)
    - UK Sites – via JointPRO or paper based questionnaires (OHS, EQ5D)
    - Non UK sites – Paper based questionnaires (OHS, EQ5D)
- Radiological Assessment (see Section 0)
- Gait analysis on treadmill (UK Sites only, year 1 and 5 only, for further information see Section 11.4)

In Cohort 1A the following additional investigations will be performed:

- Postoperative low or ultralow dose CT scans immediately postoperatively (2 days), 6 weeks, 3, 6, 12, 24 months to evaluate implant migration (see Section 11.7)
- Metal ion measurements in whole blood (see Section 11.8**Error! Reference source not found.**)

In Cohort 1B the following additional investigations will be performed:

- Postoperative ultralow dose CT scans immediately postoperatively (2 days), 6 weeks, 3, 6, 9, 12, 24 months to evaluate implant migration. (see Section 11.7)
- Metal ion measurements in whole blood (see Section 11.8) for the fist 14 patients only

11.3.5 Follow-up Procedures – remote visits

All effort will be made to ensure patients attend their follow up visits. However if a patient is unable to attend for a particular reason, they will be followed up remotely (phone, skype and/or email) so that no data is missed. If the patient has an imaging scan locally and is able to get a copy of this data, a copy should be retained and used as part of this scheduled visit point. If no imaging scan has been taken, then this will be noted down as a missed data collection point.

The following data points will be collected

- All Adverse Events and Serious Adverse Events must be reported.
- Concomitant medication recorded.
- Modified Harris Hip Score will be collected in place of Harris Hip Score
- Patient Reported Outcome Measures (see Section 11.5)
    - UK Sites – via JointPRO (OHS, EQ5D, IHS) or paper based questionnaires over skype/phone/email (OHS, EQ5D)
    - Non UK sites – Paper based questionnaires over skype/phone/email (OHS, EQ5D)

11.4 Objective Outcome Measures

A Harris Hip Score (HHS) will be completed at all postoperative visits.

A gait analysis on a treadmill (MSk Lab, Michael Uren Hub) will be performed in all UK patients who have given permission as per study consent form, pre-operatively and postoperatively at 1 and 5 years. The gait analysis will take place at the MSk Lab using an instrumented treadmill (h/p/cosmos Gaitway II S), equipped with 2 calibrated force plates. The gait parameters will be assessed for each side (prosthetic and non-operated), at a treadmill speed starting from 3/4kph and then at increasing 0.5kph increments to the maximum walking speed of the patient and will include walking on a flat surface and walking on an incline. Leg length measurements will be taken. Patient will be free to terminate the session at any time.

11.5 Patient Reported Outcome Measures (PROMS)

Patients will be required to complete the following questionnaires: Oxford Hip Score (OHS), EQ5D and Imperial Score (online only). Sites within the UK will be required to complete OHS, EQ5D and Imperial Score via an online web-based outcome tool JointPRO. However if for some reason patients are unable to complete these online then they will be provided a paper version of OHS and EQ5D for completion. Those patients who complete the questionnaires on paper will not be required to do the Imperial Score as this is only available on the online platform. The validated translations of the OHS and EQ5D scores will be used in the respective non-UK sites Participating sites outside the UK will complete all scores as paper-based questionnaires except for the Imperial Score as this is only available via the JointPRO online platform and is only available in the English language.

Patients will be required to complete the questionnaires pre-operatively and post-operatively at 6 weeks, 6,months, 1, 2, 3, 5, 7 and 10 years. Additionally cohort 1A and 1B patients will be requested to fill out the PROM questionnaires via the on-line platform at 3, 9 months (Cohort 1B only), 4, 6, 8 and 9 years.

11.6 Radiological Assessment

Standard AP pelvis and lateral views of the hip and/or 3D CT models will be evaluated as follows.

Table 10. Radiological assessment criteria

Component/ Bone	Assessment	Absolute or relative	Time point (s)	Modality
Cup	Inclination angle, °	Absolute	2 days post op	Radiograph or CT scout
Cup	Increase or decrease in inclination angle	Relative	All time points except 2d	Radiograph or CT scout
Cup	Anteversion angle, °	Absolute	2 days post op	3D CT only
Cup	Increase or decrease in anteversion angle	Relative	All time points except 2d	Radiograph or CT scout
Pelvis	Presence of acetabular radiolucency ≥2mm at the pole (Nakasone et al.)	Both	2 days post op	Radiograph
Pelvis	Increasing acetabular radiolucency in 3 zones	Both	All time points except 2d	Radiograph
Pelvis	Presence of stress shielding in 3 zones (DeLee and Charnley)	Both	All time points except 2d	Radiograph
Pelvis	Presence and size (if present) of cavities in cancellous bone in 3 zones (DeLee and Charnley)	Both	All time points except 2d	Radiograph
Head	Stem shaft angle, °	Absolute	2 days post op	Radiograph or CT scout
Head	Increase or decrease in stem shaft angle	Relative	All time points except 2d	Radiograph or CT scout
Femur	Presence of neck narrowing and percentage of narrowing (if present) in zones 1, 7, 8, 14 (De Smet et al)	Both	All time points except 2d	Radiograph or CT scout
Femur	Presence of osteophytes in zones 1, 7, 8, 14 (De Smet et al)	Both	All time points	Radiograph or CT scout
Femur	Neck notching and depth measure (if present) in zones 1, 7, 8, 14 (De Smet et al)	Both	All time points except 2d	Radiograph or CT scout
All	Any other notable abnormalities	Both	All time points	Radiograph or CT scout

In case of abnormal radiographic findings associated with clinical symptoms, an AE form should be completed.

11.7 CT Assessment

CT scans will be performed preoperatively in all patients at UK sites.

11.7.1 Cohort 1A and Cohort 1B

In Cohort 1A and 1B, 0.5 to 1.0mm tantalum markers will be applied in the bone (9 in the acetabulum and 9 in the proximal femur) in order to be able to measure possible acetabular or femoral component migration in relation to those markers on ultralow dose postoperative CT scans [42]. These ultralow-dose CT scans will be performed postoperatively at a several time points, for different reasons as explained in Table 3. All CT scans will be done over short exposure length (20cm) to include acetabulum and proximal femur. Information is summarised in Table 11. The measurement of migration from the CT shall be carried out with a validated computational migration analysis protocol. Validation reports are available on request.

Table 11. Schedule of CT scans

CT Scan	Time	Tube current (mA)	Energy (mSv)	Reason for scan	Cohort(s)
1	Pre-op	100	1.5	Hip alignment	All UK
2	2-3 days	20	0.31	Implant migration time zero	1A and 1B
3	6 weeks	20	0.31	Implant migration	1A and 1B
4	3 months	20	0.31	Implant migration	1A and 1B
5	6 months	100	1.5	Bone ongrowth & Implant migration	1A
6	6 months	20	0.31	Implant migration	1B
7	9 months	20	0.31	Implant migration	1B
8	12 months	20	0.31	Implant migration	1A and 1B
9	24 months	20	0.31	Implant migration	1A and 1B

11.7.2 Radiation Dose

Cohort 1A

These patients will receive a total of 5 AP pelvis exposures and 5 lateral hip exposures. They will also undergo 2 low dose CT scans and 5 ultra low dose CT scans. This results in a total effective dose of approximately 8.5mSv.

Cohort 1B

These patients will receive a total of 5 AP pelvis exposures and 5 lateral hip exposures. They will also undergo 1 low dose CT scan and 7 ultra low dose CT scans. This results in a total effective dose of approximately 7.6mSv.

Cohort 2

These patients will receive a total of 8 AP pelvis exposures and 8 lateral hip exposures. If at a UK site then they will additionally undergo 1 low dose CT scan. This results in a total effective dose of approximately 8mSv.

Bilateral cases

Some patients will receive bilateral hip replacements and due to the timings of their procedures (relative to the study time points) they may be in one cohort for one hip but the other cohort for the second hip. Where patients are undergoing bilateral procedures unnecessary duplication of scans will be avoided by using existing images from the other procedures wherever possible.

DEXA scans

Some patients (in all cohorts) will additionally receive one DEXA scan. The dose and risk from the DEXA scan (~10µSV) is several orders of magnitude smaller than the dose and risk from the other imaging components. It adds an additional risk of fatal cancer of approximately 1 in 2 million.

Maximum dose

The maximum possible dose in this study will be for staggered bilateral patients who were in cohort 1A for their first procedure and cohort 2 for their second. As a consequence of avoiding duplicate imaging, this group will receive two low dose CT scans, 5 ultra low dose CT scans, 13 AP Pelvis exposures, 13 lateral hip exposures and a potentially an additional DEXA scan. A dose constraint of 15mSv is therefore proposed for this study.

An effective dose of 15 mSv has an associated cumulative lifetime risk of fatal cancer induction of approximately 1 in 1300, using a nominal risk coefficient for cancer in the adult population of 5% per Sievert (ICRP Publication 103). For comparison, the natural incidence rate for cancer in the UK is approximately 1 in 2.5 (CRUK 2010).

Regardless of the cohort or combination of cohorts that the participants are involved in, the majority (approximately 75%), of the radiation dose that they will receive is additional to standard of care in the UK.

11.8 Toxicology

Metal ion testing (whole blood Co, Cr and Ti concentrations) will be performed in Cohort 1A and 1B preoperatively and at 3, 6, 12 and 24 months postoperatively.

11.8.1 Analytical methodology

All metal ion measurements will be performed at a laboratory with experience in metal ion measurements (the Trace Element Laboratory in the Department of Clinical Biochemistry at Charing Cross hospital – Dr Nick Martin) using high resolution, inductive-coupled plasma mass spectrometry (Element 2 HR-ICP-MS, Thermo Scientific, Waltham, MA, USA). A minimum quantification limit should be 0.5 µg/l with a reproducibility of 95%. The analyses should be controlled using IQC and where possible EQA (Quebec Multi-element External Quality Assessment Scheme and/or UK National External Quality Assessment Scheme for Trace Elements).

11.8.2 Sample Sources

For the assessment of metal ion levels in patients with a MoM hip prosthesis various matrices, such as whole blood, serum, urine and hip fluid are used. Analyses in whole blood or serum are preferable, since the metal ion concentration in urine samples are variable and depend on the hydration of the patient. Twenty-four hour urine concentrations are more reliable but a 24-hour urine collection is cumbersome and often incomplete. In this study whole blood samples will be used, as there is no need for centrifugation after the blood is drawn and the samples can thus be stored at the participating sites for up to 1 week in the refrigerator at 4°C. Temperature is to be recorded in the Temperature Log with a validated thermometer.

11.8.3 Collection Techniques

One of the major technical challenges of biological metal ion testing is the risk for contamination from needles, collection tubes or containers and thus rigorous protocols are advocated for every step of the process.

11.8.4 Collection tubes

For whole blood, Becton-Dickinson (BD) Trace Elements K2EDTA tubes 368381 are recommended. The blood can be shipped as such, without centrifugation for the analysis of whole blood.

To minimise the risk of contamination unopened trace metal rated collection tubes must be used.

11.8.5 Sample volume needed for metal ion analysis

2 ml of whole blood is sufficient for analysis.

11.8.6 Sample Collection Procedures

A blood sample of 2 ml will be collected for each patient in a K2EDTA collection tube.

11.8.7 Protocol for blood sampling

It is preferable to use a non-metal needle but a metal needle can also be used provided the first 5ml of blood are discarded in order to eliminate the metal ions from the needle. If a venflon is placed to draw the blood, the needle is removed and the first 5ml of blood are thrown away in order to eliminate the metal ions from the venflon needle. If a vacutainer or a butterfly needle is used to draw the blood, the first 5ml of blood must be discarded before the K2EDTA 2.0 ml is collected for the metal ion analysis.

11.8.8 Labelling K2EDTA collection tube

Tubes and labels will be provided by the co-ordinating centre. Please complete the following information on for each collection tube:

Subject number:

Date of visit:

Time point:

Site:

11.8.9 Stability of the blood samples and transportation or shipping recommendations

Metals are rather stable in whole blood and shipping at room temperature is allowed if it takes less than 3 days.

The samples can be stored at 4°C for up to one week before shipping them.

The samples can be stored frozen (- 20°C) for months.

11.8.10 Blood Sample Shipping Procedures

Each centre will be responsible for organising the courier shipment of all samples. Each shipment must be accompanied by a sample manifest form, provided by the co-ordinating centre.

The samples may be kept refrigerated at 4ºC if shipped within 14 days. Otherwise they need to be frozen at -20 ºC.

The blood samples must be shipped to:

Trace Element Lab Charing Cross Hospital
FAO: Therese Panetta
Ground Floor Laboratory
Medical Oncology Block
Charing Cross Hospital
Fulham Palace Road
London
London W6 8RP
United Kingdom
Tel: +44 (0)20 33133642, Fax: +44 (0)20 33111433
The courier will ensure the samples are shipped to arrive Monday to Friday only, and must ensure that wherever possible samples are transported to arrive between the hours of 09:00 and 16:00. Please remember to notify the recipient as soon as possible, but at least two working days in advance of any shipment.

11.9 Lost to Follow-up

Some actively enrolled subjects will not return for their follow-up visits due to a variety of reasons. The investigator/study site must use every reasonable measure to obtain follow-up clinical data: phone calls, regular mail and e-mail, certified letters to urge subjects to return for clinic follow-up or ascertain if a patient has moved, died, or otherwise become lost to follow-up. Reasons for loss to follow-up will be recorded if known.

11.10 Documentation of Study Completion Status

The completion status of the patient (e.g. completed per protocol, withdrawal, device removed, death, lost-to-follow-up, or other reason) should be recorded on the withdrawal/off study case report form.

12 Monitoring plan

12.1 Source data

Investigators are responsible for obtaining and maintaining complete subject health information in the medical record for each patient (source documents). Examples of source documents are e.g., hospital records, clinic and office charts, memoranda, dispensing records, patient questionnaires, clinic evaluation transcriptions, operative notes, radiographs, radiology reports, blood collection and shipment records, research subject files, etc. As a minimum entry, the principal investigator shall ensure that clinical records are clearly marked to indicate that the patient is enrolled in a particular clinical investigation.

12.2 Direct access

The investigator will provide direct access to source data/documents to permit possible study-related monitoring, audits, Ethics Committee review, and regulatory inspections. This study can be monitored by the study manager or a qualified person designated by the chief investigator. During these visits, the monitor will check for completion of the entries on the case report forms, their compliance with the study protocol and will compare the CRF entries with the source data. In addition, the monitor will determine whether all adverse events have been appropriately reported within the time periods required. The investigator will also provide Sponsor, Sponsor's agents, IRB/IEC and regulatory agencies with direct access to all source data/documents to permit Study-related monitoring, audits, IRB/IEC review, and regulatory inspections if requested.

12.3 Data handling and record keeping requirements

Case report forms (CRFs) will be supplied by the Co-ordinating centre (Imperial College London). Patients will be identified by patient identification number as recorded in the subject identification log. Only the investigator will have the key to identify individual patients. The clinical investigator is responsible for the timely and accurate completion of CRFs as per ICH-GCP guidelines.

Data required according to this protocol are to be recorded on the case report forms (CRFs) at the time of the scheduled visits and transcribed to the online electronic data capturing (EDC) platform, Castor. All data should be transcribed and uploaded to the online EDC within 2 weeks of the scheduled visit.

If the investigator relocates, retires, or for any reason withdraws from the study, the chief investigator and the Sponsor (Embody Orthopaedic Limited) should be prospectively notified. The study records must be transferred to an acceptable designee.

12.4 Participating centre day-to-day monitoring

Day-to-day monitoring should be carried out by those responsible for the running of the study at each participating site. This would normally include the following checks:

- Data collected are consistent with the protocol
- The case report forms (CRFs) are only being completed by authorised staff
- No key data are missing
- A review of recruitment rates, withdrawal and losses to follow-up
- All queries and validation alerts generated when data is transcribed to the EDC platform are resolved

12.5 Central monitoring

The investigation manager will be responsible for centralised monitoring, which can indicate problems, and can be used to efficiently direct monitoring activities to those sites requiring further investigation and/or additional training support.

Central monitoring of data will be used to assess the following:

- Unusual patterns or trends
- Issues with plausibility or consistency
- Safety signals
- Other deviation from the protocol/trial requirements such as poor/late completion of CRFs.

12.6 Risk-based monitoring

A Risk Based Monitoring (RBM) approach will be used, which will focus on triggered monitoring visits to identify potential issues. RBM will focus on risk assessments highlighted as part of the study that will have high potential impact to patient safety and data quality. However, the co-ordinating centre retains the rights to increase on-site monitoring in case of issues or problems and if deemed necessary.

12.7 Monitoring report

The principal investigator will be provided with a monitoring report including action items.

13 Data management

13.1 Data Submission

Sites will be required to enter trial data into Castor's electronic case report forms (eCRF). Trial data should be entered into the appropriate eCRF within one week of each scheduled visit. Images will be anonymised and sent to the coordinating site in a secure format. All AEs and SAEs should be reported as per Section 16. Blood toxicology reports will be obtained from Imperial Healthcare NHS Laboratory. The coordinating centre will keep a log of all eCRFs, scans and reports received throughout the investigation.

13.2 Quality Control

Data validation will be performed on the data collected. Data validation checks for missing or incomplete information. This is carried out in two ways:

1. **Field validations** are encoded in the eCRFs to warn users of incomplete or incorrect information. These checks are performed automatically on each field as data is entered into the field.
2. **Source data verification** will be performed on a sample of completed forms. eCRF forms will be compared to the original paper form entries to ensure data has been entered correctly. This will be undertaken by the lead coordinating site.

If any inconsistencies are found, a "query" will be raised with the PI at the site in question. Records of all queries raised will be maintained. Corrective actions will also be documented, including the timeframe of response.

All stored CRFs will be kept in a secure environment such as a locked filing cabinet in a locked room at each participating centre.

13.3 Data Management Software

An electronic data capturing system (Castor EDC) will be used to store the study data, designed in accordance with the protocol.

13.4 CRF completion by the PIs

At the site initiation visit, the coordinating centre will go over the requirements of completing the CRF and eCRF. Validation via monitoring will be performed to ensure accurate data.

13.5 Data entry in the database

A single data entry with control checks will be performed to reduce errors. Alerts will be set up on the EDC database indicating when certain values are entered outside of the expected range or if the type of value entered is incorrect.

13.6 Logical Checks

The EDC database will include a list of all values outside the pre-defined range and checks performed to ensure consistent reporting between relevant fields and there is no implausible difference between fields.

13.7 Data Protection

During the data management and validation process, the study data will be kept secure and in accordance with the terms of the Data Protection Act 2018. Participant confidentiality will always be maintained. The study analysis will take place at the Sir Michael Uren Hub by the coordinating centre, Imperial College London, MSk Lab. All data will be anonymised at point of consent. A copy of the patient consent form will be sent to the coordinating site (ICL) to the clinical project manager's NHS account. All consent forms and any other identifiable participant information at each site will be stored separately in a locked filing cabinet within a secure office, restricted to the research team only. Each site will be responsible for transcribing and uploading the anonymised data to the EDC database. The EDC database meets all relevant regulations such as ICH E6 Good Clinical Practice, GDPR, HIPAA, FDA 21 CRF Part 11,

ISO 27001 and ISO 9001. Appropriate levels of user access will be granted to the participating sites by the coordinating centre ensuring there is no data protection breach.

Any personal information required to contact Imperial Healthcare NHS Trust patients for booking follow-up appointments will be held on a secure MSk server that meets the college criteria for storage of patient identifiable data. All local sites will store identifiable data in accordance with local guidelines and the Data Protection Act. All paper-based documents will be stored in a locked filing cabinet at the MSk Laboratory (Imperial College London) in a code protected office.

All site data collected will be stored at the prospective sites for the duration and until the completion of the 10 year follow-up study. Once the study has ended, all anonymised study data will be stored with the co-ordinating site at Imperial College London. In the event the study has to be revisited and patient identification is required, the following clause is added to the study consent form allowing Imperial College to have access to a copy of the patient consent form: "I agree for my identifiable data study including a copy of my consent form to be stored with Imperial College London".

Online questionnaires will be completed via the JointPro website. JointPro database is registered with and has been developed in consultation with the Information Commissioner's Office. All data is stored on a single dedicated server built to rigorous standards and conforming to ISO 27001 certification. The data will be encrypted at rest and when in transit. The data is accessed via user accounts, each with varying and appropriate levels of access to the dataset. The investigator or named research team member at each site will have an account where they can export the online questionnaires and electronically submit the anonymised data to the co-ordinating site.

The anonymised data may be shared with the manufacturers of the H1 HRA, Embody Orthopaedic Limited and their partners such as Zimmer Biomet as the study data may be used by the manufacturer to demonstrate the safety and efficacy of the implant to the regulatory authorities and receive a CE marking enabling them to distribute the implant. The UK manufacturer's (Embody) commercial partner, Zimmer Biomet is based in the United States where national data protection laws do not provide the same level of data protection as do the laws of the United Kingdom. Therefore the following clause is added to the study consent form 'I agree to the transfer of my encoded data, to Zimmer Biomet, the manufacturer's Embody commercial partner in the United States, for the purposes discussed in the Patient Information Sheet. I agree to the processing and storage of my encoded data in the United States. I am aware that laws in the United States do not provide the same level of data protection as do the laws of the United Kingdom.'. If participants are happy to share their data with third parties they will be asked to initial this clause in the study consent form.

Sites will be required to comply with the applicable privacy laws and regulations as determined by the country of submission.

14 Amendments to the CIP

After the clinical investigation plan has been approved by the main REC and the MHRA, no changes may be made without the agreement of both the Chief Investigator and the sponsor. The MHRA, main REC and HRA do not need to approve any substantial changes to the clinical investigation plan that needs to be implemented urgently to avoid an immediate hazard to trial patients. The chief investigator will ensure that the Sponsor, MHRA, main REC and HRA are informed of urgent amendments.

Any amendment made to the device will be notified to the sponsor and submitted to MHRA. If content, MHRA will issue a no objection to the amendment, a copy is provided to the main REC.

Substantial amendments will be submitted to main REC and HRA. The main REC will issue an opinion on the amendment within 35 days and will send the substantial amendment to HRA for approval if applicable. A copy of the REC opinion letter and HRA will be sent to MHRA.

The coordinating site will notify all participating sites of the substantial amendment and facilitate, hospital permission before the substantial amendment can be released.

For centres outside the UK, all substantial amendments will be submitted to local REC in collaboration with competent authorities in other EU Member states, as necessary.

The version number and date of amendments shall be documented through standard documentation control procedures.

14.1 Deviations from the CIP

Investigators are not permitted to deviate from the clinical investigation plan. The investigator should complete the clinical investigation deviation form for any CIP deviations, which should be sent via email to the CI within 5 days of the investigator becoming aware. The CI will assess the deviation and respond accordingly to the site with the corrective and or preventative actions. The following shall be provided to the EC: requests for deviations, and reports of deviations, if the deviation affects subject's rights, safety and wellbeing, or the scientific integrity of the clinical investigation;

Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to the sponsor and the EC as soon as possible.

14.1.1 Principal disqualification criteria

Deviation from the CIP, which impacts patient health, safety and wellbeing.

15 Device Accountability

15.1 Device failure and retrieval analysis procedure

The Sponsor requests Investigators to return any revised H1 hip resurfacing components for retrieval analysis. If any surplus tissue is removed as part of the revision procedure, this must also be sent to the Sponsor for analysis along with the device. The tissue will be stored in the freezer at MSk Lab, Sir Michael Uren Hub for analysis.

Explanted components must be cleaned and disinfected or sterilised by appropriate methods or according to standard cleaning, disinfection and sterilization procedures as requested by the Sponsor. Any method of cleaning must be recorded on a disinfection/sterilization document.

If possible, the Investigator will collect histological (adverse tissue reactions, bony in-growth quality, bone quality, response to potential wear debris, etc.) and metallurgical (metal wear, deformation, cracking, corrosion, etc.) information from explants, and this information will be reported in the annual reports.

All retrieved surgical implants and any surplus tissue which are intended for shipment shall be packed in a manner which minimises the potential for breakage, surface damage, and contamination of the environment or exposure of those handling such packages during transit.

Retrieved surgical implants and, if applicable, associated tissue samples and fluids shall be packed using three layers of packaging, namely a primary container, a secondary container and an outer shipping container. Each retrieved surgical implant, tissue sample or fluid shall be packed separately in its own primary container, which shall be durable, watertight and securely closed. Each primary container(s) shall be placed in a secondary container, which shall be durable and securely closed. If there is a potential for leakage from the primary container, the secondary container shall be watertight and may contain absorbent material. The secondary container(s) shall be placed in an outer shipping container using shock-resistant packing material to withstand shocks, pressure changes and ordinary handling. The outer shipping container shall make use of absorbent or leak-proof material, if there is a potential for leakage from the secondary container. Suitable containers include envelopes, bags, jars, pots and boxes. Adhesive tape is normally used to seal the containers.

The primary, secondary and outer shipping containers shall each bear a label, which gives the following information: the name, address and the telephone number of the sender, the biological risks symbol, the word “Decontaminated”, if the surgical implant has been decontaminated. If the package contains an un-decontaminated surgical implant, the outer shipping container shall include a label, which states that upon discovery of damage or leakage the package should be isolated and the sender notified.

For all explants, the investigator must record and forward a description of intraoperative findings, including presence of wear debris, components being replaced, and intraoperative findings relating to the device failure.

Furthermore, the sender should provide an accurate description of the contents of the container, including

- article number and batch number/serial number,
- name or initials of retriever;
- date, time and place of retrieval;
- study identification number of patient;
- container number or identifier, if there is more than one container;
- location and type of damage, if damage occurs during explanation.

The labels used shall be of a non-removable type (labels that tear when someone tries to remove them). Only properly packaged explants should be shipped, and the Sponsor should be notified before any shipment. The retrieved implants will be shipped to the manufacturer for further failure analysis. A Device Accountability form will be kept by the sponsor.

If surplus tissue is being shipped, please make sure the sample is packed in a cool box on dry ice. Tissue samples can be stored in Fridge (4°C) for up to 3 days after collection prior to shipment. If the samples are stored for longer than three days, they must be

stored in the Freezer (-20°C). Samples must be shipped to the Sponsor within 1 month of collection.

Please send samples and retrieved implants to, with prior notification via email:

Dr. Susannah Clarke

Email: susannah.clarke@embody-ortho.com
Tel: +44 (0)20 7594 3600
2nd Floor Sir Michael Uren Hub
Imperial College London
White City Campus
Wood Lane
London W12 0BZ

16 Safety Management - Adverse Events, Adverse Device Effects and Device Deficiencies

16.1 Definitions

Definitions according to ISO 14155 [44]:

Adverse event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device or to the surgery, anticipated or unanticipated.

- This definition includes events related to the investigational medical device or the comparator.
- This definition includes events related to the procedures involved.
- For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse device effect (ADE)

Adverse event related to the use of an investigational medical device

- This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
- This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious adverse event (SAE)

Adverse event that:

- led to death,
- led to serious deterioration in the health of the subject, that either resulted in
- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient or prolonged hospitalization, or
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- led to foetal distress, foetal death or a congenital abnormality or birth defect

whether or not related to the investigational medical device or to the surgery, anticipated or unanticipated.

Planned hospitalisation for elective treatment of a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious adverse device effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event

Unanticipated Serious Adverse Device Effect (USADE)	A USADE is a serious adverse device effect, which by its nature, incidence, severity or outcome has not been identified in the Risk Management Document.
Device deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance – Device deficiencies include malfunctions, use errors, and inadequate labelling.

In case of adverse events (AE or SAE), necessary additional investigations and treatments will be performed to obtain a correct diagnosis and the best possible resolution of the problem.

In the case of an anticipated serious adverse event with a higher than expected prevalence, this will be reclassified as unanticipated.

16.3 Reporting Procedures

All adverse events should be reported. The flow chart (Figure 5) should be followed for all adverse event reporting.

The standard National Research Ethics Service (NRES) non-CTIMP SAE form should be used. All Device related adverse events and all serious adverse events, whether device related or not, will be reported immediately to the Chief investigator (CI) and to the sponsor (Embody Orthopaedic Limited), who will notify the Ethics Committees of all participating sites, the regulatory bodies and the manufacturer in due course.

16.4 Foreseeable adverse events and adverse device effects

All surgical procedures have associated risks. The following table ([45] unless otherwise stated) lists the current evidenced risks of hip resurfacing surgery, for which there are published incidences and known mitigation and treatment techniques.

Table 12. Adverse events

Description	Likely incidence	Mitigation	Treatment
Hematoma or damage to blood vessels resulting in large blood loss	0.2-0.3%	Standard technique	Standard technique
Peri-prosthetic Fracture	<1%	Standard technique	Standard technique
Delayed wound healing [46]	18%	Standard technique	Standard technique
DVT [47]	3.3%	Standard technique	Standard technique
Transient nerve palsy	0-3%	Standard technique	Standard technique
Thromboembolic disease	2-3%	Standard technique	Standard technique
Infection	0.4-1.5%	Standard technique	Standard technique

For a full description of foreseeable adverse device effects, please refer to the risk analysis, the risk management plan and the risk management report [34, 36, 48].

16.5 Reporting device deficiencies

If an investigator notices a device deficiency prior to surgery (such as mislabelling or the implant is defective in some way), the device must not be used in the investigation. The device should be returned to the manufacturer immediately. If the device mal-functions or is misused during surgery, the surgery should be stopped and an alternative device used. The implant and associated instruments should be returned to the manufacturer immediately.

16.6 Contact details for reporting AEs and SAEs

Device related AEs and SAEs:
Prof Justin Cobb – Chief Investigator
j.cobb@imperial.ac.uk

Other AEs:
Mariam Al-Laith – Clinical Trial Manager
m.al-laith@imperial.ac.uk

MSk Lab
2nd Floor Sir Michael Uren Hub
Imperial College London
White City Campus
Wood Lane
London W12 0BZ

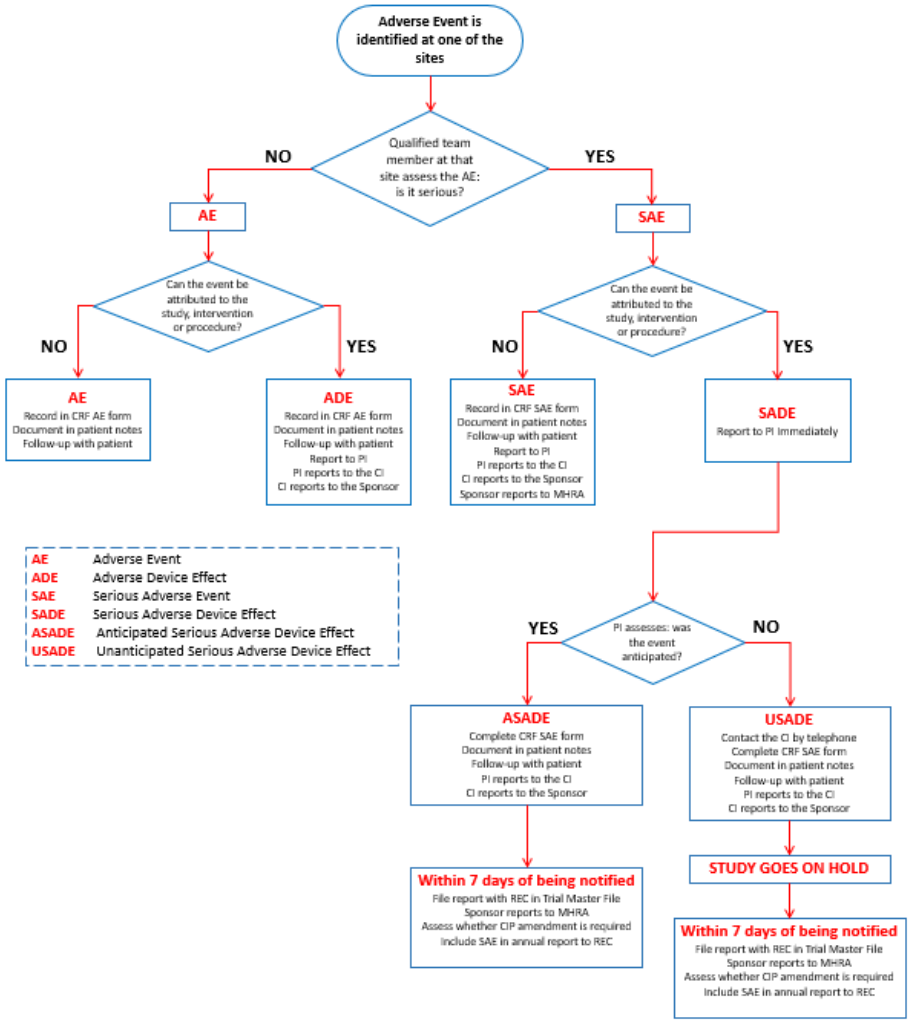

Figure 5. Safety reporting flow diagram

17 Ethical considerations

17.1 Responsibilities

All parties involved in the conduct of the clinical investigation shall share the responsibility for its ethical conduct in accordance with their respective roles in the clinical investigation.

17.2 Ethical Committee Approval

The Chief Investigator has obtained the appropriate approvals including Ethics Committee approval and HRA (NHS sites) for all UK participating sites. In accordance with the Declaration of Helsinki [2] and local regulations of the participating countries, centres outside the UK, must obtain written Ethics Committee approval prior to enrolling research participants in the study.

During the trial, Ethics Committee Approval is required for amendments and deviations that can affect the subject's rights, safety and well-being or the scientific integrity of the clinical investigation. For non-substantial changes (e.g. minor logistical or administrative changes, change of monitor(s), telephone numbers, renewal of insurance], which does not affect the rights, safety and well-being of human subjects or not related to the clinical investigation objectives or endpoints, a minor amendment will be submitted.

17.3 Communication with the Ethical Committee

The ethical committee shall receive the following:

- Reports of Serious Adverse Events (see Section 16)
- Requests for deviations (see Section 14.1)
- Progress and final reports, including safety summaries and deviations
- Amendments to documents already approved by the Ethics Committee (see Section 17.2)

18 Suspension or Premature Termination of the Clinical Investigation

Analysis reports are scheduled as outlined in Table 1. If the analysis report is said to have a significant impact on patient safety, the study will be suspended or terminated accordingly. If the study is temporarily suspended, a full report will be sent to both the ethics committee and competent authority with corrective plans and actions to allow for continuation of the study. While the study is suspended, no new patients will be recruited, however patients registered thus far will continue to follow the schedule of visits as detailed in the table of schedule of procedures. If the study is terminated, patients will be contacted and the findings discussed at the earliest time possible. Patients will be invited back to clinic to discuss the issue with them.

Patients lost to follow up or who choose to withdraw will be followed up by healthcare professionals accordingly. The investigator will decide on the nature and frequency of the follow-up as long as the patient is happy with it. For example, the investigator may deem it acceptable to follow up via telephone call, where they may be asked about adverse events if the patient is happy for the follow up to continue this way. If the study is terminated early, these patients will be notified and asked to attend a clinic appointment for further discussion.

19 Publication policy

19.1 CE Marking

A safety and efficacy report will be sent to the manufacturer's Notified Body as part of technical documentation to receive CE marking. For post-marketing surveillance requirements, reports will then be sent yearly to the notified body.

19.2 Publication policy

All presentations and publications pertaining to this study require authorisation from the Chief Investigator, who is responsible for the intellectual property arising from this study.

The Chief Investigator will review submissions for publication. Any publications or presentations relating to this study will be submitted in accordance with Imperial College policy.

19.3 Patient involvement group

A patient involvement group has been created who are asked to formulate their opinion on the research protocol and study schedule. Their comments on the study's direct interest and relevance to the study participants but also on the global hip patient population and society will be recorded and taken into account. They will also be asked their opinions on the burden of engagement for those entering the study and compliance with the necessary postoperative intervals and investigations.

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