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

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Research Article

Keywords: H1 Hip resurfacing arthroplasty, ceramic-on-ceramic, H1 System, disease-damaged hip.

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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

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Abstract (350 words)

Background: Advantages of hip resurfacing arthroplasty over total hip arthroplasty include the preservation of the thigh bone, reduction in the risk of dislocation due to the large size of the ball, revision surgery being easier, and higher activity level in younger participants. However, metal-on-metal hip resurfacings has been shown to cause higher metal ion levels and some participants reported progressive pain leading to early revision. By exchanging the metal material of the bearing with BIOLOX®*delta* ceramic, the main cause of early revision is removed. The H1 Implant is innovative both in its anatomical shape and in its materials as there is currently no all-ceramic, completely cementless hip resurfacing implant in clinical use.

Methods: This is a multicentre, prospective, non-randomized, observational study to evaluate the clinical outcome of the H1 System, which consists of the H1 Implant and the H1 Instruments. The intended application of the H1 Implant is to replace the diseased areas

of the articular surface and restore joint function. The aim is to recruit 250 participants. Adult participants up to the age of 70 years will be recruited and followed-up for 10 years from the date of surgery. 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. The assessment of the safety and performance characteristics as well as establish the superiority of the ceramic-on-ceramic bearing couple of the H1 Implant will be evaluated and compared to metal-on-metal hip resurfacings in the literature.

Discussion: This study protocol describes the H1 Clinical Investigation. The protocol was designed by clinicians, experienced trialists and patients, in order to test the safety and performance of The H1 System.

Trial registration: ISRCTN registry with study ID ISRCTN91554748

Keywords: H1 Hip resurfacing arthroplasty, ceramic-on-ceramic, H1 System, disease-damaged hip.

Administrative information

Title {1}	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
Trial registration {2a and 2b}	ISRCTN registry with study ID ISRCTN91554748
Protocol version {3}	Version 11 Dated 25/08/2021
Funding {4}	Embody Orthopaedic Limited
Author details {5a}	Mariam Al-Laith, Susannah Clarke, Camilla Halewood, Rob Wozencroft, Brogan Guest, Catherine Van Der Straeten, Dr Francesca Fiorentino, Justin Cobb
Name and contact information for the trial sponsor {5b}	Embody Orthopaedic Limited Sir Michael Uren Hub 86 Wood Lane London W12 0BZ
Role of sponsor {5c}	The role of the study sponsor and funder is to oversee the safety and the performance of the device, and report any adverse events device related or not device related to the MHRA. The sponsor contributes to, the management, analyses, interpretation of the data, writing of the reports to the MHRA and the decision to submit the protocol for publication.

Introduction

Background and rationale {6a}

Total hip arthroplasty

Total Hip Arthroplasty (THA) provides significant pain relief and improvement of hip function and mobility [1]. THA patients, even elderly people, are more active, have a better quality of life, fewer comorbidities and a longer life expectancy than in the population generally [2]. In this elderly and less active patient population, THA can be considered a lifelong solution, while, both implant survivorship and clinical performance are poorer in young and active people [3]. In this demanding patient group, revision rates are higher. The Orthopaedic

Device Evaluation Panel (ODEP) sets a benchmark revision rate of 5% at 10 years for an 'A*' rating. This benchmark is not met by conventional THA in young and active patients according to national joint registry figures, where young women experience an even higher revision rate [4, 5].

Hip resurfacing arthroplasty

Modern hip resurfacing arthroplasty (HRA) was introduced in the 1990s to address the inferior implant survivorship and unsatisfactory clinical results with THA in young and active patients [2, 6]. Metal-on-Metal (MoM) hip resurfacings have been shown to be safe and effective in younger patients over the longer term [7-11]. 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, which is often presented as the gold standard of hip replacement [13-15]. However, patients (especially females) with poorly positioned HRAs, poorly designed HRA implants and smaller sizes have reported progressive pain leading to early revision [16-18]. This pain is commonly caused by one of two problems: either metal ion particles generated by excessive wear associated with adverse local tissue reactions (ALTRs) to metal debris or soft tissue impingement on the hard metal edges of the components. Despite these two problems, national registry data continues to report significantly lower all-cause long-term mortality of HRA compared with age and gender matched THA [5, 13].

The H1 Implant

The H1 Implant is ceramic-on-ceramic (CoC), cementless HRA (Figure 1). By exchanging the metal material of the bearing with BIOLOX®*delta* ceramic (CeramTec, Germany), a better wearing and more inert material, the positive clinical performance aspects of MoM hip resurfacings are retained, while the main cause of early revision is removed. Thus, the H1

Implant could be used for wider indications than the currently restricted group of large men that applies to MoM HRAs. Patients with smaller head sizes, females and patients with metal sensitivity may all be H1 Implant candidates. BIOLOX®*delta* is a zirconia toughened alumina (ZTA). This ceramic has an 18-year history of worldwide use in hip arthroplasty, with an excellent track record. CoC bearings consist of the hardest material with the lowest wear rate of all bearing couples used in hip arthroplasty [19]. The very low volume of inert ceramic nanoparticles and the absence of elevated cobalt (Co) and chromium (Cr) ion levels in the bloodstream [20] virtually abolishes the risk of ALTR, allergic reactions and systemic cobalt toxicity. The fracture risk of BIOLOX®*delta* is much reduced compared to earlier generations of ceramic and in the arthroplasty registries and as assessed by CeramTec the fracture rate is now estimated at <0.001%. The use of BIOLOX®*delta* bearings also reduces the risk of periprosthetic infection due to a significant reduction in biofilm formation and adherence to ceramic surfaces compared to metal and polyethylene [4, 5, 21]. In a review of over 600,000 patients, infection rate was significantly reduced in patients with ceramic-on-ceramic bearings, in comparison with other forms of THA [22]. Toxicity related to release of ions from BIOLOX®*delta* has not been reported, despite the use of this material in millions of patients over 18 years. The cementless fixation of the H1 Implant is not novel, employing a rough coating of plasma sprayed titanium and hydroxyapatite applied by a leading implant coating specialist (Medicoat, Switzerland). Acetabular and femoral components using these coatings have been safe and effective products for more than 30 years [4, 5, 23]. Cementless MoM HRAs using this coating type have also been demonstrated to be safe and effective in large clinical series [24, 25]. Titanium sensitivity is very rare, but has been described, particularly in the dental literature related to large volumes of wear particles [26]. It has not been described in relation to ion release from coatings.

Objectives {7}

Primary Objective

The primary objective is to confirm the safety and performance of the H1 Implant, implanted using the H1 Instruments (Figure 2), by demonstrating non-inferiority of the cumulative percent success compared to a literature reference rate of 97.7%, 96.4% and 92.4% cumulative survivorship of the Birmingham hip resurfacing (BHR) at 3, 5 and 10 years (the BHR is the best performing and most used HRA in the National Joint Registry 17th Annual Report 2020 [27]).

Secondary Objectives

Preliminary Safety Study

In the first cohort of 20 patients (Cohort 1A), the safety of the H1 Implant, implanted using the H1 Instruments, will be determined via assessment of complication rate, toxicology and CT assessment. The secondary objective is to demonstrate superiority of the H1 Implant, implanted using the H1 Instruments, compared to MoM HRA in the absence of metal ion release at 2 years.

Second Safety Study

In a second cohort of 46 patients (Cohort 1B), the safety of the H1 Implant, implanted using the H1 Instruments, 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 H1 Implant, implanted using the H1 Instruments, compared to MoM hip resurfacing in the absence of metal ion release at 2 years.

Safety and Performance Study

Additional goals are to compare the H1 Implant, implanted using the H1 Instruments, to other hip resurfacings and total hip arthroplasty with regard to patient reported outcome measures, objective clinical and functional outcomes, and radiological assessment at each follow up visit.

CE Marking Study

Additional objectives are included for conformity assessment:

1. Overall safety and effectiveness of the H1 Implant, implanted using the H1 Instruments, by matching the Orthopaedic Data Evaluation Panel's "ODEP A" benchmark at 3 years follow-up.
2. Stable fixation of the H1 Implant, implanted using the H1 Instruments, via measurement of component migration.
3. Improvement in patient reported outcome measures (PROMS) and objective clinical outcomes compared to pre-operative values.

Trial design {8}

The H1 Clinical Investigation is a multi-centre, prospective, non-randomised, observational study to evaluate the safety and clinical outcome of the H1 System which consists of the H1 Implant and the H1 Instruments (designed to implant the H1 Implant). In order to evaluate the safety of the H1 System, the study will be subdivided in a short-term safety study and a long-term safety and performance study. The safety study (Cohort 1A – 20 participants) will record complication rate, toxicology and radiological assessment. Due to the observation of femoral crush fractures in the first cases (Cohort 1A), a second safety cohort was introduced – Cohort 1B. Cohort 1B will consist of a further 46 participants. Cohort 2 will consist of the remaining participants out of the 250-procedure cohort. The study design is shown in the flow diagrams in Tables 3 to 5.

Methods: Participants, interventions and outcomes {9}

Adult participants up to the age of 70 years old, suitable for HRA, are approached in the out-patient clinics from five hospital sites in England and invited to take part in the H1 Clinical Investigation instead of receiving a THA or MoM HRA.

Eligibility criteria {10}

Study centres and surgeons selected to participate in this study, have a longstanding experience with hip resurfacing implants and their implantation. Only surgeons who have received appropriate training and are familiar with the H1 System, surgical technique, patient indications and contra-indications, adverse events and risks will use the H1 System and become investigators.

The H1 System is intended for use in participants requiring primary hip resurfacing arthroplasty due to primary osteoarthritis or osteoarthritis secondary to e.g., trauma, avascular necrosis, developmental hip dysplasia or other self-limiting conditions and who meet the inclusion criteria.

Inclusion criteria:

- Patient requires primary hip arthroplasty due to degenerative joint disease (primary osteoarthritis, posttraumatic osteoarthritis, avascular necrosis, developmental hip dysplasia)
- Participants femoral bone stock is adequate for hip resurfacing on plain radiographs.
- Patient is between 18 and 70 years old.
- Patient is willing to comply with study requirements.
- Patient plans to be available throughout the ten (10) years postoperative follow-up.
- Patient can 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 (participants 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.

Who will take informed consent? {26a}

All participants will be given both verbal and written explanations of the study by an experienced and informed clinician. If participants wish to take part, they will be asked to sign the study informed consent form. A separate consent form will be signed for each hip for participants undergoing bilateral H1 HRAs (either simultaneous or staggered).

Interventions

Explanation for the choice of comparators {6b}

The H1 Clinical Investigation is a single-arm study with a single investigational device, the H1 System.

Preoperative Procedures

1. Demographic information will include age at surgery, height (in cm) and weight (in kg), measured at the preoperative assessment visit.
2. Medical history will be obtained and will include:
    - Significant comorbidities (HEENT, respiratory, blood/lymphatic, cardiovascular, digestive, 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)
3. Clinical evaluation:
    - Harris Hip Score
    - Patient Reported Outcome Measures (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 (optional)

- Preoperative CT scan.
- Bloods (metal ion testing) and Metal ion exposure questionnaires – Cohort 1A and first 14 patients of Cohort 1B
- All Adverse Events and Serious Adverse Events must be reported.
- Relevent concomitant medication recorded.

Operative Procedures

Intra-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
- Patient record stickers for the device components used are to be adhered to a page within the record and one set for the H1 Implant only is to be affixed to the Patient Implant Card for the patient to keep.

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
- 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

Follow-up Procedures

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. Tables 3-5

The following data points will be collected at the scheduled postoperative visits:

- All Adverse Events and Serious Adverse Events.
- Concomitant medication.
- Harris Hip Score.
- Patient Reported Outcome Measures:
  - JointPRO (OHS, EQ5D, Imperial Hip Score (IHS)) or paper based questionnaires (OHS, EQ5D).
- Radiological Assessment.
- Gait analysis on treadmill (optional assessment, year 1 and 5 only).

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.
- Metal ion measurements in whole blood.

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.
- Metal ion measurements in whole blood for the first 14 patients only.

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:
    - JointPRO (OHS, EQ5D, IHS) or paper based questionnaires over skype/phone/email (OHS, EQ5D)

Provisions for post-trial care {30}

There are no arrangements for taking care of the subjects after their participation in the clinical investigation has ended, because such additional care is not necessary as a result of the subjects' participation in the clinical investigation, and it does not differ from that normally expected for patients being treated with either a THA or HRA.

Outcomes {12}

The outcome measures and endpoints for the study is summarised in **Error! Reference source not found.**

Participant timeline {13}

All participants will be seen postoperatively (2 days) 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.

Sample size {14}

For the performance study, the sample size is calculated based on the non-inferiority of the H1 Implant in terms of the well-documented metric of implant survival, reported using Kaplan-Meier survival estimates, compared to a benchmark. The following hypotheses will be tested to establish the difference in survival of the H1 Implant with the benchmark, non-inferiority margin $\delta > 0$:

$$H_0: \mu_0 - \mu \geq \delta$$

$$H_1: \mu_0 - \mu < \delta$$

Where μ is survival of the H1 Implant and μ_0 is the benchmark survival. For these hypotheses, rejection of the null hypotheses will imply non-inferiority of the H1 Implant in terms of survival compared to the benchmark. Using the case of large n to achieve a fixed value for the control group, the general formula for determining sample size in non-inferiority trials can be specified with given α risk and power $(1-\beta)$ as [42]:

$$n = \frac{(z_{1-\alpha} + z_{1-\beta})^2(\mu(1-\mu))}{(\mu_0 - \mu - \delta)^2}$$

The success rate for the H1 Implant is unknown for this population but there is no reason to believe that it would be less than 10 year survival rate of the BHR of 92.4% [38]. Therefore, a conservative success rate of 92.4% of the H1 Implant is used for the 10 year follow-up timepoint. Including an allowance for patients lost to follow up by the end of 10 years, and using δ=5%, 250 subjects are required to achieve 80% power to demonstrate non-inferiority at the significance level of α = 2.5%.

For the safety study, the sample size is calculated based on the superiority of the H1 Implant compared to MoM HRAs in terms of cobalt (Co) and chromium (Cr) metal ion release. The following hypotheses will be tested to establish the difference in metal ion release of the H1 Implant with a benchmark, superiority margin $\delta < 0$:

$$H_0: \mu - \mu_0 > \delta$$

$$H_1: \mu - \mu_0 \leq \delta$$

Where μ is the metal ion release of the H1 Implant and μ_0 is a benchmark metal ion release level. For these hypotheses, rejection of the null hypotheses will imply superiority of the H1 Implant compared to the benchmark. For the above hypotheses, the sample size for a specified α and power $(1 - \beta)$ is given by:

$$n = \left(\sigma \frac{z_{1-\alpha} + z_{1-\beta}}{\mu - \mu_0 - \delta}\right)^2$$

Previous research investigating metal ion measurements from well-functioning MoM unilateral HRAs (n = 251) found mean Co levels of 1.8 µg/L (SD 1.2) and mean Cr levels of 2.0 µg/L (SD 1.5) [19]. Studies have demonstrated that hip replacements using ceramic bearings are not associated with metal ion release (levels below detection limits of most labs, < 0.5 µg/L [43]), therefore the Co and Cr levels of the H1 Implant are both expected to be < 0.5 µg/L.

Using the benchmark values of mean chromium levels, a superiority margin of $\delta = -0.05$ and including an allowance for patients lost to follow up by the end of 2 years, 20 subjects are required to achieve 80% power to demonstrate superiority at the significance level of α = 2.5%.

The ODEP A Rating at 3 years stipulates the following sample sizes:

- Minimum number of centres and surgeons: 3
- Minimum total cohort: 150
- Minimum implants at risk at 3 years: 72

Recruitment {15}

Participants suitable for hip resurfacing arthroplasty will be identified from the clinic list and theatre waiting list. Those participants 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 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 a decision to participate will be accepted. The patients will be given the opportunity to ask questions and highlight any concerns they may have. Participants will be told they are free to withdraw at any time. If a participant wishes 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 contraception, which will be noted in the concomitant medications (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.

Data collection and management

Plans for assessment and collection of outcomes

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

Baseline Data

Following screening, all participants will undergo baseline study visits. Baseline data collection will include imaging, clinical questionnaires, demographical data, medical history and data related to the surgery and the implant used. All participants in the study will undergo hip resurfacing with the H1 Implant, implanted using the H1 Instruments. Operative data, including any complications or adverse events relating to the H1 Instruments, will be collected along with discharge information.

Patient reported outcome measures and objective 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 Patient Reported Outcome Measures (PROMs), and the Harris Hip Score (HHS). PROMs used will be the Oxford Hip Score (OHS) [30] and EQ-5D questionnaire [31]. 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 will include standard anteroposterior (AP) pelvis and lateral hip radiographs, or 3D CT-scans where available.

Gait analysis

A gait analysis on a treadmill will be performed on patients who have given permission as per the 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 or 4 km/h and then increasing in 0.5 km/h 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.

Cohort 1A Only

CT Assessment

Cohort 1A (20 participants) 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 (2 days), 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 Cobalt (Co), chromium (Cr), and Titanium (Ti) concentrations) will be performed in all Cohort 1A participants. 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 on growth process of the non-cemented components but are not associated with toxic reactions. Since previous studies have demonstrated that CoC bearings are not associated with adverse metal ion release it is not deemed necessary to subject all participants to metal ion testing provided the results from the Cohort 1A participants 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-month run-in phase of

metal ion release is followed by a steady-state phase of much lower and decreasing metal ion release.

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 (2 days), 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 and metal ion testing, as described in Cohort 1A toxicology section, will be performed only in the first 14 participants.

Data management {19}

To eliminate the potential for selection bias, investigators will consecutively screen all their participants who could be eligible for an H1 Implant. Participants meeting the eligibility criteria will be approached for informed consent and subsequent enrolment in the investigation. Screening assessment data will be entered by sites onto a web-based Castor Electronic Data Capture (EDC) system hosted on a dedicated secure web site using only the participant's initials and date of birth as identifiers. The EDC system will automatically assign a unique participant identification number (PIN) to each participant as they are registered onto the EDC system. Only participants who consent and subsequently had their operation will be recorded in the EDC system.

Confidentiality {27}

All study data will be kept secure and in accordance with the terms of the Data Protection Act 2018 (GDPR), and 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 (ICL), MSk Lab. All data will be anonymized at point of consent. A signed copy of the patient consent form will be sent to the coordinating site 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 anonymized 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.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Survivorship data with the endpoint as 'revision for any reason' will be determined for the whole cohort, at all reporting time points. Data will be presented in both life tables and Kaplan–Meier implant survival curves with 95% confidence intervals. The results will be compared with the following cumulative implant survivorship data of the BHR (revision for any reason) from the National Joint Registry to demonstrate non-inferiority.

Toxicology data will be presented as plots only. Since metal ion levels are not normally distributed, box and whisker plots will be used for graphical representation of medians and distribution of the results. If a measured sample does not register a measurable amount, a value of half the reference rate seen in the normal population shall be used to calculate a substitute value for the data point. Cr and Co ion data at 12 and 24 months will be compared to published ion levels in unilateral MoM HRA patients with well-functioning implants to demonstrate superiority.

OHS and HHS data will be presented in tables and plots. Descriptive statistics (mean, standard deviation, median, range) shall be reported. Since outcome scores data may not be normally distributed, box and whisker plots will be used for graphical representation of the medians and distribution of the results.

Subgroups shall be compared using a two-sided t-test if data are shown to be normal, and a Wilcoxon rank-sum test otherwise. $\alpha = 0.05$.

Interim analyses {21b}

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

Methods for additional analyses (e.g., subgroup analyses) {20b}

The following pre-defined subgroups will be analysed:

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

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

In order to evaluate the potential impact of interim and final analyses, the reason of uncompleted 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, will be provided in the interim and final study analyses.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

The planned reports are described in **Error! Reference source not found.**. These reporting time points are the minimum datasets to be produced by Imperial College London – the Sponsor may request data at other time points for clinical evaluation purposes.

Oversight and monitoring

Adverse event reporting and harms {22}

Any untoward medical occurrence, unintended disease or injury, or unexpected clinical signs (including abnormal laboratory findings) in participants, whether related to the investigational medical device or to the surgery, anticipated or unanticipated, will be investigated and the severity of each adverse event will be assessed as mild, moderate, or severe. This includes events related to the investigational medical device and events related to the procedures.

Frequency and plans for auditing trial conduct {23}

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.

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 coordinating centre retains the rights to increase on-site monitoring in case of issues or problems and if deemed necessary. The principal investigator (PI) and local teams will be provided with a monitoring report including action items.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Once the protocol has been approved by the main Research Ethics Committees (REC) and the Medicines and Healthcare products Regulatory Agency (MHRA), no changes may be made without the agreement of both the Chief Investigator and the sponsor. 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 MHRA. Once approval

is issued by the MHRA, a copy of the approval letter will be provided to the main REC. Any substantial amendments will be submitted to main REC. A copy of the REC opinion letter 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.

Dissemination plans {31a}

The investigators and sponsor plan to communicate trial results to participants, healthcare professionals, the public, and other relevant groups once the trial is concluded. The publication includes the CE Marking for H1 Implant and H1 Instruments. The Clinical Evaluation Report (CER) and a Summary of Safety and Clinical Performance (SSCP) will be sent to the manufacturer's Notified Body as part of technical documentation to receive CE marking. Once CE marking is achieved, for both the H1 implant and H1 instruments, Periodic Safety Update Reports (PSUR), SSCP and post-market clinical follow-up (PMCF) reports shall be sent to the Notified Body on an annual basis, as well as the CER if it has been updated.

Discussion

This study protocol describes the H1 Clinical Investigation. The protocol was designed by clinicians, experienced trialists and patients, in order to test the safety and efficacy of The H1 System.

To evaluate the safety of the H1 System, the study initially was subdivided in a short-term safety study and a long-term safety and efficacy study. The safety study (Cohort 1A, 20 participants) to record complication rate, toxicology, and radiological assessment. Cohort 2 consists of the remaining participants out of the 250-procedure cohort.

A high occurrence of femoral crush-fractures was observed in Cohorts 1A and 2. Cohort 1A was followed up 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 into the observed movement. The movement was found to be because 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 femoral head implant has been modified to be more forgiving to implant placement error. Following this observation, a second safety cohort was introduced; Cohort 1B. Cohort 1B consisted of a further 46 participants.

The data from the study will be used to compile a report for submission to the manufacturer's notified body to obtain an MDR CE marking for the H1 Implant and H1 Instruments. If the H1 Implant receives a CE mark during the Clinical Investigation, an amendment will be placed to the main REC and the competent authority 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, the study will continue as per protocol. If the H1 Instruments receive a CE mark during the Clinical Investigation, the Clinical Investigation will carry on without amendment.

Data collected during this study may also be used for other orthopaedic research into the genesis of disease and the effectiveness of treatments in the MSk Lab at Imperial College London.

Trial status

The H1 study trial received ethical approval on 12 September 2017. The first study participant was recruited on 26 September 2017. Recruitment is estimated to be completed by the end of 2021.

Abbreviations

AE	Adverse Event
AVN	Avascular Necrosis
BHR	Birmingham hip resurfacing
CI	Chief Investigator
CER	Clinical Evaluation Report
DVT	Deep vein thrombosis
EDC	Electronic Data Capture
ED	Essential Document
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HHS	Harris Hip Score
HIPAA	Health Insurance Portability and Accountability Act
HRA	Hip Resurfacing Arthroplasty
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ISO	International Organization for Standardization
JointPRO	Joint Patient Reported Outcomes
MoM	Metal-on-Metal
MHRA	Medicines and Healthcare products Regulatory Agency
MSk	Musculoskeletal
OHS	Oxford Hip Score
OA	Osteoarthritis
PI	Principal Investigator,
PIS	Patient Information Sheet
PMCF	Post-market clinical follow-up
PSUR	Periodic Safety Update Reports
REC	Research Ethics Committee
RBM	Risk Based Monitoring
SAE	Serious Adverse Event
THA	Total Hip Arthroplasty
TiAlV	Titanium-aluminium-vanadium
TiO2	Titanium dioxide

Declarations

Acknowledgements

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Authors' contributions {31b}

(SC), (CH), (RW), (BG), (CVDS), (JC), contributed to study design and reviewed the manuscript. (FF) prepared the statistical analytical plan and oversaw sample size calculations. JC conceived the study and wrote the manuscript with CH and M.A-L and coordinated the submission.

Funding {4}

The H1 Hip Resurfacing Arthroplasty study is funded by Embody Orthopaedic.

Availability of data and materials {29}

Further information regarding the logistics of H1 Hip resurfacing study operations are available from the authors upon reasonable request.

Ethics approval and consent to participate {24}

This Clinical Trial has been approved by, East of England-Cambridge Central Research Ethics Committee (Ref. 17/EE/0330), the Health Research Authority (HRA) and the Medicines and Healthcare products Regulatory Agency (MHRA) (reference CI/2017/0040). The ethics committee approved all amendments Ethics approval date: 12th September 2017

Consent for publication {32}

N/A

Competing interests {28}

(MAL), (SC), (CH), (RW), (BG), (CVDS), (FF), and (JC) declare no competing interests relating to this study.

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Table 1. Outcome measures and endpoints

Study	Cohort(s)	Endpoint	Outcome measure	Timepoint(s)
Safety & Performance	All	Survivorship	Revision for any reason†	3Y,5Y,10Y
CE Marking	All	Survivorship	Revision for any reason†	3Y
Safety & Performance	All	Pain and function	Oxford Hip Score	6W,3M*,6M,9M**,1Y,2Y,3Y,4Y*,5Y,6Y*,7Y,8Y*,9Y*,10Y
CE Marking	All	Pain and function	Oxford Hip Score	6W,3M*,6M,9M**,1Y,2Y,3Y
Safety & Performance	All	Pain and function	Imperial Score	6W,3M*,6M,9M**,1Y,2Y,3Y,4Y*,5Y,6Y*,7Y,8Y*,9Y*,10Y
Safety & Performance	All	Pain and function	EQ-5D	6W,3M*,6M,9M**,1Y,2Y,3Y,4Y*,5Y,6Y*,7Y,8Y*,9Y*,10Y
CE Marking	All	Pain and function	EQ-5D	6W,3M*,6M,9M**,1Y,2Y,3Y
Safety & Performance	All	Pain and function	Harris Hip Score	6W,3M*,6M,9M**,1Y,2Y,3Y,4Y*,5Y,6Y*,7Y,8Y*,9Y*,10Y
CE Marking	All	Pain and function	Harris Hip Score	6W,3M*,6M,9M**,1Y,2Y,3Y
Safety & Performance	All	Function	Gait Analysis††	1Y, 5Y
Safety & Performance	All	Implant orientation	Radiograph/CT scan	2D
Safety & Performance	All	Implant osseointegration	Radiograph/CT scan	6W,3M*,6M,9M**,1Y,2Y,3Y,5Y ,10Y
Safety	All	Complication rate	All adverse events†	1Y,3Y,5Y,7Y,10Y
Safety	1A, 1B	Toxicology	Blood metal ion measurements	3M,6M,1Y,2Y
Safety	1A, 1B	Implant migration	CT-based spatial analysis (CTSA)	2D,6W,3M,6M,9M**,1Y,2Y
CE marking	1A, 1B	Implant migration	CT-based spatial analysis (CTSA)	2D,6W,3M,6M,9M**,1Y,2Y

**Cohorts 1A and 1B only*

*** Cohort 1B only*

†Calculated at these timepoints but recorded as soon as they take place and in the case of serious adverse events, reported appropriately

††Optional assessment

Table 1. Reporting time-points. The time point must have been reached by all the patients in the relevant cohort(s).

Report Title	Time point	Cohort(s)	Independent Review?	Data	Data ready (estimated)
Gateway Safety Analysis 1	2 days	1A	Yes	Complication rate, Radiological Assessment	February 2018
Safety Evaluation 6 weeks	6 weeks	1A	Yes	Complication rate, Functional Outcomes, Radiological Assessment	April 2018
Safety Evaluation 3 months	3 months	1A	Yes	Complication rate, Functional Outcomes, CT Assessment, Toxicology	June 2018
Safety Evaluation 6 months	6 months	1A	Yes	Complication rate, Functional Outcomes, CT Assessment, Toxicology	September 2018
Gateway Safety Analysis 2	6 months	1B	Yes	Complication rate, Functional Outcomes, CT Assessment, Toxicology	November 2021
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	June 2022
Safety Evaluation 1 year	1 year	1B	Yes	Complication rate, Functional Outcomes, CT Assessment, Toxicology	May 2022
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	December 2022
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	December 2023
MDR Clinical Evaluation Report	3 years	1A,1B,2	Yes	Clinical evaluation report for at least 150 patients in total with at least 72 patients at 3 years follow-up	October 2021
Interim Analysis 3 years	3 years	1A,1B,2	No	Complication rate, Radiological Assessment, Functional Outcomes, PROMS, Survivorship	December 2024
Interim Analysis 4 years	4 years	1A,1B	No	Complication rate, PROMS, Survivorship	May 2025
Interim Analysis 5 years	5 years	1A,1B,2	No	Complication rate, Radiological Assessment, Functional Outcomes, PROMS, Survivorship	December 2026
Interim Analysis 6 years	6 years	1A,1B	No	Complication rate, PROMS, Survivorship	May 2027
Interim Analysis 7 years	7 years	1A,1B,2	No	Complication rate, Functional Outcomes, PROMS, Survivorship	December 2028
Interim Analysis 8 years	8 years	1A,1B	No	Complication rate, PROMS, Survivorship	May 2029
Interim Analysis 9 years	9 years	1A,1B	No	Complication rate, PROMS, Survivorship	May 2030
Final Analysis 10 years	10 years	1A,1B,2	No	Complication rate, Radiological Assessment, Functional Outcomes, PROMS, Survivorship	December 2031

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	-2days / +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	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Figure 1. Schedule of procedures: Cohort 1A

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	-2days / +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

Figure 1. Schedule of procedures: Cohort 1B

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	-2days / +1day	±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)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Figure 1. Schedule of procedures: Cohort 2

* Optional

** Questionnaire is online only

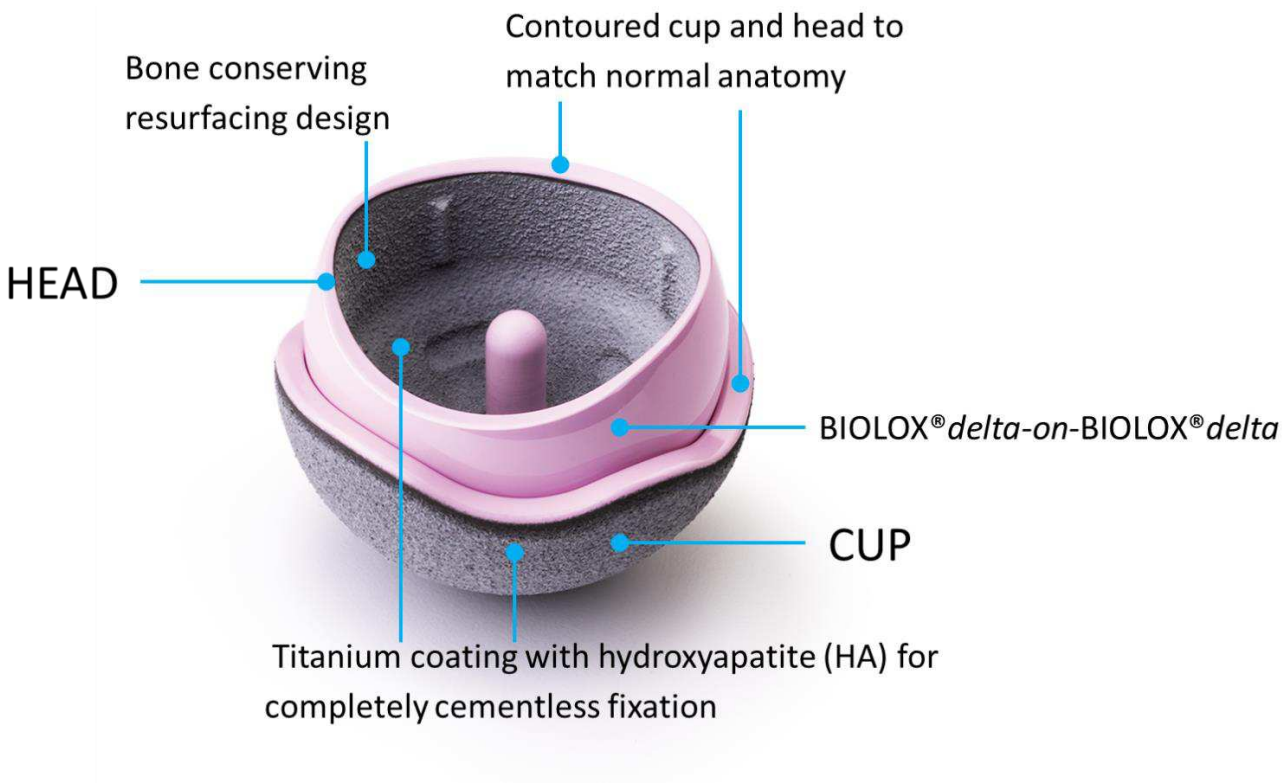
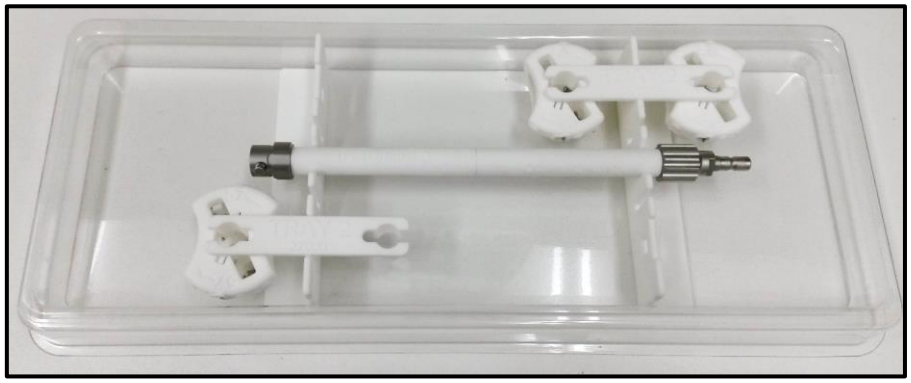


Figure 1 **The H1 Implant**

(Tray 1)



(Tray 2)

(Tray 3)

Figure 2. The H1 Instruments (top to bottom: Tray 1, Tray 2, Tray 3)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITFillablechecklist15Aug2013H1study.doc
- Appendix1Cohort2UKsitesPatientConsentFormV8Clean.pdf
- Appendix2Cohort2UKSitesPISV8CLEAN.pdf
- Appendix3AdditionalInformation.pdf