DePuy Synthes
JOINT RECONSTRUCTION
COMPANIES OF Johnson&Johnson

CLINICAL INVESTIGATION PLAN

Study Title:	GLOBAL ICON Stemless Shoulder System Post Market Clinical Follow Up Study
Protocol Number:	CT 1401
Protocol Revision:	3.0
Revision Date:	14MAY2020
Author:	PPD
Sponsor Name:	Medical Device Business Services, Inc. (hereafter referred to as DePuy Synthes)
Sponsor Address:	700 Orthopaedic Drive P.O. Box 988 Warsaw, IN 46581 United States Tel PPD Fax: PPD

PPD

PPD

Investigator Signature Page

I have read this protocol and agree to conduct this clinical investigation in accordance with the design and specific provisions outlined herein.

I understand I am solely responsible to ensure the investigation is conducted with the general principles of BS EN ISO 14155:2011 entitled Clinical investigation of medical devices for human subjects – Good Clinical Practice as the Sponsor considers appropriate for PMCF Studies, the current version of the Declaration of Helsinki, applicable local regulations, the signed agreement with Medical Device Business Services, Inc. (hereafter referred to as DePuy Synthes.) and with the protocol outlined herein.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who will assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the device and the conduct of the study.

I will fulfil the requirements of my Ethics Committee (EC) and other applicable oversight committee, to ensure complete and continual oversight of this clinical investigation.

I will use an Informed Consent Document approved by Medical Device Business Services, Inc. (hereafter referred to as DePuy Synthes and my reviewing oversight committee.

I will report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in this protocol to Medical Device Business Services, Inc. (hereafter referred to as DePuy Synthes) and my reviewing oversight committee.

I will permit Medical Device Business Services, Inc. (hereafter referred to as DePuy Synthes), FDA, or other regulatory authorities direct access to all records, including source data/documents, relating to the clinical investigation, whether paper-based or electronic data capture (EDC).

The below signature confirms I have read and understand this clinical investigational protocol and its associated amendments or attachments, and will accept respective revisions or amendments provided by DePuy Synthes.

_____	_____	_____
Printed Name Clinical (Principal) Investigator	Signature	Date

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SUMMARY/SYNOPSIS

Protocol Title	GLOBAL ICON Stemless Shoulder System Post Market Clinical Follow Up Study
Protocol Number	CT 1401
Version Date	14MAY2020
Sponsor	Medical Device Business Services, Inc. (hereafter referred to as DePuy Synthes)
Study Device and Description	GLOBAL ICON Stemless Shoulder System. The intended use for the device, applicable to this study, is as follows: Candidates for total shoulder arthroplasty with severely painful and/or severely disabled Non-Inflammatory Degenerative Joint Disease (NIDJD) resulting from osteoarthritis (OA) or post traumatic arthritis.
Investigators and Sites	Up to 20 sites will be selected to participate in the study where the GLOBAL ICON Stemless Shoulder System is cleared for use.
Sample Size	A total of 157 subjects will be implanted with the GLOBAL ICON Stemless Shoulder System in Total Shoulder Arthroplasty (TSA). It is anticipated that attrition will be no greater than 15% at 24 months post-op, so that there will be at least 133 subjects with follow-up at 24 months for the primary endpoint analysis.
Study Design	Prospective, multi-centre, non-comparative, uncontrolled Post Market Clinical Follow Up (PMCF) Study. There is no control device.
Study Duration	Approximately 144 months total – 24 months of enrolment and 120 months of follow-up.
Visit Evaluations	Subjects will be evaluated preoperatively, at the time of surgery, immediately post operatively and at 3, 12, 24, 60 and 120 months post operatively
Primary Objective and Endpoint	The primary objective of this PMCF study is to confirm device survivorship of the GLOBAL ICON stemless humeral component at 24 months post-operative. The primary endpoint in this study is a composite success endpoint at 24 months post-operative, where an individual study subject is deemed to be a composite success if each of the following criteria is met at the 24 months follow-up visit: • Radiographs indicate that there is no continuous radiolucent line around the GLOBAL ICON stemless humeral component • The adjusted Constant-Murley score is greater than 85 • No GLOBAL ICON humeral component has been removed for any reason • There have been no device-related serious adverse events
Safety Objective and Endpoint	The safety objective of the study is to confirm survivorship of the Global Icon stemless shoulder at 24, 60 and 120 months post-operative and collect information related to the type and frequency of adverse events.

	The safety endpoints are: • Overall survivorship of the GLOBAL ICON device at 24, 60 and 120 months post-operative, where a device is deemed to be surviving if no components have been removed for any reason • The type and frequency of all adverse events (AEs) in this study will be summarised, with distinction of serious AEs, operative and device related AEs.
Secondary Objective and Endpoints	Secondary objectives include the evaluation of clinical and radiographic performance and safety outcomes. The secondary endpoints are: • Mean adjusted Constant-Murley Score at baseline and 3, 12, 24, 60 and 120 months post-operative • Mean Oxford Shoulder Score at baseline, and 3, 12, 24, 60 and 120 months post-operative • Mean EQ-5D-5L Scores by dimension and EQ-VAS at baseline, and at 3, 12, 24, 60, and 120 months post-operative • Radiographic evidence of aseptic loosening of the GLOBAL ICON stemless humeral component immediate post-operative and 3, 12, 24, 60, and 120 months post-operative
Tertiary Endpoints	Tertiary endpoints in the study will include the following: • Mean change from baseline for the adjusted Constant-Murley Score at 3, 12, 24, 60 and 120 months post-operative • Mean change from baseline for the Oxford Shoulder Score at 3, 12, 24, 60 and 120 months post-operative • Mean change from baseline for EQ-5D-5L dimension score and EQ-VAS scores at 3, 12, 24, 60 and 120 months post-operative • Periprosthetic fracture survivorship of the GLOBAL ICON stemless humeral component at 24, 60 and 120 months post-operative

TABLE 1: Time and Events

EVENT/VISIT	PRE-OP (BASELINE)	SURGERY	IMMEDIATE POST-OP / DISCHARGE	3 MONTHS	12 MONTHS	24 MONTHS	60 MONTHS	120 MONTHS	Unscheduled Visit
Required Timing (days)	-180 days to day of surgery (0)	0	0 - 10	35 – 126	281 - 449	646 – 1644	1645-2005	3470-3830	As required
Screening/Enrolment Log	X								
Discuss Study with Subject	X								
Informed Consent	X								
Determine Eligibility	X								
Subject Demographics & History	S								
Constant-Murley Score	S			S	S	S	S	S	As required
Oxford Shoulder Score	P			PP	PP	PP	PP	PP	As required
EQ-5D-5L	P			PP	PP	PP	PP	PP	As required
Operative Detail		S							
Device Log		S							
Study Visit Form	S		S	S	S	S	S	S	
Radiographic Examinations **Grashey AP & Axillary views as required* - send to MMI**	X		X	X	X	X	X	X	As required
Adverse Event Reporting		X	X	X	X	X	X	X	As required
Device Deficiencies		X	X	X	X	X	X	X	As required
Unscheduled Visit									S

S —Completed at visit by the site

P —Completed by the patient (PP - can be completed by post)

*** —Please note Axillary view is not required at immediate post-op time point and Standard AP is acceptable at pre-op visit if Grashey view was not obtained**

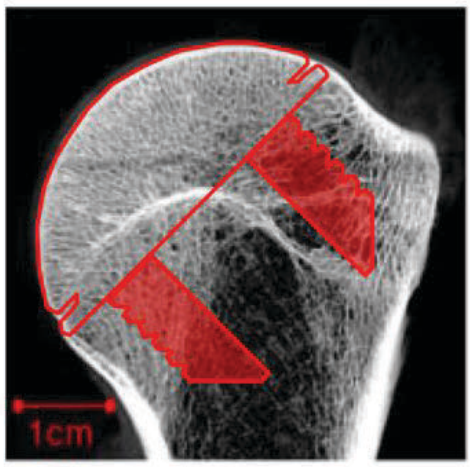
NCT03168672

1. INTRODUCTION

The current gold standard of shoulder arthroplasty uses a stemmed implant in the humerus as part of a hemi or total joint replacement. Shoulder resurfacing was the first attempt to address opportunities for shoulder arthroplasty such as bone conservation; however, the procedure is technically demanding and does not allow for anatomic reconstruction. More recently, stemless shoulder devices have been in use, where the implant is independent of the humeral canal allowing the humeral head to be replaced in the optimal anatomic position. Stemless implants also have the potential to provide increased procedural efficiency through simplified instrumentation and implant selection, and to conserve bone for future revision operations.

GLOBAL ICON is a stemless shoulder system, for use in total shoulder arthroplasty in patients with osteoarthritis and post traumatic arthritis. It is similar in design and intended use to other stemless shoulder prostheses which are currently available and in clinical use.

The GLOBAL ICON stemless humeral component is intended to replace the proximal humeral head in total shoulder arthroplasty. The GLOBAL ICON stemless humeral component construct includes a Humeral Head and an Anchor Plate, for articulation with the glenoid component and for fixation into the resected proximal humerus, respectively. The system is bone conserving relative to stemmed arthroplasty; it does not violate the humeral canal allowing surgeons to properly position the component with fewer surgical steps. The GLOBAL ICON implants were designed by leveraging the fact that the epiphyseal structures can be characterized by a sphere and by constraining the design of the construct within this sphere.



The GLOBAL ICON stemless humeral component has received CE marking following demonstration that is it safe and effective by a systematic review of the literature available on stemless shoulder devices.

2. STUDY PURPOSE

3.1 Study Rationale

This is a Post Market Clinical Follow Up (PMCF) study to monitor the safety and performance of the GLOBAL ICON stemless humeral component. The data gathered will be used to support post market surveillance of the device and may potentially be used for additional market access purposes.

3.2 Study Design

This study will be multi-centre and non-comparative. Subjects will be recruited and followed up at similar intervals to reflect the standard clinical practice and intended population for wider use of the device.

3.3 Study Population

157 non-randomised subjects will be recruited from up to 20 sites. Investigational sites will be located in the European Union and Canada. A maximum of 30 subjects may be recruited from one site. More than one implanting surgeon may recruit subjects at each site as a designated sub-Investigator.

3.4 Study Objective and Endpoints

3.4.1 Primary Objective and Endpoint

The primary objective of this PMCF study is to confirm device survivorship of the GLOBAL ICON stemless humeral component at 24 months post-operative.

The primary endpoint in this study is composite success at 24 months if each of the following criteria is met:

- Radiographs indicate that there is no continuous radiolucent line (RLL) around the GLOBAL ICON stemless humeral component, with continuous RLL defined as a radiolucent line > 1mm in all five zones of either AP or Axillary views
- The adjusted Constant-Murley score is greater than 85, with the adjustment based on the method of Constant[1]
- No GLOBAL ICON humeral component has been removed for any reason
- There have been no device-related serious adverse events

[1] Katolik, Leonid I., Romeo, Anthony A., Cole, Brian J., Verma, Nikhil N., Hayden, Jennifer K., Bach, Bernard R. Normalization of the Constant Score. Journal of Shoulder and Elbow Surgery 2005; 14:279-285.

3.4.2 Safety Objective and Endpoints

The safety objective of the study is to confirm survivorship of the Global Icon stemless shoulder at 24, 60 and 120 months postoperative and collect information related to the type and frequency of adverse events

The safety endpoints are:

- Overall survivorship of the GLOBAL ICON stemless humeral component survivorship at 24, 60 and 120 months post-operative, where the device is deemed to be surviving if no components (anchor plate and humeral head) have been removed for any reason
- The type and frequency of all adverse events (AEs) in this study will be summarised, with distinction of serious AEs, operative and device related AEs.

3.4.3 Secondary Objective and Endpoints

The secondary objectives include the evaluation of clinical and radiographic performance s at 3, 12, 24, 60 and 120 months post-operatively.

Secondary endpoints in the study will include the following:

- Mean adjusted Constant-Murley Score at baseline and 3, 12, 24, 60 and 120 months post-operative
- Mean Oxford Shoulder Score at baseline and 3, 12, 24, 60 and 120 months post-operative
- Mean EQ-5D-5L Scores by dimension and EQ-VAS, at baseline and 3, 12, 24, 60, and 120 months post-operative
- Radiographic evidence of aseptic loosening of the GLOBAL ICON stemless humeral component immediate post-operative and 3, 12, 24, 60 and 120 months post-operative

3.4.4 Tertiary Endpoints

Tertiary endpoints in the study will include the following:

- Mean change from baseline for the adjusted Constant-Murley Score at 3, 12, 24, 60 and 120 months post-operative
- Mean change from baseline for the Oxford Shoulder Score at 3, 12, 24, 60 and 120 months post-operative
- Mean change from baseline for EQ-5D-5L dimension score and EQ-VAS scores at 3, 12, 24, 60 and 120 months post-operative
- Periprosthetic fracture survivorship of the GLOBAL ICON stemless humeral component at 24, 60 and 120 months post-operative

4 PROTOCOL

4.1 Study Design

This is a prospective, multi-centre, non-comparative, uncontrolled post market clinical follow up study to evaluate the mid-term survivorship, safety and effectiveness of the GLOBAL ICON stemless shoulder component using clinical, patient and radiographic outcomes.

157 subjects will be enrolled at up to 20 centres. Each subject may participate in the study only once. Subjects will be assessed pre-operatively, intra-operatively, immediately post-operative/at hospital discharge, and at 3, 12, 24, 60 and 120 months post operatively.

The overall duration of the study is anticipated to be 144 months; 24 months to complete enrolment, and 120 months to complete subject follow up.

The study device is the GLOBAL ICON stemless humeral component, consisting of the Anchor Plate and Humeral Head.

The corresponding glenoid component used must be a glenoid component cleared for use with GLOBAL ICON stemless humeral component. A list of product codes for the GLOBAL ICON humeral components, and the corresponding DePuy Synthes glenoid system that may be implanted within the scope of this study protocol are listed in Section 9, Study Devices.

4.2 Eligibility

Subjects will be assessed for their eligibility to participate in the study according to the screening process described in Section 4.3, which is documented on the Screening and Enrolment Log.

Subjects will be recruited according to the following inclusion/exclusion criteria.

4.2.1 Inclusion Criteria

Subjects meeting **all** the following specific criteria will be considered for participation in the study:

- severely painful and/or severely disabled Non-Inflammatory Degenerative Joint Disease (NIDJD) resulting from osteoarthritis (OA) or post traumatic arthritis
- Patient is willing and able to complete the required post-operative schedule
- Patient has provided written Informed Consent to participate

4.2.2 Exclusion Criteria

Subjects will be excluded from participation in the study if they meet **any** of the following criteria:

- Subjects under the age of 21 or over the age of 80 on the day of consent
- Subjects who have not reached skeletal maturity, regardless of age
- Either preoperatively or intraoperatively bone stock in the proximal humerus or glenoid fossa is determined to be inadequate for supporting the GLOBAL ICON stemless humeral components

- Intraoperatively, bone is determined to be too soft or porous to support the implant or that is too hard or brittle to allow for proper bone preparation and fixation, i.e. osteoporosis or sclerotic bone, where there could be considerable migration of the prosthesis and/or a chance of fracture of the humerus or glenoid
- Fractures of the proximal humerus that could compromise the fixation of the GLOBAL ICON stemless humeral components
- Subjects who have undergone previous treatment on the study shoulder that may compromise fixation of the GLOBAL ICON stemless humeral components
- Revision of a failed hemi, total or reverse shoulder arthroplasty
- Active local or systemic infection
- Absent, irreparable or nonfunctional rotator cuff or other essential muscles
- Subject is receiving, or is scheduled to receive, treatment that the Investigator considers could affect bone quality, such as chemotherapy or high dose corticosteroids
- Subjects who, at the point of enrolment, already have a GLOBAL ICON shoulder replacement or are scheduled to receive, a contralateral shoulder replacement device
- Subjects who are known to be pregnant or breastfeeding
- Subjects who are known drug or alcohol abusers or with psychological disorders that could affect follow-up care or treatment outcomes
- Subjects with a known medical condition that the Investigator believes would impact the study outcomes (including, but not limited to osteomyelitis, Paget's disease, neuropathies such as Charcot's disease, metastatic or neoplastic disorders)
- Known polyethylene and/or metal sensitivity or allergy

4.3 Subject Screening

All patients who present and potentially meet the study inclusion/exclusion criteria, will be screened for eligibility and will be listed on the Study Screening and Enrolment Log in order to document that the subject selection was unbiased.
The date of screening, the results of screening (included or not) and the primary reason for not including the patient (*e.g.*, does not satisfy eligibility criteria, not interested in participating) will be recorded on this log. The original log is to be retained at the Site and a copy sent to the Sponsor regularly during enrolment.
A flowchart demonstrating the screening process and definition of enrolment is illustrated in Figure 1.

Qualified patients who agree to participate in the study will be required to sign an Informed Consent Document (ICD). After signing the Informed Consent, study Subjects are defined as "enrolled" and will be allocated a study number.

It is expected that complete data collection will be obtained for all enrolled Subjects.

4.4 Informed Consent

In compliance with BS EN ISO 14155:2011, no subject shall be enrolled, and no study-related procedure or form associated with this study be completed, until informed written consent is obtained for that subject. The Investigator is responsible for ensuring that no subject is included in the study without adequate informed consent being provided. Failure to obtain and properly document this process is in violation of BS EN ISO 14155:2011, the Declaration of Helsinki, and this study protocol.

All Informed Consent Documents (ICD) must have the favourable opinion of the Ethics Committee at each site. Many institutions request modification of the ICD to satisfy specific institutional requirements. The use of a modified or unique Informed Consent Document is permitted provided that all the requirements of BS EN ISO 14155:2011 are met and the document is approved by the Sponsor.

Consent of a subject needs to be from the subject themselves and documented on an Informed Consent Document in the primary language of the subject. All translated consent forms will be submitted for Ethics approval.

The Investigator or delegated representative (see Section 12) shall offer study participation to those subjects who appear to be a good candidate for the study. If the subject is interested, the Informed Consent process is followed. If the subject meets all of this protocol's Inclusion Criteria and none of the Exclusion Criteria (see Section 4.2), the Investigator or delegated representative shall confirm the subject understands each of the following points of the study:

- The purpose of the study
- The potential risks or adverse events that are posed by their treatment
- The potential risks or adverse events related to study participation
- Possibility of failure and the need for subsequent treatment(s)
- Alternative procedures/treatments available to the Subject
- Requirements of the study including rehabilitation and follow-up visits
- All of the Subject's rights as a participant in the clinical investigation

Following the explanation of the study intent, the Investigator or designee shall offer to answer any of the Subject's questions. If the Subject then agrees to participate, his or her willingness must be documented by their personally handwritten signature and date on the Ethics approved ICD.

If the ICD signatures are acquired on the day of surgery, the time that the consent was given must also be recorded on the ICD signature page.

This document must be signed and dated by the Subject prior to any study-specific related procedures being performed (i.e. procedures or assessments that cannot be considered as standard care)
No dates should be pre-populated or completed by someone other than the person providing the signature.

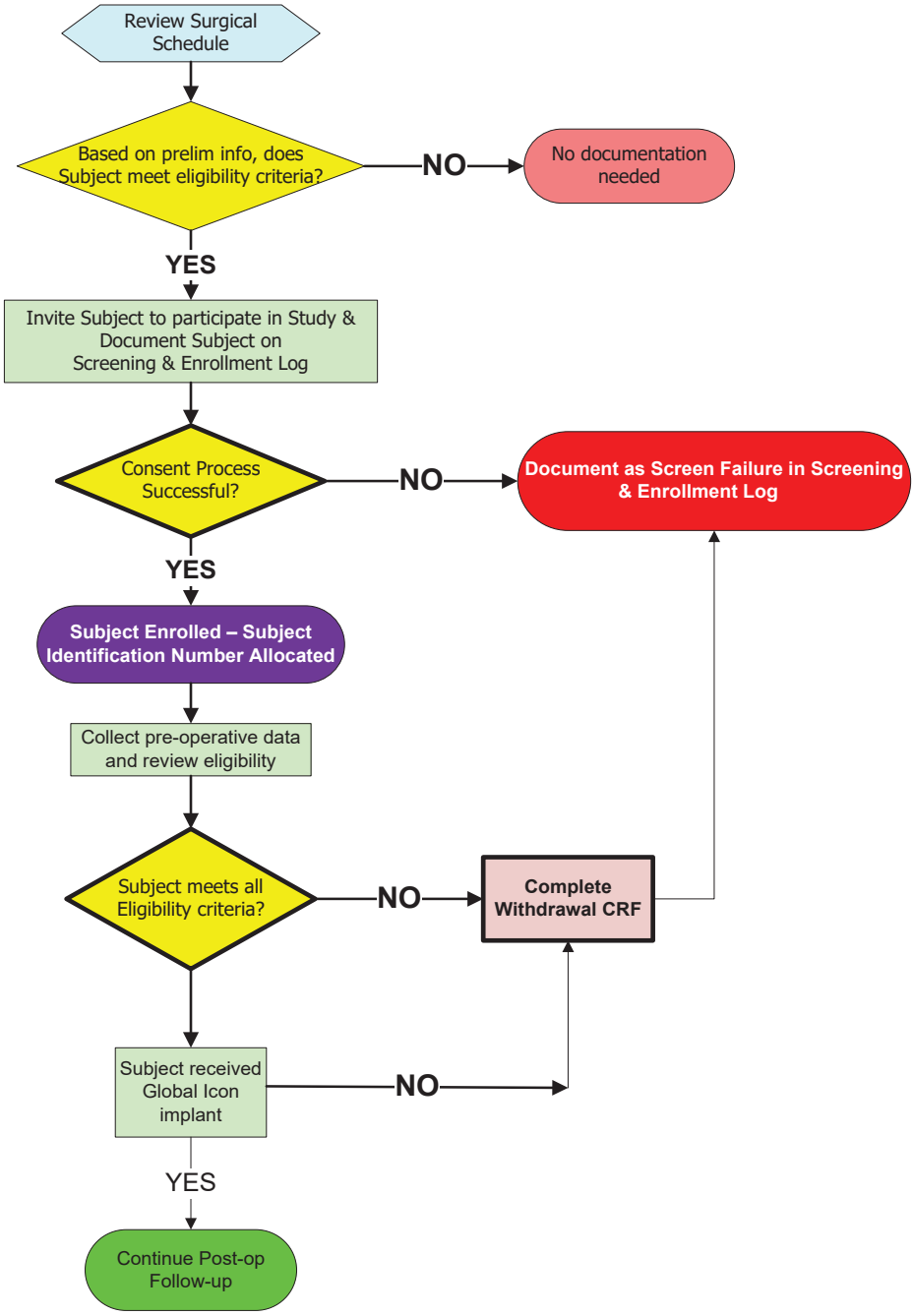
4.5 Definition of Enrolment

As illustrated in Figure 1, a patient will be considered enrolled when they have:

- Completed the Informed Consent Documents to participate in this Investigation
- Been entered into the electronic database and a subject number has been generated

Should new information become available during the course of the study that may affect a subject's decision to participate, the information sheet will be updated, appropriate approvals sought, and the subject will be required to provide their consent on the new, approved version.

Figure 1: Screening and Enrolment Process



5 STUDY PROCEDURES

5.1 Pre-operative assessment

Each subject considered eligible for entry into this clinical investigation will have the following information, procedures and assessments recorded at the pre-investigational examination. All preoperative assessments must be completed within 180 days before surgery and those assessments are:

- Demographic details including age, gender, weight, height
- Diagnosis
- Previous shoulder surgery(ies)
- Other medical conditions
- Radiographic examination – Standard or Grashey AP and axillary x-rays (Please note that pre-operatively a standard AP view is acceptable if a Grashey view is not available)
- Clinical Assessment
  - Constant-Murley Score
- Patient Assessment
  - Oxford Shoulder Score
  - EQ-5D-5L

5.2 Operative assessment

The operative management of each subject enrolled in this clinical investigation will be as per the standard regime used at the investigation site.

- **Anaesthesia**
  The anaesthetic procedure will be as per the standard regime used at the investigation sites for subjects undergoing a total shoulder replacement.

- **Procedure**
  The delto-pectoral surgical approach will be used exclusively in this clinical investigation. All devices and instruments must be used in accordance with the manufacturer's instructions. The surgical technique for the implantation of the GLOBAL ICON stemless humeral component is located in Exhibit A.

- **Intra-operative assessments**
  During the operative procedure an assessment must be performed. The following information must be recorded in the subject's case report form:
  - Surgeon name
  - Date of surgery
  - Method of anaesthesia
  - Surgical approach

- Passive range of motion
- Bone quality
- Duration of the surgical procedure
- Details of all devices and components implanted
- Details of any peri-operative adverse events
- Details of any device deficiencies

5.3 Follow-Up Assessments

The Investigator will also inform the subject's local doctor / General Practitioner (GP) in writing of the subject's participation in this investigation at the same time as advising of the surgical procedure, providing the subject gives their consent to this process.

Subjects will be followed up as part of the clinical investigation at the following time points (date range for acceptable time window):

- Discharge/immediate post-operative (0-10 days)
- 3 months (35-126 days OR 5-18 weeks) post treatment
- 12 months (281-449 days OR 40-64 weeks) post treatment
- 24 months (646-1644 days OR 92-234 weeks) post treatment
- 60 months (1645-2005 days OR 235-286 weeks) post treatment
- 120 months (3470-3830 days OR 495-547 weeks) post treatment

All follow-up assessments and applicable unscheduled (*i.e.,* unplanned or unscheduled that occur between the protocol defined visit windows) visits will be recorded in the subject's eCRF by the Investigator study team unless otherwise indicated.

Both study and unscheduled office visits are defined as any visit at the study site where a study subject is seen by one of the site staff including the Principal Investigator (PI), any Sub-investigator (as appropriate), or anyone identified on the PI's team/delegation of authority.

An unscheduled visit is to be documented on an Unscheduled Visit eCRF/CRF when:

1. A subject returns for an additional visit during a study visit interval as described in **Table 1 - Time and Events**.
2. A subject returns between study visit intervals

If the previous protocol-defined study interval visit was missed, the required eCRFs/CRFs in the previously missed interval visit are also required to be completed along with the Unscheduled Visit eCRF.

If an unscheduled visit is related to a new, worsening, or resolved adverse event, both an AE eCRF and the Unscheduled Visit eCRF are to be completed.

Important note: Adverse Event (AE), including serious AEs, information is to be collected at ALL interactions with the study subject. This includes when non-site staff treats the study subject in a manner where the source documentation is available to the site staff. The site staff is responsible to review the medical event and report it per the protocol.

5.3.1 Clinical Assessments

At 3, 12, 24, 60 and 120 months post-treatment the following assessments will be performed:

- Constant-Murley Score
- Confirmation of implant survival (Study Visit Form)

5.3.2 Radiographic Assessments

Radiographs will be taken at the following time points:

- Immediate post-operative (0-10 days) – only Grashey AP view required
- 3, 12, 24, 60 and 120 months post treatment – Grashey AP and Axillary view required

The investigator will not be required to complete any eCRF's for per protocol radiographic assessments.

5.3.3 Patient Assessments

At 3, 12, 24, 60 and 120 months post-treatment, subjects will be asked to complete the following assessments:

- Oxford Shoulder Score
- EQ-5D-5L

This information will be transferred from a paper copy into the eCRF by the study site. These assessments will be completed by the subject, and may be completed at a clinic visit, or returned to the site by post, within the required assessment window.

5.4 Adverse event and Device Deficiency reporting

Pre-operatively, and at each follow-up assessment (immediate post-operative, 3, 12, 24, 60 and 120 months post-treatment), details of any device deficiency, adverse event or adverse device effect reported will be recorded in the eCRF. Details to be recorded include the nature, onset, duration, seriousness, relationship to the device and outcome of the event (see Section 6.3).

The occurrence of adverse events (including new illnesses, worsening symptoms of coexisting disease(s) or additional symptoms) will be identified by spontaneous reports from the subject in response to a standard question (e.g. how have you been since your last visit?) or by clinical/radiological assessment.

5.5 Radiographic Assessments

All radiographs will be submitted to an imaging vendor, Medical Metrics Inc. (MMI) for review and evaluation. MMI will complete eCRFs to document the radiographic findings under the scope of the study specific Radiographic Evaluation Protocol (Exhibit B).

5.6 Subject Discontinuation

Subjects are free to withdraw their consent to participate in the study at any time.

Subjects may be withdrawn by the investigator if they consider that the subject is unable to fulfil their requirements of participation.

Subjects may be documented as lost to follow up at the end of the study where they have not formally withdrawn their consent, but do not attend all required follow up visits/study schedule assessments on the request of the investigator.

A subject will be documented as withdrawn in the event of their death during the study.

The maximum recruitment limit at each site applies to subjects that successfully receive the study device.
In the instance of a consented subject withdrawing from the study pre-operatively or intra-operatively, they can be replaced by the investigator with another suitable subject.

6. RISK ANALYSIS

6.1 Study Related Risks

Any surgical procedure poses a potential risk and the procedures undertaken as part of this clinical investigation are no exception. There are known risks associated with the method of anaesthesia (general, epidural, local). In addition to these there are risks associated with a surgical procedure that involves a device. The risks that are associated with the study devices are similar to those of any total shoulder arthroplasty.
As specified in the Instructions For Use (IFU) (Exhibit C and included in the implant packaging), the following are generally the most frequently encountered adverse events and complications in total shoulder arthroplasty. Some of the identified risks are not directly applicable to this study, however any adverse events should be reported.

- Early or late loosening of the prosthetic components(s), often related to factors listed in **WARNINGS** and **PRECAUTIONS**.
- Change in position of the prosthesis, often related to factors listed in **WARNINGS** and **PRECAUTIONS**.
- Subluxation or dislocation of the replaced joint.

- Temporary inferior subluxation (this condition generally disappears as muscle tone is regained).
- Early or late infection.
- Hematoma and/or delayed wound healing.
- Cardiovascular disorders including venous thrombosis, pulmonary embolism and myocardial infarction.
- Pneumonia and/or atelectasis.
- Systemic or local adverse events or complications resulting from anaesthesia.

6.2 Study Participation Benefit Analysis

There are no potential benefits to study subjects from participation in this study. The knowledge gained from this investigation may help future shoulder arthroplasty patients.

6.3 Adverse Event Determination and Reporting

Adverse Event Determination will be done by the Principal Investigator or appropriate designee.

An Adverse Event (AE) is defined as an untoward medical occurrence, unintended disease or injury, or untoward clinical signs (or change or worsening of a pre-existing medical condition) in a patient, which may or may not have an association with the device.

Adverse Device Effect (ADE)* is defined as an Adverse Event related to the use of an investigational medical device.
NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
NOTE 2- This includes any event that is a result of a use error or intentional misuse.

Serious Adverse Device Effect (SADE)* is defined as an Adverse Device Effect that has resulted in any of the consequences characteristic of a serious adverse event.

***Per MEDDEV 2 12-1 rev.8 Vigiliance - Section 3.1.4: Users should report INCIDENTS with MEDICAL DEVICES to the Manufacturer or the Competent Authority depending on national practice.**

Serious Adverse Event (SAE) is defined as an Adverse event that:
a) led to a death,
b) led to a serious deterioration in health that either:
1) resulted in a life-threatening illness or injury, or
2) resulted in a permanent impairment of a body structure or a body function, or
3) required in-patient hospitalization or prolongation of existing hospitalization, or
4) resulted in medical or surgical intervention to prevent life threatening illness or

injury or permanent impairment to a body structure or a body function.
c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

NOTE 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.
Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

This protocol requires each site to report adverse events to the Sponsor according to the timelines below, record them in the subject's CRF, and inform their respective Ethics Committee (EC), per the Committee requirements.

Reporting Timelines

- **Serious Adverse Events (SAES)/Serious Adverse Device Effects (SADEs) and Unexpected Adverse Device Effects (UADES) - AS SOON AS POSSIBLE but no later than 72 hours after becoming aware**
- **Adverse vents (AEs) and Adverse Device effects (ADEs) AS SOON AS POSSIBLE but no later than 14 days after becoming aware**

Determination of ADEs and SADEs: The determination whether the AE is related to the device or procedure will be based upon whether a causal relationship between the device or procedure and the AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. A causal relationship cannot be ruled out if, in the medical judgment of the Investigator, the effect follows a reasonable temporal association with the use of the device and/or is confirmed by the improvement of the effect upon discontinuation of the clinical use of the device, and/or the effect is not reasonably explained by the Subject's clinical state.

Anticipated/Unanticipated Adverse Events (Expected/Unexpected)

The PI is responsible for determining whether an AE is **anticipated** or **unanticipated**. This determination is based on whether, in the opinion of the PI, the severity, type and frequency of the AE is consistent with the Instructions for Use (IFU). Please note that since TSA is a routine elective procedure, the vast majority of adverse events are anticipated and included in IFU.

When a PI classifies an AE as unanticipated, the Sponsor will also review and classify anticipated/unanticipated based on the reported event and in consideration of the IFU and internal risk reports. If the Sponsor has a different opinion on an anticipated/unanticipated classification a query will

be generated. When there is a discrepancy between the site and the Sponsor, both opinions will be recorded and reported as required to the relevant EC.

Relationship to study device or procedure should be rated as follows:
none (definitely not related): there is no relationship between study device or procedure and the event.
possible (remote possibility, possibly, or probably related): the relationship between study device or procedure could exist if there is no contradicting evidence that can reasonably explain the Subject's condition.
definite (definitely related): the relationship between study device or procedure and event does exist and is confirmed upon further investigation by the Investigator.

Pre-existing medical conditions or symptoms reported prior to device implantation are not to be recorded as AEs. In the event there is an exacerbation of the pre-existing medical condition or symptoms, then an AE must be reported.

AEs are reported beginning from implantation/operative procedure until subject participation has ended (study completed or consent withdrawn). AEs must be followed to resolution, or until the study completion or consent withdrawal. When a subject ends participating in the trial (either study completion or consent withdrawal), an AE must be designated either as "resolved" (end date must be provided), or as "ongoing."

Subjects should be encouraged to report AEs spontaneously and may volunteer AE information at any time. At each evaluation, the Investigator will determine whether an AE has occurred. If it is determined that an AE has occurred and is reportable, the Investigator should obtain all the information required to complete the appropriate AE form eCRF. If an event occurs at an outside institution, the Investigator should attempt to obtain, if possible, required AE information.

The Investigator will record the nature, severity, treatment and outcome of the AE, and will determine their association to the device or the study procedure.

The following categories of AE severity are to be used:

mild: awareness of a sign, symptom or event that is easily tolerated and transient in nature with minimal or no impairment to normal activity.

moderate: moderate symptoms that are poorly tolerated, sustained, interfere with normal activity and require medical attention.

severe: symptom(s) require intervention, and the activities of daily living are significantly altered.

6.4 Minimization of Risks

The Sponsor will further minimise the identified and/or emergent risks throughout the study, by reviewing the reported adverse events and adverse effects. A Medical Monitor will be assigned to the project and complete a quarterly review of safety data to ensure no trends or signals are evident. Additionally, a Clinical Events Committee (CEC) comprised of an independent group of orthopaedic surgeons will meet prior to primary analyses to review and adjudicate AE data. Details about the CEC may be found within the associated charter.

Device related AEs will be reviewed and reported as per the required current regulatory requirements to the Notified Body. Based upon an evaluation of such events, the Sponsor may either amend the investigational plan or terminate the investigation to protect the rights, safety and welfare of the study subjects.

Should an EC decide to suspend or withdraw its approval for an Investigator to conduct the study at that institution, based on unacceptable risks to the study subjects, the study Sponsor will notify all reviewing ECs and Investigators of this action. To further minimise risks, any new information obtained during the course of the study relating to unanticipated adverse findings will be provided to all subjects, Investigators, and ECs.

The study has been designed to minimize the number of subjects yet provide sufficient numbers of subjects for valid scientific analysis of the compiled study data. The study design, the procedures for monitoring and the documentation, reporting and evaluation of the results from its surgical use will further control risks.

Only trained orthopaedic surgeons with expertise in treating this condition will conduct surgeries.

6.5 Early Termination or Suspension

The Sponsor, Ethics Committee or Regulatory Authority may prematurely terminate or suspend the clinical study as a whole or at an individual investigational site for significant and documented reasons. The Investigator may also prematurely terminate or suspend the clinical study at his/her site, for significant and documented reasons. Reasons for premature termination or suspension by any party include, but are not limited to safety, inadequate recruitment, Investigator issues, device related problems, alignment with business strategy or administrative issues.

If suspicion of an unacceptable risk to subjects arises during the clinical study, or when instructed by an Ethics Committee or Regulatory Authority, the Sponsor shall suspend the clinical study at all active sites while the risk is assessed. The Sponsor shall terminate the clinical study if an unacceptable risk is confirmed, or resume the clinical study following appropriate communication and approval from the Ethics Committee and Regulatory Authority as required.

In terminating the clinical study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subject's interests and all documentation is archived and the appropriate bodies such as the Ethics Committees and Regulatory Authorities are informed as appropriate.

7. STATISTICAL METHODOLOGY

Statistical analysis will be performed using SAS® (SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513) software version 9.3 or higher. Any further software, such as MEDRA coding, that may be necessary will be described in the final study report.

7.1 Study Design

This is a prospective, multicentre, uncontrolled, one-arm study. During this study, 157 subjects will be implanted with the device. Approximately 20 sites will be approved to participate in this study.

Patients will be clinically followed after surgery at immediate post-op, 3, 12, 24, 60 and 120 month visits. Data collected at the 24-month interval visit will be used in determining success on the primary endpoint.

7.2 Treatment Assignment

The GLOBAL ICON stemless humeral component is the **only** device of interest in this study; there will be no control group.

7.3 Levels of Significance

Unless otherwise stated, confidence intervals will be 2-sided 95% confidence intervals, and p-values below 0.05 will be deemed to be statistically significant. Unless otherwise stated, there will be no adjustment of significance levels because of testing multiple hypotheses.

7.4 Interval Windows

The following scheduled visits as shown in Table 1, Section 1 have the following visit windows:

Table 2: Interval Windows

Analysis Visit	Study Visit	Study Interval (Days from Surgery)	Visit Window
Baseline	**Pre-Op**	--180 days to day of surgery (day 0)	-180 to 0 days
Surgery	**Surgery**	0	
Immediate Post-Op	**Immediate Post-Op**	0-10	**5** (-5 to +5 days)
3 Months	**3 Months**	35 – 126	**80** ± 45 days
12 Months	**12 Months**	281 - 449	**365** ± 84 days
24 Months	**24 Months**	646 - 1644	**730** - 84 days **730** + 914 days
60 Months	**60 Months**	1645 - 2005	**1825** ± 180 days

120 Months	**120 Months**	3470 – 3830	**3650** ± 180 days

The intervals defined in the visit window column will be used to determine if data are collected within the protocol specified visit windows. Data collected at planned and unscheduled visits will be allocated according to the visit windows based on the collection date. The primary endpoint will use the data collected within the 24-month interval window. Secondary and tertiary endpoints will make use of the analysis visit, that is, the visit to which the data are mapped. If multiple records are allocated to the same analysis visit and one of the records is the planned collection, that record will be maintained for the primary, secondary and tertiary analyses. If none of the records are from planned collections, the record closest to the target study day for the visit will be used. Any planned visits conducted outside of the window will be considered a protocol deviation.

7.5 Handling of Missing Data for the Primary Endpoint

For analysis of the primary endpoint, subjects who withdraw prior to the 24-Month Interval will be included in the analysis as composite endpoint failures if they had one of the following events either intra-operatively or post-operatively:

- A post-operative radiograph indicated a continuous radiolucent line (RLL) around the humeral prosthesis, with continuous RLL defined as a radiolucent line > 1mm in all five zones of either AP or Axillary views
- A revision occurred in which a GLOBAL ICON humeral component was removed
- The subject had a device-related serious adverse event (SADE)

Participants who withdraw prior to 24-month follow-up and did not experience any of the clinical outcomes listed above will be considered to have missing values on the clinical outcomes/primary endpoint, which will be addressed through multiple imputation methods (see SAP for further details).

7.6 Hypothesis Testing of Primary Endpoint

The primary endpoint analysis will seek to demonstrate that at 24 months after surgery, the composite success (p), which is based on the absence of all four clinical outcomes (continuous RLL around the component, adjusted Constant-Murley Score$\leq$ 85, component removal, SADE), is significantly greater than a performance goal of 75%. The null and alternative hypotheses for this endpoint are as follows:

Null hypothesis H_o: $p \leq 75\%$

Alternative hypothesis H_A: $p > 75\%$

Decision Criterion: The null hypothesis will be rejected and the alternative hypothesis will be concluded if the lower bound of a 2-sided 95% confidence interval is greater than 75%.

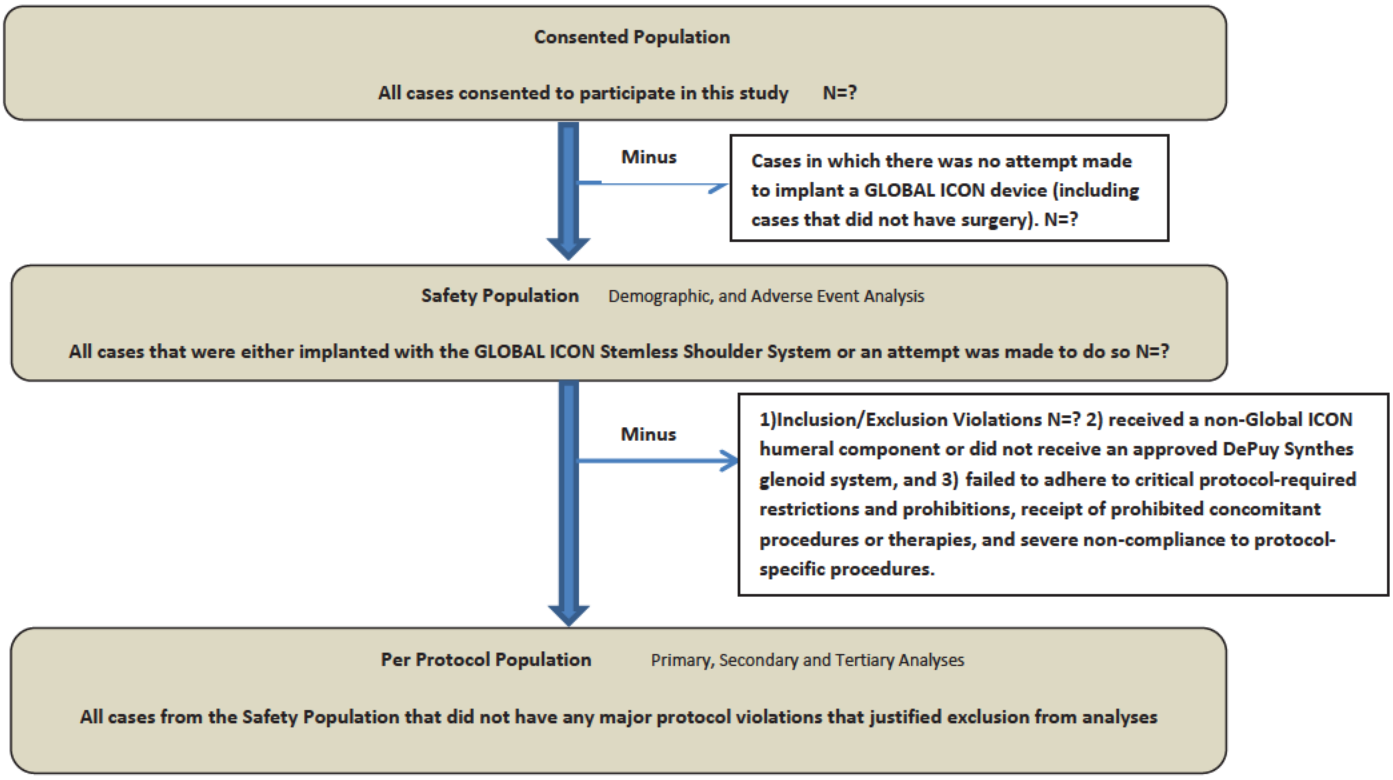
7.7 Study Populations

This study defines 3 study populations, Consented/Enrolled Population, Safety Population, and Per Protocol Population, as defined in the table and the flow chart below:

Table 3: Study Populations

Population	Subjects Included
Consented/Enrolled Population	The Consented/Enrolled Population will consist of all subjects who were consented and enrolled in the study based on preliminary subject eligibility.
Safety Population	The Safety Population will consist of all subjects who were enrolled and were either implanted with the GLOBAL ICON stemless humeral component or an attempt was made to do so. Demographic data and analysis of the primary, safety, secondary and tertiary endpoints will be based on the Safety Population.
Per Protocol Population	The Per Protocol Population will consist of the subset of the Safety Population without specific protocol deviations (see Figure 2 or SAP for further details). The final Per Protocol Set will be determined prior to database hard lock and in agreement with clinical research and clinical operations. Analyses using the Per Protocol Population will be used to complement analyses based on the safety population.

Figure 2: Primary Analysis Populations Flowchart



7.8 Sample Size Justification

The sample size was determined based on the primary endpoint using the one-sample exact-test of a proportion as implemented in PROC POWER in SAS, version 9.3 or higher. For the calculation, we assume the composite success proportion at 24 months after surgery is 85% and implement a one-sided test at the 0.025 alpha-level to determine the minimal N which provides more than 80% power; this sample size is 133. To accommodate potential 15% attrition, the sample size will be increased to 157.

The sample size applies to patients enrolled and actually treated. Some patients who were enrolled in a study may not be ultimately treated for various reasons. Patient enrolment will continue until the proposed sample size for treated patients is complete.

NOTE: Although the sample size was originally determined based on the anticipated use of a one-sample exact-test of a proportion, it has been determined after enrolment was complete that a one-sample Z-test of a proportion using a normal approximation would be utilized in the final primary endpoint analysis to facilitate data imputation methods.

7.9 Analysis Plan

All analyses will be presented for the safety population as described in Table 3 above. Baseline subject characteristics, procedure characteristics and the primary, secondary and tertiary endpoints will be

presented across all patients. Descriptive statistics for dichotomous and categorical variables will include the number and the percentage of subjects. Descriptive statistics for continuous variables will include the number of subjects, mean, standard deviation, median, minimum, and maximum.

7.9.1 Primary Endpoint

The primary endpoint is a composite success at 24 months post-operatively. The components of this endpoint characterizing success consist of all of the following: 1) based on two-year post-operative radiographs, there is no continuous radiolucent line around the GLOBAL ICON stemless humeral component, 2) Two-year post-operative adjusted Constant-Murley Score > 85, 3) absence of component removal, and 4) absence of serious adverse events related to the device. The primary endpoint analysis will be conducted on subjects who are in the Safety population. As described in Section 7.4 Interval Windows will be implemented for the primary endpoint analysis.

The primary endpoint analysis will be conducted using a one-sample Z-test of a proportion using a normal approximation, with multiple imputation methods as described in the SAP to account for missing data.

7.9.2 Safety Endpoints

1. Overall survivorship of the GLOBAL ICON device at 24, 60 and 120 months post-operative, where a subject is deemed to be surviving if no humeral components (anchor plate, humeral head) have been removed for any reason

   An estimate of device survivorship of the GLOBAL ICON stemless humeral component will be presented using the Kaplan-Meier method. Removal of any humeral components, defined as revision, for any reason is the event of interest. Cases not revised will be censored at their date of last follow-up, death, or withdrawal from the study. Survivorship point estimates and 95% confidence intervals will be presented for a time point if at least 40 subjects remain at risk. The conventional Greenwood estimate will be used to calculate the variance and the complementary log-log transformation will be used to construct 95% confidence intervals using PROC LIFETEST.

2. The type and frequency of all adverse events (AEs) in this study will be summarised, with distinction of serious AEs, operative and device related AEs.

   The type and frequency of AEs through 120 months post-operative will be presented in table form and via a listing. An overall summary of adverse events (AE) will be provided, including the number and the percent of subjects with all AEs, all serious AEs, all related AEs (device and procedure related), and all AEs by severity. In addition, all adverse events, serious, and non-serious adverse events will be summarised and tabulated by preferred term, both overall and by severity, and by time period of onset. As described in Section 7.4 Interval Windows will be implemented for the radiographic loosening endpoint.

7.9.3 Secondary Endpoints

All secondary endpoint analyses will be presented for the Safety Population as described in Table 3 above. For the purpose of analysis, baseline is defined as last available result prior to surgery.

Secondary endpoints in the study include the following:

1. Mean adjusted Constant-Murley Score at baseline and 3, 12, 24, 60 and 120 months post-operative
2. Mean Oxford Shoulder Score at baseline and 3, 12, 24, 60 and 120 months post-operative
3. Mean EQ-5D-5L Scores by dimension and EQ VAS, at baseline and 3, 12, 24, 60, and 120 months post-operative
4. Radiographic evidence of aseptic loosening of the GLOBAL ICON stemless humeral component immediate post-operative and 3, 12, 24, 60, and 120 months post-operative.

   The number and percentage of radiographic evidence of loosening will be presented at each planned time point through 120 months, including estimates of survival.

Secondary endpoints 1 through 3, listed above, will be analysed identically, using descriptive summaries for continuous data, at baseline, and each follow up visit through 120 months. Where appropriate, analyses will also be presented for subscales, dimensions, components, or index values. For secondary endpoint the frequency and percent will be reported for each post-operative time. As described in Section 7.4 Interval Windows will be implemented for the above secondary endpoints.

7.9.4 Tertiary Endpoints

All Tertiary endpoint analyses will be presented for the Safety Population as described in Table 3.

Tertiary endpoints in the study will include the following:

1. Mean change from baseline for the Constant-Murley Score at 3, 12, 24, 60 and 120 months post-operative
2. Mean change from baseline for the Oxford Shoulder Score at 3, 12, 24, 60 and 120 months post-operative
3. Mean change from baseline for EQ-5D-5L dimension score and EQ-VAS scores at 3, 12, 24, 60 and 120 months post-operative
4. Periprosthetic fracture survivorship of the GLOBAL ICON stemless humeral component at 24, 60 and 120 months post-operative.

   The tertiary endpoints 1 through 3, above, will be analysed at each time point of interest in the same manner as described for the corresponding secondary endpoint with the modification post-surgical measurements will be represented as a change from baseline (with baseline measurement included as a covariate in a linear regression model). As described in Section 7.4 Interval Windows will be implemented for these endpoints (1 through 4).

7.10 Interim Analysis

There are no planned interim analyses for the purpose of stopping the study early. An interim analysis is planned to support a US marketing application, which will include demographic summaries, the primary endpoint analysis, a Kaplan-Meier analysis of device survivorship, and summaries of safety

outcomes. Additional ad-hoc analyses may be performed to support conference presentations or abstracts prior to the end of the study.

8. DATA MANAGEMENT

Data Management for Subject Operative Details and Follow-up Evaluations

Electronic Case Report Forms (eCRFs) entered into an electronic data collection system will be used to collect all subject data once a Subject is enrolled in the study. Study sites will be asked to enter subject data into the eCRFs via the electronic data capture (EDC) web based database portal promptly after each study visit (best practice would be within 2 weeks from the date of the subject's visit).

Detailed description of the eCRF components and eCRF completion instructions are included in the required pre-study training provided by the Sponsor. This training will be provided to the Investigators and their delegated study staff prior to initiating Subject enrolment. The respective eCRFs must be fully completed for each subject and signed electronically.

The patient-reported outcome measures (EQ-5D-5L and Oxford Shoulder Score) will be recorded on paper-based questionnaires. The data will then be entered into the respective eCRF within the EDC system by the PI or designee. The patient-reported outcomes measures captured on paper-based questionnaires must be stored in the Subject's medical notes, as these are considered to be the source document. Any errors on paper forms should be crossed out with a single stroke, initialled and dated. Typing correction fluid must not be used.

For all Subjects, detailed information related to the primary diagnosis, anaesthesia type and time, if a specific surgical exposure, and other surgical variables will be recorded on the Operative Details eCRF OP. Any occurrence of an operative complication must be recorded on the Operative Adverse Event eCRF AE. An intra-operative complication is defined as a complication that occurs from the start of anesthesia to when the Subject returns to their room. Please complete a separate Adverse Event eCRF AE for each intra-operative complication. Labels for each device or component used during the procedure must be recorded on the Device eCRF.

Data collected during the study for each subject will be maintained as accurately and completely as possible with entries into an electronic data capture system (EDC) provided by DePuy Synthes. The personal data recorded on all documents, including copy documents, and within the system will be regarded as confidential. The PI will be responsible for the timing, completeness and accuracy of the details entered within the EDC system. All data entered in the database must have source documents in the subject's medical records.

The study database has been validated in accordance with 21 CFR Part 11, European Commission's Directive on Data Protection and US Safe Harbor Certification. Prior to being released for importation of patient activity and study data, validation of the study level components will be conducted in

accordance with approved user acceptance testing procedures. Access to this system will be controlled so that only authorized users will have the ability to enter into the system. The system is considered a closed system according to 21 CFR Part 11 Electronic Records; Electronic Signatures.

9. STUDY DEVICE

The GLOBAL ICON stemless humeral component is intended to replace the proximal humeral head in total arthroplasty. The implant construct includes a Humeral Head and an Anchor Plate, for articulation with the glenoid and for fixation into the resected proximal humerus, respectively. The system is bone conserving relative to stemmed arthroplasty, in that it does not violate the humeral canal and allows surgeons to properly position the component with fewer surgical steps. The GLOBAL ICON stemless humeral implants were designed by leveraging the fact that the epiphyseal structures can be characterized by a sphere and by constraining the design of the construct within this sphere.

The Humeral Head components are available in diameters ranging from 40 to 56mm, in 2mm increments and are available in two thicknesses (anatomic and +3mm). The small increments of Humeral Head size should allow surgeons to better approximate the native humeral head's radius of curvature. The Anchor Plate components are also available in 2mm size increments from 40 to 56mm, which allows the system to better leverage features for short and long term fixation.

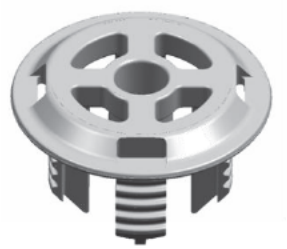
Humeral head
Material:

- Cobalt Chrome Molybdenum alloy

The GLOBAL ICON Anchor Plates were designed to provide a strong metaphyseal fixation by taking advantage of the best bone in the proximal humerus. The Anchor Plate component has four peripheral legs that take advantage of the good metaphyseal bone stock located around the periphery of the proximal humeral head. The legs have a T-shape design with grooves on their most peripheral surface. The T-shape helps to provide rotational stability while the grooves were designed to increase the surface area for biological coating and also provide resistance against pull-out. The legs, as well as the underside

of the Anchor Plate component, are coated with hydroxyapatite. Short term fixation of the implant is provided by the macro-structure of the legs and by the positioning of the collar on the cortical rim of the resected humerus.

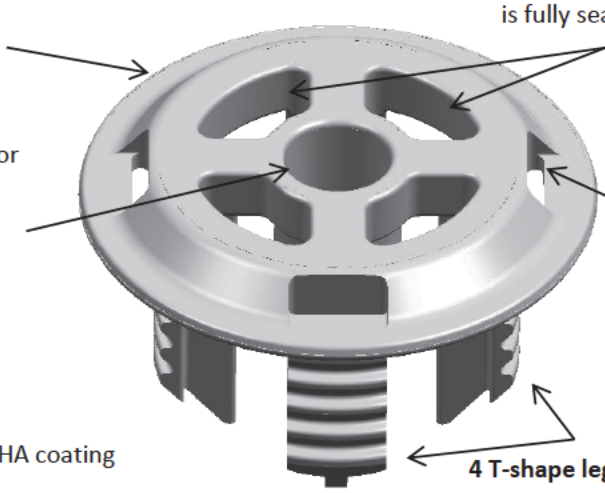
Anchor Plate:



Materials:

- Titanium 6-Aluminum 4-Vanadium ELI (ASTM F136)
- Hydroxyapatite coating (30-60µm thickness)

Figure 3: Global ICON Anchor Plate Design Features



The following table lists the GLOBAL ICON stemless humeral component product codes available for implantation in study subjects:

Table 4: GLOBAL ICON stemless humeral component product codes

Product Code	Description
1140-10-040	ANCHOR PLATE SZ40
1140-10-042	ANCHOR PLATE SZ42
1140-10-044	ANCHOR PLATE SZ44
1140-10-046	ANCHOR PLATE SZ46
1140-10-048	ANCHOR PLATE SZ48
1140-10-050	ANCHOR PLATE SZ50
1140-10-052	ANCHOR PLATE SZ52
1140-10-054	ANCHOR PLATE SZ54
1140-10-056	ANCHOR PLATE SZ56
1140-20-040	HUMERAL HEAD SIZE 40
1140-20-042	HUMERAL HEAD SIZE 42
1140-20-044	HUMERAL HEAD SIZE 44
1140-20-046	HUMERAL HEAD SIZE 46
1140-20-048	HUMERAL HEAD SIZE 48
1140-20-050	HUMERAL HEAD SIZE 50
1140-20-052	HUMERAL HEAD SIZE 52
1140-20-054	HUMERAL HEAD SIZE 54
1140-20-056	HUMERAL HEAD SIZE 56
1140-20-340	HUMERAL HEAD SZ40 +3
1140-20-342	HUMERAL HEAD SZ42 +3
1140-20-344	HUMERAL HEAD SZ44 +3
1140-20-346	HUMERAL HEAD SZ46 +3
1140-20-348	HUMERAL HEAD SZ48 +3
1140-20-350	HUMERAL HEAD SZ50 +3
1140-20-352	HUMERAL HEAD SZ52 +3
1140-20-354	HUMERAL HEAD SZ54 +3
1140-20-356	HUMERAL HEAD SZ56 +3

The GLOBAL ICON Stemless Shoulder System is designed for total shoulder arthroplasty. In accordance with the Instructions For Use (Exhibit C) the GLOBAL ICON humeral component is compatible only with DePuy Synthes glenoid systems. All study subjects must therefore receive a DePuy Synthes glenoid.

Examples of compatible DePuy Synthes glenoid systems that may be implanted are:
Anchor Peg Glenoid
Five Peg Glenoid
Keeled Glenoid

The Sponsor will offer support to supplement professional education of the surgeon on the implant and surgical instruments, as required.

Device Accountability
No study specific device accountability is required as this is a PMCF study being conducted on a CE marked device.

10. DEVIATIONS & NON-COMPLIANCE HANDLING

With the exception of emergency situations, no deviations to this clinical investigation plan will be permitted. In the event of an emergency situation, the Principal Investigator must notify the sponsor immediately. A full written report of the situation must be forwarded to the Ethics Committee who approved the original clinical investigation plan, and DePuy Synthes, promptly.

There may be study subjects who will not, or cannot, return for follow up as per the requirements of this protocol. These subjects will be considered as non-compliant and listed as missing data. This includes, but is not limited to, the following criteria:

- Subjects who refuse to return for follow up
- Relocation of the subject who does not inform the investigator, and can therefore not be located to request follow up appointments

Subjects who are documented as lost to follow up will not be considered withdrawn from the study. The Investigator shall make every effort to contact these subjects, and document evidence of each attempted correspondence in the study files.

11. ETHICAL PRINCIPLES

This investigation will be conducted in accordance with the relevant articles and ethical principles of the current version of the Declaration of Helsinki.

12. INVESTIGATOR RESPONSIBILITIES

An Investigator is responsible for ensuring that an investigation is conducted according to the signed Clinical Research Agreement, this Clinical Investigational Plan (CIP) and applicable regulations for protecting the rights, safety, and welfare of Subjects under the Investigator's care. The Investigator is

also responsible for ensuring that informed consent is obtained in accordance with BS EN ISO 14155:2011 entitled Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice.

Prior to the initiation of this clinical study, the Investigator will approve this CIP by signing the signature page. This signature confirms that the clinical study will be performed in compliance with the CIP. The Investigator(s) agrees to conduct the study in accordance with this protocol. Prior to beginning the study, the Investigator(s) must sign the protocol signature page.

An Investigator must not make any changes in a study without first receiving approval from the Sponsor and Ethics Committee, except when necessary, to eliminate apparent immediate hazards to a Subject. With the exception of emergency situations, no deviations to this CIP will be permitted. In the event of an emergency situation, the Investigator must notify the Monitor immediately. A full written report of the situation must be forwarded to the Ethics Committee who approved the original CIP and DePuy Synthes promptly.

Each Investigator must obtain EC approval by an EC, prior to consent of the first Subject; no study-related procedures can occur without the approval and oversight of a registered EC.
All Principal Investigators must submit for initial review a copy of the clinical investigational plan (CIP) and the Informed Consent Document (ICD) to their institution's initial EC approval, or favourable opinion, are to be filed at the site and Sponsor.

Continuing review and any other additional required submissions will be forwarded for EC review according to their policies and procedures. Approval, favourable opinion, or acknowledgement must be documented and filed at the site and Sponsor.

Each site is identified uniquely. Each subject will be added to the database and allocated to the next available study Subject number. This number will consist of the site number followed by 001 for the first subject, 002 for the second subject and so on. Together the Site number and the subject number will then become the unique identifier of the subject and will be recorded on each page of the eCRF and all other clinical investigation documentation relating to that subject.

The Investigator will retain copies of all documents pertaining to this study (including source documentation, the informed consent document and any other documents to identify the subjects) for at least two years after this clinical investigation is completed. In addition, if the Investigator moves/retires, etc., she/he will provide the Sponsor with the name and address of the person who will look after and be responsible for the subjects' study related records.

The Investigator maintains overall responsibility for the study conduct at their site. They may choose to delegate specific study related tasks, such as obtaining informed consent, to other designated study team members. This delegation must be fully documented on the site Delegation Log.

13. SPONSOR OBLIGATIONS

13.1 EC Approval

Each Investigator must obtain EC approval prior to consent of the first subject. Each Investigator must also maintain continuous approval. Documentation of approval and renewals must be provided to the Sponsor, and filed on site in the Investigator Site File. Additionally, amendments to the protocol will be submitted for review before implementation.

The Sponsor must have copies of the initial and annual approval(s) from the EC (as applicable), and maintain that documentation in the Trial Master File.

13.2 Investigator Training, Site Initiation Visit

Prior to enrolling subjects in this study, the Investigator and/or appropriate Site personnel will be trained in general aspects of study administration, content and manner of administration of the questionnaires, all procedures in the protocol, and the procedure for e-data acquisition and transmission. Training may be conducted by teleconference, Web-Ex conference and on-site training as appropriate. Site visits, if required, will be arranged once EC approval is obtained and the Clinical Research Agreement is executed.

13.3 Study Monitoring

The Sponsor of this clinical investigation will be responsible for monitoring this study. The monitor's duties are to aid the Investigator in the production and maintenance of complete, legible, well-organised and easily retrievable data. In addition, the Monitor will be responsible for assuring the Investigator understands the CIP and all applicable regulations. Approaches to monitoring may include both remote and on-site visits as appropriate and the rationale and frequency for monitoring will be at the Sponsor's discretion.

The Monitor may check the eCRF entries with source documents. In order to perform this role effectively, the Monitor must be given access to primary subject data which supports the information recorded on the eCRF, i.e. hospital notes, appointment books, original laboratory records, etc. Access to these documents must also be given should the regulatory authority instigate an external audit. Since a subject has the right to refuse access to these documents on the grounds of confidentiality, consent to access is included in the informed consent document, which the subject signs.

The Sponsor will be responsible for establishing the schedule and procedures to be followed for monitoring this clinical investigation and may also include the monitoring of the operative procedure. The Investigator will receive reasonable notification prior to each monitoring visit during the course of this clinical investigation. At each visit, the Investigator will be expected to co-operate with the Monitor for the review and verification of eCRFs and any additional records as may have been previously arranged between the Investigator and the Monitor.

The monitoring frequency will be determined by the Sponsor for each Site based on factors including: the planned enrolment, the rate of enrolment, the level of experience of the clinical investigation team and the current study conduct. Study conduct can be evaluated remotely based on compliance percentage, discrepancy rate and discrepancy type. In general, the source data verification will be performed on a random sample of subject records. In order to perform this role effectively, the Monitor must be given access to primary subject data which supports the information recorded on the CRF, *i.e.* appointment books, original laboratory records, etc. Consent to access this information is included in the patient consent form, which the Subject signs.

13.4 CIP Amendments

If it becomes necessary to amend the Clinical Investigation Plan, the nature of the amendment may be discussed, if required, between the Sponsor and the Lead Investigator. Protocol amendments will be submitted to the appropriate Ethics Committee(s) for review and approval if required, before they are implemented.

13.5 Product Labelling

Refer to Exhibit C for Product Labelling.

13.6 Sponsor Study Termination

The Sponsor may prematurely terminate or suspend the clinical study as a whole or at an individual investigational site for significant and documented reasons. Reasons for premature termination or suspension include, but are not limited to safety, inadequate recruitment, Investigator issues, device related problems, alignment with business strategy or administrative issues.

If suspicion of an unacceptable risk to subjects arises during the clinical study, or when instructed by an Ethics Committee or Regulatory Authority, the Sponsor shall suspend the clinical study at all active sites while the risk is assessed. The Sponsor shall terminate the clinical study if an unacceptable risk is confirmed, or resume the clinical study following appropriate communication and approval from the Ethics Committee and Regulatory Authority as required.

In terminating the clinical study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subject's interests per Section 11 and all documentation is archived per Section 12 and the appropriate bodies such as the Ethics Committees and Regulatory Authorities are informed as appropriate.

13.7 Insurance

The Sponsor recognizes its liability in law to compensate for any injury sustained by a subject participating in this clinical investigation as a result of negligence or breach of duty of care; adequate insurance provisions have been made by DePuy Synthes Joint Reconstruction to compensate any Subject so injured.

13.8 Financial Agreement

Funding of this clinical investigation will be the subject of a separate agreement between the Sponsor and the Institution where the clinical investigation is being conducted and the Principal Investigator (where permitted by the Institution).

14. PUBLICATION PLAN

All manuscripts of data obtained from this clinical investigation will be reviewed and approved by the Sponsor, and each author, prior to any submission. The current and applicable J&J Publication Policy will be followed.

DePuy Synthes will require a written agreement for any external author(s) prior to initiating any publication. All authors must disclose financial or personal affiliations that could be considered a conflict of interest.

15. EXHIBITS

Exhibit
A. Surgical Technique
B. Radiographic Protocol
C. Instructions For Use

16. REFERENCES

1. Self-Reported Population Health: An International Perspective based on EQ-5D. Eds. Szende A, Janssen MF, Cabases J. Springer, 2014.
2. Katolik, Leonid I., Romeo, Anthony A., Cole, Brian J., Verma, Nikhil N., Hayden, Jennifer K., Bach, Bernard R. Normalization of the Constant Score. Journal of Shoulder and Elbow Surgery 2005; 14:279-285