A Longitudinal Outcomes Study of the Subchondroplasty® Procedure in the Hip

Post-Market Clinical Follow-Up (PMCF)

CSU2017-03KC

Version 2.0

March 7, 2023

AMER

STUDY SPONSOR

Zimmer Biomet

Clinical Affairs

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1 Document History

Protocol Version Number	Date	Description of Changes	Change Author
1.0	27-DEC-2017	Initial Version	
2.0	23-FEB-2023	Sample size decreased to 50 End point changed from 5 years to 2 years Update to new protocol template format	Branden Kemp

Note:

Administrative Changes (Full CIRC review/approval not required) updates the Protocol Version to the next incremental decimal, e.g. 1.0 → 1.1

Substantive Changes (Full CIRC review/approval required) updates the Protocol Version to the next incremental integer, e.g. 1.0 → 2.0

2 Contact Information/List of Investigators

Title	A Longitudinal Outcomes Study of the Subchondroplasty® Procedure in the Hip
Protocol Number	CSU2017-03KC
Study Sponsor Contact Information	Branden Kemp Clinical Research Specialist Zimmer Biomet 1800 West Center Street Warsaw, IN 46580 United States 800-613-6131 Branden.kemp1@zimmerbiomet.com
Monitoring Contact Information	Zimmer Biomet or Designee
Name(s) and Address(es) of Principal Investigators(s) and Coordinating Investigator(s), as appointed (Clinical Investigation only as per Annex XV of EU MDR)	A complete listing and details including name, address, contact details and professional position of the Principal and Coordinating Investigators, as appointed, will be maintained in the Sponsor's Trial Master File.
Investigational Site Information (Clinical Investigation as per Annex XV of EU MDR)	The study will include up to 15 sites. Details regarding the site name(s) and address(es) will be maintained in the Sponsor's Trial Master File.
External Organizations, if applicable	N/A

3 Abbreviations

The following abbreviations are used throughout this study protocol.

ADE	Adverse Device Effect
AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CTA	Clinical Trial Agreement
DD	Device Deficiency
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU MDR	European Regulation (EU) 2017/745
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation (Harmonization)
IRB	Institutional Review Board
ISO	International Standards Organization
OR	Operating Room
PMCF	Post-Market Clinical Follow-Up
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
UADE	Unanticipated Adverse Device Effect

4 Study Synopsis

Complete Protocol Title	A Longitudinal Outcomes Study of the Subchondroplasty® Procedure in the Hip
Protocol Number	CSU2017-03KC
Short Protocol Title	SCP Hip Outcomes Study
Sponsor	Zimmer Biomet, Warsaw, Indiana, United States
Manufacturer	Zimmer Biomet AccuFill® BSM ETEX Corporation 55 Messina Drive Braintree, MA 02184 USA
Study Device(s)	AccuFill® Injectable Calcium Phosphate SCP® Surgical Instrumentation
Study Objectives/Endpoints	To collect data on the short- and long-term outcomes for subjects undergoing the Subchondroplasty® (SCP®) Procedure in the hip in a standard clinical setting. Outcomes to be assessed include medication usage, pain, function, activity levels and patient satisfaction.
Indications/Target Population	Candidates with at least one subchondral bone defect in the form of a cyst and/or bone marrow lesion (BML), insufficiency fracture or bone defect associated with early stage avascular osteonecrosis (AVN) in the femoral head, femoral neck and/or acetabulum who have elected to undergo or who have undergone the Subchondroplasty Procedure, will be enrolled in the study.
Inclusion/Exclusion Criteria	Candidates must meet ALL of the following: 1. Surgeon considers the patient appropriate for the SCP Procedure of the hip. 2. Subchondral bone defect(s) in the femoral head, femoral neck and/or acetabulum has been confirmed via radiographic finding on MRI or x-ray. 3. Subject provides voluntary signature on the IRB approved Informed Consent Form. 4. Subject is at least 18 years of age. 5. Subject must be physically and mentally willing and able, in the Investigator's opinion at the time of enrollment, to be compliant with the protocol and complete outcome forms via email, telephone, in-person or by regular mail.

	Candidates will be excluded if they meet ANY of the following: 1. Subject has collapse of subchondral bone. 2. Subject is pregnant at the time of surgery. 3. Subject is incarcerated. 4. Subject is involved in active litigation related to the condition being treated. 5. Subject is **not** comfortable with speaking, reading, and understanding questions and providing responses in an available language for the PROs in the protocol.
Study Design	This study is a post-market, single arm, non-randomized multi-center investigation.
Clinical Phase	Post-market
Sample Size	Approximately 50 study subjects implanted with the study device per cohort.
Length of Study	7 years (5 years of enrollment (all sites) and 2 years of follow-up)
Materials and Methods	Case report forms will be completed either in-office or hospital at Pre-op, Surgery, Discharge, and 6 weeks, 1-year, and 2-years.
Data Collection	Paper/Electronic
Statistical Reporting	Data collected will be summarized and reported to each participating investigator. Statistical analysis will be conducted by Zimmer Biomet or its designee.

Scores/Performance Assessments	Pre-Operative
	Initial study procedures include patient demographics, medical history and hip history. Additionally, the following measures will be obtained pre-operatively:
	• Use of pain medication and therapy
	• Subject-reported outcomes:
	  ○ Numeric Pain Scale
	  ○ Modified Harris Hip Score
	  ○ Hip Outcome Score
	  ○ EQ-5D
	Subjects will complete only the Numeric Pain Scale at 2 weeks post-operatively.

	Post-Operative
	Thereafter, subjects complete self-reported outcomes measures post-operatively at 6 weeks, 12 weeks, 6 months, 1 year and 2 years. These measures include:
	• Use of pain medication and therapy
	• Subject-reported outcomes:
	  ○ Numeric Pain Scale
	  ○ Modified Harris Hip Score
	  ○ Hip Outcome Score
	  ○ EQ-5D
	  ○ Subject Global Satisfaction Survey
	The post-operative visit data must be collected for each enrolled subject via email, telephone, in-person or by regular mail. If the subject is not seen in person, a member of the study staff will contact the subject by telephone at the above time points to inquire about their outcomes, any conversion surgeries, and/or adverse events.

Standards	The PMCF is compliant with the below: • ISO 14155: 2020 - Clinical investigation of medical devices for human subjects - Good clinical practice. • The Declaration of Helsinki (DoH) - Ethical principles for medical research involving human subjects. • European Regulation (EU) 2017/745
Study Funding	Funding for this clinical study is made available by Zimmer Biomet to support clinical data collection, IRB/EC review fees and other expenses associated with the conduct and execution of this study protocol as outlined in the fully executed Clinical Trial Agreement.

5 Data Collection Overview

Table 1 - Schedule of Events						
	Enrollment		**Follow-Up**			
Event/Visit	Pre-Operative	Surgery	2 Weeks	6 Weeks	12 Weeks 6 Months	1 Year 2 Years
Visit Window	≤60 Days Prior to Surgery		±7 Days	±7 Days	±14 Days	±60 Days
Informed Consent	X					
CRF 1: Inclusion & Exclusion Criteria	X					
CRF 2: Subject History	X					
CRF 3: Numeric Pain Scale	P		P	P	P	P
CRF 4: Pain Medication & Therapy	X			P	P	P
CRF 5: Modified Harris Hip Score	P			P	P	P
CRF 6: Hip Outcome Score	P			P	P	P
CRF 7: EQ-5D	P			P	P	P
CRF 8: Subject Global Satisfaction Survey				P	P	P
CRF 9: Operative Details		X				
CRF 10: End of Study/Withdrawal[1]		(X)	(X)	(X)	(X)	(X)
CRF 11: Adverse Event[2]		(X)	(X)	(X)	(X)	(X)
CRF 12: Protocol Violation[2]	X	X	X	X	X	X

X Investigator or designated staff completed forms

1 End of Study/Withdrawal form will be completed if the subject is no longer participating in the study for any reason.

(X) Investigator completed forms, if applicable

2 Case Report Form to be completed if/when event occurs.

P Subject completed form

6 Introduction and Purpose

6.1 Clinical Background

Subchondral bone defects are MRI-visible defects that can be seen on fat-suppressed MRI sequences (T2FS, PDFS, etc.) where they appear as a hazy white area against the background of darker bone [1].

Subchondral bone defects are frequently associated with pain [2], cartilage defects, cartilage volume loss [3] and increased odds of progression to joint replacement [2]. Similarly, subchondral bone defects of the hip are associated with hip pain and hip joint space narrowing [4] that typically resolves spontaneously in approximately 6 to 9 months [5]. Treatment usually consists of avoiding load on the hips as well as the use of nonsteroidal anti-inflammatory drugs (NSAID), bisphosphonates, and prostacyclin, which can improve local hemodynamic characteristics [6, 7]. Unfortunately, in some cases, conservative treatment approaches do not relieve symptoms. In these cases, the disease becomes prolonged and intractable, causing a great deal of discomfort. Various treatments have been proposed in an attempt to shorten the natural course of the disease, which is frequently associated with severe and long-lasting disability [6].

In general, the therapeutic approach to subchondral bone defects of the hip is based on its suspected etiology and ranges from various symptomatic therapies [6, 7] to more invasive treatments, such as core decompression or even Total Hip Arthroplasty (THA) [8]. Because it is considered a fully reversible disease [6], there is controversy regarding whether treatment should be conservative or invasive. Total Hip Arthroplasty is an invasive treatment and can result in complications, including bleeding, wound complication, thromboembolic disease, neural deficit, vascular injury, dislocation/instability, periprosthetic fracture, abductor muscle disruption, deep periprosthetic joint infection, heterotopic ossification, bearing surface wear, osteolysis, implant loosening, cup-liner dissociation, implant fracture, reoperation, revision, readmission, and death [9]. Therefore, there is a need for an effective less invasive treatment.

Subchondroplasty® (SCP®) is a minimally-invasive procedure first described in 2007 to fill subchondral osseous defects associated with subchondral bone defects using an injectable bone substitute material (BSM), AccuFill® [10]. AccuFill has unique properties that allow it to flow through the osseous defects in trabecular bone and then set up hard at body temperature [11]. Two year results from a clinical study of the knee on 66 subjects considering total knee arthroplasty (TKA) has shown improvements in subject reported pain and function with only 30% of subjects undergoing revision to TKA at 2 years [12]. The goal of this study is to track outcomes in a population undergoing SCP of the hip.

6.2 Preclinical Studies

Preclinical studies in established animal models were used to evaluate safety and effectiveness of AccuFill for treatment of a critical sized bone defect. A rabbit bilateral lateral femoral condyle defect model (4.8 mm diameter x 6 mm length cylindrical defect) through 24

weeks demonstrated that AccuFill caused bone induction and osteointegration at the implant site, and was well tolerated.

No significant adverse events or indications of infections or rejections of the AccuFill material were observed in the preclinical evaluations of AccuFill. Studies demonstrated bone induction, osteointegration and potential for use as bone void filler.

6.3 Regulatory Overview of Subchondroplasty

This study will evaluate the on-label use of AccuFill during the Subchondroplasty Procedure.

The Subchondroplasty Procedure will be performed using two commercially available devices. The regulatory status of each component of the system is described below:

1. AccuFill® Injectable Calcium Phosphate – Class II device; 510(k) Number K093447 - Calcium Salt Bone Void Filler Device, cleared by FDA. The package insert provides product description, indications, and usage information.
2. SCP® Surgical Instrumentation – These are Class I manual surgical instruments. Per 21 CFR 888.4540 and 21 CFR 878.4800, these manual surgical instruments are premarket exempt.

6.4 Risk Analysis

This study was designed to assure that the benefits and knowledge gained by studying clinical outcomes associated with Subchondroplasty for treatment of subchondral bone defects in the hip outweigh the potential risks to the subjects. Alternative treatment options may require more invasive surgical therapy to treat the hip pain, up to and including Total Hip Arthroplasty (THA).

6.4.1 Risks of Surgical Intervention

Risks of surgical intervention include those risks currently associated with arthroscopic surgical interventions in the hip. These risks include intra-articular adhesions (scar tissue), superficial and/or deep wound infection, nausea and/or vomiting, bleeding, hip pain, muscle weakness, and postoperative blood clot (hematoma). There are possibilities of wound re-opening, deep vein thrombosis (blood clot), pulmonary embolus (lung clot), vascular or nerve injury and an allergic response to the anesthetic or medications. Some additional risks related to local anesthesia are swelling, pain, bleeding, bruising, nerve pain and loss of sensation in the skin and ligament around the hip.

6.4.2 Risks Associated with Subchondral Implantation of AccuFill

Risks specific to the implantation of a bone substitute material may include tissue thinning over the implant site, tenderness/redness/edema, seroma/hematoma, infection, swelling/fluid collection, loss of contour. Additionally, material extravasation may occur in the joint. In the event of this occurrence, any extravasation of material into surrounding soft tissues should be thoroughly irrigated at the time of the procedure. If not initially planned, arthroscopy or mini-open approach to the hip may

be necessary to remove extravasated material. Migration, extrusion, dehiscence, fracture and sloughing of AccuFill can occur as a result of excessive trauma. Neurovascular injury may occur due to surgical trauma. A pulmonary embolism may result from using this injectable bone void filler.

6.4.3 Methods to Minimize Risk

Only appropriate subjects, who meet the inclusion and exclusion criteria, will be recruited into the study. Study subjects will be monitored post-operatively to assess the surgical site for any acute and chronic adverse reactions to ensure proper medical treatment can be administered. Validated and standardized outcome scales and surveys will be used to collect subjects' data. Experienced orthopedic surgeons will participate as Investigators and have experienced staff to perform the study procedures.

6.4.4 Benefits and Justification for the Study

This is an observational study and there are no direct benefits to the subject, other than those associated with the treatment of a subchondral bone defect of the hip. The justification for this study is to learn more about patient outcomes following the Subchondroplasty procedure in the hip.

7 Study Device Information

7.1 Study Device

The Subchondroplasty Procedure targets and fills subchondral bone defects in the form of a cyst and/or bone marrow lesion (BML), insufficiency fracture or bone defect associated with early stage avascular osteonecrosis (AVN) with AccuFill BSM utilizing an arthroscopic / percutaneous approach as follows. Preoperatively, the subchondral bone defect is identified on a fat-suppressed MRI, and the approach and trajectory is planned based on defect location. Using intraoperative fluoroscopy, the bone defect is localized relative to MRI findings. The appropriate AccuPort® Delivery Cannula is drilled to the bone defect. AccuFill BSM is then injected into the subchondral bone defect. The AccuFill fills the defect and hardens within the subchondral bone defect, and is resorbed over time and replaced with new bone during the healing process.

It is recommended that a hip arthroscopy be performed prior to or after the Subchondroplasty procedure. In either case, the arthroscope should be placed into the joint after injection of AccuFill to check for possible material extravasation. Using standard arthroscopic surgery techniques, skin incisions are made for the insertion of arthroscopic instrumentation.

7.2 Instrumentation

The SCP® Surgical Instrumentation is a set of manual surgical instruments used to target and

deliver AccuFill® to the osseous defect.

7.3 Compatibility

To determine whether devices have been authorized for use in a proposed combination with Zimmer and/or Biomet products, please contact your sales representative or visit the Zimmer Electronic Labeling Service (eLabeling) website: https://labeling.zimmerbiomet.com/

8 Study Population

Approximately 50 subjects, each with at least one subchondral bone defect in the form of a cyst and/or bone marrow lesion (BML), insufficiency fracture or bone defect associated with early stage avascular osteonecrosis (AVN) in the femoral head, femoral neck and/or acetabulum who have elected to undergo or who have undergone the Subchondroplasty Procedure, will be enrolled in the study.

8.1 Inclusion Criteria

Candidates must meet ALL of the following:

Surgeon considers the patient appropriate for the SCP Procedure of the hip.

Subchondral bone defect(s) in the femoral head, femoral neck and/or acetabulum has been confirmed via radiographic finding on MRI or x-ray.

Subject provides voluntary signature on the IRB approved Informed Consent Form.

Subject is at least 18 years of age.

Subject must be physically and mentally willing and able, in the Investigator's opinion at the time of enrollment, to be compliant with the protocol and complete outcome forms via email, telephone, in-person or by regular mail.

8.2 Exclusion Criteria

Candidates will be excluded if they meet ANY of the following:

Subject has collapse of subchondral bone.

Subject is pregnant at the time of surgery.

Subject is incarcerated.

Subject is involved in active litigation related to the condition being treated.

Subject is not comfortable with speaking, reading, and understanding questions and providing responses in an available language for the PROs in the protocol.

9 Study Objectives

The purpose of this post-market clinical study is to collect short- and long-term outcomes for subjects undergoing the Subchondroplasty Procedure in the hip in a standard clinical setting. Outcomes to be assessed include medication usage, pain, function, activity levels and patient

satisfaction.

10 Study Design and Endpoints

10.1 Disease/Condition Being Treated

Subchondral bone defects in the form of a cyst and/or bone marrow lesion (BML), insufficiency fracture or bone defect associated with early stage avascular osteonecrosis (AVN) in the femoral head, femoral neck and/or acetabulum.

10.2 Number of Sites and Regions

Up to 15 sites in the United States

10.3 Number of Cases and Maximum Enrollment per Investigation Site

A total number of approximately 50 subjects across 15 sites in the United States.

10.4 Study Design

This study is designed as a post-market, single arm, non-randomized multi-center investigation.

Male and female subjects, at least 18 years of age, with at least one subchondral bone defect in the form of a cyst and/or bone marrow lesion (BML), insufficiency fracture or bone defect associated with early stage avascular osteonecrosis (AVN) in the femoral head, femoral neck and/or acetabulum who are suitable candidates for use of AccuFill during the Subchondroplasty Procedure are eligible for enrollment in this study.

A maximum of 15 study sites, in the United States of America, will enroll a target of 50 subjects.

Each Investigator must obtain IRB approval, or favorable opinion by an EC, prior to consent of the first subject; no study-related procedures can occur without the approval and oversight of a registered IRB or EC. If the study site does not have an IRB of record, a central IRB may be utilized upon approval by Zimmer Biomet.

Demographics, medical history, hip history and use of pain medication and therapy will be recorded at the time of subject consent. Additionally, patient reported outcomes measures will be obtained pre-operatively. Operative details including the SCP Procedure, concomitant surgical procedures and intraoperative safety events will be recorded at the time of surgery. Prospective subjects will be considered enrolled in this study once their Subchondroplasty Procedure has been performed.

Subjects will complete only the Numeric Pain Scale at 2 weeks post-operatively. Thereafter, subjects will complete self-reported outcomes measures post-operatively at 6 weeks, 12 weeks, 6 months, 1 year and 2 years. These measures include information on pain medication and therapy, pain levels, function, activity and subject satisfaction. Screening for adverse events and conversion will occur throughout the study.

Subjects will complete the study at 2 years or will be withdrawn if they undergo conversion of the Subchondroplasty site. For the purposes of this protocol, a conversion will be defined as

total hip arthroplasty or any procedure involving removal of the AccuFill material on the index hip.

10.5 IRB/EC Approval

Institutional Review Board (IRB)/Ethics Committee (EC) approval will be obtained prior to conducting this study. Sequentially, all consecutive patients will be offered study enrollment at each study site to avoid potential selection bias. All potential subjects will be required to participate in an informed consent process and sign the IRB/EC approved written informed consent prior to study enrollment. Once Informed Consent has been obtained, eligibility will be determined and preoperative study data collected via direct interview with the patient. Study data cannot be collected until the candidate has completed the informed consent process and signed and dated the IRB/EC approved Informed Consent.

10.6 Type and Timing of Observations

This study is designed to be prospective to ensure that the study population is representative of the type of population that the device is intended to treat. To reduce bias, a consecutive subject series will be recruited. After the initial visit followed by the surgery, the subject is expected to participate in the study for a time period of 2 years. Subjects will be enrolled during a period of 24 months, and the study will last until complete collection of the 2-year follow-up data. All subjects will undergo pre-operative, intra-operative and post-operative assessments including physical examinations and collection of quality-of-life metrics. The visit intervals will be pre-op, operative, 2 weeks, 6 weeks (± 7 days); 1 and 2 years (± 90 days).

10.7 Primary and Secondary Endpoint

The study device is intended to relieve pain and restore function in patients with adequate quality and quantity of bone stock to support the prosthesis. The objective of this PMCF study is to confirm the long-term safety, performance and clinical benefits of the AccuFill® and SCP® Surgical Instrumentation in patients with at least one bone marrow lesion in the hip.

10.7.1 Primary Endpoint

The primary endpoint is defined by the overall group mean improvement from baseline of the Modified Harris Hip Score at the two year time point. The safety of the system will be assessed by monitoring the frequency and incidence of adverse events. Relation of the events to implant (Accufill®), instrumentation (SCP® Surgical Instrumentation) and/or procedure should be specified.

10.7.2 Secondary Endpoint

The secondary endpoint is defined by the functional performance and clinical benefits of the study device and is assessed by:

- Pain and functional performance will be measured by the Numeric Pain Scale and Modified Harris Hip Score
- Subject quality-of-life will be measured by the EQ-5D-5L.

10.8 Financing of the Study

Funding for this clinical study is made available by Zimmer Biomet to support clinical data collection, IRB review fees and other expenses associated with the conduct and execution of this study protocol as outlined in the fully executed Clinical Trial Agreement.

Zimmer Biomet will provide each investigative site with Investigator Binder including the protocol, paper copies of case report forms and logs, study tools, and subject stipend cards. The Zimmer Biomet Study Representatives are available to provide additional supplies upon request.

10.9 Definition of Completion of the Study

The study will be completed when all enrolled subjects have completed all follow-up visits.

11 Study Procedures

11.1 Offer of Study Participation

For each consecutive patient presenting as a study candidate for the SCP procedure, study participation shall be offered based on the indications and patient selection factors contained in the Information for Use (IFU). Based on the patient's response, the patient may be invited to enroll in the clinical study.

11.2 Informed Consent

All study subjects are required to undergo the process of Informed Consent and sign an Institutional Review Board (IRB) approved Informed Consent Form, compliant with 21 CFR Part 50-Protection of Human Subjects, and in accordance with institutional policies. Failure to obtain and properly document this process is in violation of the US Code of Federal Regulations, the Declaration of Helsinki, and this study protocol.

Two copies of the informed consent will be made and distributed as follows: (1) the original of the signed informed consent will be kept in the subject's file at the study site and (2) a copy will be provided to the subject.

11.3 Determination of Eligibility and Enrollment

Potential subjects will be screened from each Investigator's patient population to determine if they meet the inclusion criteria described in Section 7.1 and none of the exclusion criteria described in Section 7.2. Subjects will not be invited to participate in the study until after approval of the protocol by the reviewing IRB.

Subjects will be considered enrolled in the study if they meet the eligibility criteria, consent to participate in the Investigation and undergo the SCP Procedure where AccuFill is injected. Valid enrollment status is not granted until after surgery due to the possibility of intra-operative exclusions where the SCP Procedure does not occur. At the conclusion of the subject's surgery, the subject will be entered into the electronic database and a subject number will be generated.

Retrospective enrollment will only be allowed with prior written approval from the Sponsor after evaluation of pre-operative data available for potential retrospective subjects. The subject will sign an Informed Consent Form prior to completing follow-up study questionnaires.

11.4 Baseline/Pre-operative Assessment

All pre-operative procedures are to be completed prior to the study surgery. The Schedule of Events is listed in Table 1.

The pre-operative visit will include collection of basic demographic information, medical history, hip history and current use of prescription and over-the-counter pain medication and therapies.

The subject is to complete a series of surveys and scales regarding their clinical outcomes at the time preceding surgery, including pain, stiffness, function, and activities. These scales include:

- Numeric Pain Scale
- Modified Harris Hip Score
- Hip Outcome Score
- EQ-5D

For subjects enrolled after the completion of the Subchondroplasty Procedure, basic demographic information, medical history, hip history and pre-operative use of prescription and over-the-counter pain medication and therapies data should be collected, if available, from the subject's medical record or via patient interview. Pre-operative Numeric Pain Scale, Modified Harris Hip Score, Hip Outcome Score, and/or EQ-5D should **only** be entered if they were collected as part of the standard of care

11.5 Surgical Techniques

All operative procedures are to be performed under aseptic conditions according to the institution's standards and following the guidelines below.

- The pre-operative MRI should be used in planning the access point, trajectory and depth of the AccuPort cannula(s) for accessing the location of the subchondral bone defect(s).
- AccuPorts should be placed using fluoroscopic guidance.
- Appropriate volume of AccuFill should be used to adequately fill the area(s) of subchondral bone defect(s), per the recommended surgical technique guide, taking care not to over-pressurize or overfill the defect. Multiple fluoroscopic images should be taken during injection to check for extravasation of material.
- Any extravasation of material into surrounding soft tissues should be thoroughly irrigated at the time of the procedure.

The Investigator is to dictate detailed operative notes that include the measures listed below, or have paper copies of the Operative Details Case Report Forms completed during surgery to serve as source documents.

- Operative Details— Description of subject's operative procedure including such items as

OR time, SCP procedure time, anesthesia type, documentation of SCP injection, treated subchondral bone defect(s) (location and size), concomitant procedures and a device log (to include lot and product numbers).

- Adverse Event (if applicable) — Description of adverse events occurring during the operative procedure..

The patient will be considered a study subject after implantation of the study device.

If the AccuFill® is not able to be used during the surgery, the subject will be considered a screen failure and withdrawn from the study. The screen failure will not count against the site's total enrollment allotment.

11.6 Surgical/Immediate Post-Operative Assessment

During the immediate postoperative period, the investigator's standard postoperative care procedures should be followed. A numeric pain score will be collected and all adverse events and complications are to be assessed and recorded on the Adverse Event Form, per Section 12.4.9 Adverse Events.

Rehabilitation should be performed per the investigator's standard of care.

11.7 Follow-up Procedures

In order to minimize the burden to patient and physician, patients will be enrolled at the physician's office, but will not be required to come back to the office for follow-up visits.

A Numeric Pain Score will be collected at the first post-operative standard of care visit at approximately 7-21 days.

Thereafter, subjects complete self-reported outcomes measures post-operatively at 6 weeks, 12 weeks, 6 months, 1 year and 2 years. These measures include:

- Use of pain medication and therapy
- Subject-reported outcomes:
    - Numeric Pain Scale
    - Modified Harris Hip Score
    - Hip Outcome Score
    - EQ-5D
    - Subject Global Satisfaction Survey

The post-operative visit data must be collected for each enrolled subject via email, in-person, regular mail or telephone (with an IRB approved phone script). If the subject is not seen in person, a member of the study staff will contact the subject by telephone at the aforementioned time points to inquire about their outcomes, any conversion surgeries, and adverse events.

Follow-up evaluations are detailed in Table 1— Schedule of Events. Follow-up is to occur within the windows described in Table 1.

The study database will be configured to send an email notification to subjects at the beginning of each specified visit window with a reminder that they need to complete the surveys. This email will contain a method to allow the subjects to complete their surveys electronically via the database's electronic Patient Reported Outcomes (ePRO) system.

Prior to contacting the study subject to assess potential adverse events by telephone, a member of the study staff will check to confirm whether these surveys have been completed electronically or not. If the subject has not completed the evaluation yet, a member of the study staff will ask if the subject would like to complete the questionnaires by phone, email or if they would like a copy of the surveys to be mailed out to them. Mailed surveys will be sent with a stamped, return envelope. The subject should be instructed to return the surveys within one week and to include the date of completion at the top of any of the pages. Any subject survey forms that are not collected via the database's ePRO system are to be maintained in the subjects' study files as source documents.

11.8 Minimization of Loss to Follow-up

Subject follow-up is extremely important for the conduct of a clinical study. The expectation is to maintain the highest rate of follow-up compliance possible throughout this study. Subjects that are study completed as lost to follow-up will not be replaced. In an effort to minimize the number of subjects lost to follow-up, the following recommendations and/or study requirements are essential to ensure proper patient selection and compliance:

- Patient Eligibility: Subjects will be selected according to the inclusion/exclusion criteria detailed in Section 8 and are expected to return for all follow-up visits.
- Patients Counseled: Patients will be counseled during the Informed Consent process on the importance of returning for follow-up visits.
- Patient Exclusion: Patients who are not willing to return for study required follow-up visits and/or are not willing to comply with the follow-up schedule will not be considered for enrollment into the study.
- Subject Due Listings: In addition to proper patient selection, Zimmer Biomet will provide subject due notices to the sites on a regular basis in order to track each study participant and monitor adherence to the required follow-up visit timeframes. The subject due listings will facilitate scheduling the subjects for their return office visits.
- Contact Tracking: Attempts to contact subjects will be documented in the study subject's medical record. It is recommended that the first three attempts be made by telephone. If after three calls, contact has not been successful, the below is suggested prior to terminating the study subject from the study:

If	Then
a response is not received following attempts to reach the subject by phone	the Investigator could send a letter to the patient explaining the follow-up agreement per informed consent.
a response is not received from the Investigator's letter	the Investigator could use any additional contacts provided by the subject to contact the subject.
The subject missed three consecutive visits and all attempts to contact the subject are unsuccessful, or the subject is contacted and chooses to withdraw from the study	the **Study Completion** form may be completed and will specify the reason the patient is no longer participating in this study.

11.9 Surgical Reoperation or Revision

A reoperation of the index hip or revision of the SCP injection site may be performed at the discretion of the Investigator (e.g., due to progressive pain or disability, etc.). A reoperation is defined as any surgical procedure on the index hip. For the purposes of this protocol, a revision will be defined as any partial or total joint arthroplasty or any fusion, bone fixation, bone grafting, or bone substitute procedure in the study hip.

If the reoperation occurs due to an adverse event, the event should be documented on a Serious Adverse Event Form and an Exit Form completed, and the subject exited from the study.

In the event that a revision occurs (defined as any partial or total joint arthroplasty or any fusion, bone fixation, bone grafting, or bone substitute procedure in the index hip), the subject will be exited from the study. A Serious Adverse Event Form and an Exit Form will be completed.

Use of any postoperative injections into the index hip should be recorded on the Medication Form at the next questionnaire completion window.

12 Reporting

12.1 Activities Required Prior to Initiation of the Study

12.1.1 Clinical Trial Agreement (CTA) and Financial Arrangements

A fully executed (signed by all required parties) CTA must be on file with the Sponsor prior to any investigator participating in this study. This agreement must explain the financial arrangement with the investigative site.

12.1.2 Institutional Review Board/Ethics Committee Protocol Approval

This study protocol must be submitted to and approved by the Investigator's Institutional Review Board (IRB) or Ethics Committee (EC). A copy of the IRB or EC approval letter must

be submitted to the Sponsor. The letter should identify the following:

- Protocol name and/or number.
- Date of IRB or EC meeting (if available).
- Date of approval.
- Date of expiration.
- Signature of IRB or EC.

12.1.3 Clinicaltrials.gov Registration

The Sponsor will be responsible for registering this study on www.ClinicalTrials.gov if required by local and national regulations.

12.2 Clinical Data Collection Submission

12.2.1 Summary of Case Report Form Data Collection

Study data will be collected on source documents which may include study-specific worksheets provided by the Sponsor. For subjects having bilateral SCP procedure, separate case report forms must be completed for each operative side.

The following source document and/or CRF completion guidelines should be followed:

- Complete carefully and accurately.
- Complete header information consistently across all case report forms for each individual study subject (when study-specific source document and/or CRFs are used).
- Be sure that data on the source documents match that which is entered through the electronic data capture (EDC) system.
- Use the study subject's unique Case ID number assigned as instructed. Do not provide information that is not requested on the source document and/or CRFs.
- Ensure that all fields are completed. For fields completed by the subject, efforts should be made to obtain any missing responses prior to the subject completing their visit.
- Source document and/or CRFs are to be completed with permanent black or blue ink.
- Do not overwrite, obscure, or whiteout an incorrect entry. To correct an error, draw a single line through the incorrect entry, add the correct entry next to it, and initial and date the correction. Corrections must be initialed and dated as they are made.
- Any change or correction to a Source Document and/or CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry in accordance ICH E6(R2) guidelines.
- The source document and/or CRFs should be easily readable.

12.2.2 Data Submission

Data will be submitted using an electronic case report form (eCRF) platform. If there is missing or out-of-range information, the system will give immediate feedback to the individual

making the entry and allow for correction and/or the assignment of a data query. **Investigative study sites will be asked to enter subject data into the eCRFs no later than 2 weeks from the time the subject was seen for their scheduled study visit.**

Submitted forms will undergo review by Zimmer Biomet personnel and questions or requests for corrections will be sent to the site via the EDCs electronic data query system. All corrections are to be made by a member of the study staff within the EDC system as well as any needed corrections to paper CRFs following GCP guidelines. Zimmer Biomet personnel will review corrected information in the study database.

12.2.3 Quality Assurance of Data

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports. Data reported on the source document CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All electronic systems used to create, modify, maintain, or transmit electronic study records will be validated. The Sponsor will maintain quality control systems, in accordance with the Sponsor's policies and procedures.

12.2.4 Patient Privacy and Identification

All personally identifiable information on the source document CRFs, as well as on any additional self-assessment form, will be pseudonymized in accordance with regional and/or national data privacy protection laws/regulations.

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this study.

The processing of personal data will comply with applicable data privacy protection laws and regulations, and all information will be treated with strict adherence to professional standards of confidentiality. Zimmer Biomet has put measures in place to ensure an adequate level of protection for the data irrespective of the country where it is transferred. All personnel in the data management team will comply with applicable data privacy protection laws and regulations.

Measures to ensure appropriate data protection are detailed in the ICFs provided and explained by participating Investigators to each participant.

12.2.5 Data Management

Investigators and their teams will collect and enter the data in a FDA 21 CFR Part 11 Compliant central database system managed by the Sponsor or third party in contractual relationship with the Sponsor. Data analysis will be conducted by internal statisticians on pseudonymized data. The database will be subjected to quality control checks and the resulting output will be used to generate data queries. Data queries will be used to record and to document the recovery of incomplete, inconsistent, or missing data.

Data is to be recorded utilizing subjects' source documentation, which includes medical records, operative and clinic notes, ancillary services reports, subject surveys and in some cases Case Report Forms. The subject-completed surveys are considered source documentation for this information. This may include electronically collected ePRO surveys where the direct data entry of survey data by the subject constitutes electronic source, paper surveys completed and submitted by the subject, or paper surveys completed on behalf of the subject by the site coordinator during phone interviews. Case Report Forms or certified copies of Case Report Forms may also serve as source documentation when the information is in addition to what is typically entered into a subject's medical record (e.g., fields documenting SCP time on the Surgical Documentation Form). Any Case Report Forms used as source documentation are to be labeled as such and made part of the subjects' case histories. Data are to be recorded accurately and in a timely manner following each event.

Questions regarding the content of the forms should be directed to the Zimmer Biomet Study Representatives.

Data analysis will be conducted by internal statisticians on pseudonymized data. The database will be subjected to quality control checks and the resulting output will be used to generate data queries. Data queries will be used to record and to document the recovery of incomplete, inconsistent, or missing data.

Each participating Investigator will receive periodic study reports on their own pseudonymized data as well as pseudonymized data for the whole study group. Anonymized study metrics, e.g. summary tables, graphical output and descriptive statistics will be produced and may be available as hard copy. Strict confidentiality of individual hospital data will be maintained.

12.3 Reporting Requirements

12.3.1 Investigator Reporting Responsibilities

The Investigator should ensure the accuracy, completeness, legibility, and timeliness of data reported to the Sponsor in accordance with this protocol. The Investigator or Designee will provide periodic reports to their IRB or EC as required to maintain IRB or EC approval throughout the study, and will provide any required final reporting to the IRB or EC upon study completion/termination. A copy of all IRB or EC re-approval letters must be submitted to the Sponsor. If the IRB or EC terminates or suspends its approval of the study, the Investigator or Designee will suspend study-related activities and will promptly notify the Sponsor. The Investigator should also promptly provide written reports to the Sponsor and the IRB or EC regarding any changes significantly affecting the conduct of the study, and/or increasing risk to the subjects.

12.3.2 Retention of Records

Study records must be retained by the Investigator or Designee for a minimum of 15 years from the Investigator's study termination date, or per applicable regulatory and/or IRB or EC requirements (whichever time period is greater). Measures shall be taken to prevent

accidental or premature destruction.

Study records are defined as the all information in original records, certified copies of original records of clinical findings, observations or other activities in a clinical study, including source data initially recorded in an electronic format, necessary for the reconstruction and evaluation of the clinical study. This may include but is not limited to: hospital records, clinic records, laboratory notes, device accountability records, photographs, radiographs, subject casebooks, regulatory records, signed informed consents and all other study-related documents

12.4 Management of Intercurrent Events

12.4.1 Failure to Obtain Informed Consent

Study participation will be offered at the time of the pre-operative visit at the hospital. Patients willing to participate in the study will be presented with the informed consent. Study data will not be collected until the Informed Consent has been signed and dated by the candidate. If a candidate does not wish to participate (does not sign and date the Informed Consent), data for that candidate will not be collected for this study.

12.4.2 Revision

In the event that revision of the SCP surgical site in the index hip is necessary, the Investigator will determine the best treatment and/or revision method for the subject. Once the revision surgery has been completed, the Investigator or qualified Designee must complete a **Serious Adverse Event** form and a **Study Exit** form.

12.4.3 Investigator Withdrawal

The Investigator can choose to withdraw a subject from the study if it is deemed to be in the subject's best interest or the subject does not consent to continue in the study after being informed of changes in the research that might affect them. The reason for the Investigator's withdrawal of the subject must be documented on the **Study Completion** case report form.

12.4.4 Subject Withdrawal

Study participation may be discontinued through surgical conversion (Total Hip Arthroplasty or total removal of AccuFill), withdrawal of consent, Investigator decision or death. A subject may voluntarily withdraw their consent from the study at any time without prejudice or affecting their future medical treatment. Investigators may withdraw a subject due to non-compliance with the protocol or follow-up questionnaire schedule, or for reasons of medical discretion.

All consented subjects who are withdrawn/ discontinued from the study should have an End of Study form completed to explain why they are no longer participating in the study.

When a subject withdraws or is withdrawn, all study procedures completed and data collected prior to the date of withdrawal will be submitted to the sponsor and included in the study database, unless the subject requests otherwise in writing.

Should a subject who previously chose to withdraw wish to re-enter the study, a new Informed Consent will be required. The site may resume scheduled follow-up visits from the subject's last follow-up visit.

12.4.5 Lost to Follow-up

Although follow-up compliance is essential to study quality, some subjects may not be able to complete follow-up evaluations. If the subject does not complete the required questionnaires through the two year time point and the Investigator or a member of the study staff has attempted to contact that subject at least three times (with any combination of an email reminder via EDC system, a phone call or an IRB approved subject follow-up letter) and receives no response, the subject may be deemed to be lost to follow-up. The research staff will document the attempts to contact the subject. The final attempt to contact the subject will be performed by register/return receipt mail. The receipt will be placed in the subject's binder. An End of Study/Withdrawal Form must be completed.

Should a subject expire, complete the Adverse Event and End of Study/Withdrawal Form. Submit copies of the death certificate, autopsy report (if applicable and available) and source documents related to the death. The Investigator will make written notification to the IRB upon the death of a subject in the study, based on the individual IRB requirements.

12.4.6 Protocol Deviations

Protocol deviations will **not** be collected for this study. A protocol deviation is an accidental or unintentional change to or non-compliance with the research protocol that does not increase risk or decrease benefit or does not have a significant effect on the subject's rights, safety or welfare, and/or on the integrity of the data. A deviation may be due to the research subject's non-adherence or an unintentional change to or non-compliance with the research protocol on the part of a researcher.

12.4.7 Protocol Violations

All protocol violations (i.e. any deviation from the protocol that may impact the subjects' rights, safety, or well-being, or the completeness, accuracy or reliability of the study data, or a deviation from FDA or IRB regulations or standards) shall be reported to Zimmer Biomet within 24 hours and to the reviewing IRB per policy. A Protocol Violation Form shall be completed that includes a full explanation of the event and outcome.

The Investigator will assist Zimmer Biomet in corresponding with the reviewing IRB, where appropriate, to determine the appropriate course of action.

12.4.8 Study Termination

Study subject participation is expected to end upon completion of the subject's two-year follow-up visit unless the subject voluntarily withdraws from the study, is withdrawn from the study by the Investigator, is lost to follow-up, undergoes revision to remove a study device, or expires. Reason(s) for study completion must be documented on the **Study Completion** case report form.

If the Sponsor decides to terminate the study early, the Sponsor will inform the Investigators of the reason for early study termination. It is the responsibility of the Investigators to inform their IRB or EC as applicable according to local and national laws/regulations.

12.4.9 Adverse Events

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 or procedure. In addition an adverse device effect is defined as 'any untoward and unintended response to a medical device'.

Each Adverse Event Form should only include one adverse event. When reporting an adverse event, it is important to record the diagnosis rather than the symptoms, event or treatment. For example, a subject who undergoes a Total Hip Arthroplasty after the Subchondroplasty Procedure may have had the procedure due to increased pain caused by hip osteoarthritis. In this case, 'Severe Osteoarthritis' or something similar (as determined by the Investigator) should be recorded as the diagnosis rather than 'Total Hip Arthroplasty'. Abbreviations/colloquialisms should also be avoided when recording the diagnosis.

For this study, **only AEs which are possibly or definitely related to the device or procedure will be reported to the sponsor**. 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.

For this study, device implies the AccuFill Bone Substitute Material and procedure implies the Subchondroplasty Procedure.

13 Safety Management – Medical Events/Adverse Events

Adverse events are required to be reported on the **Adverse Event Report** case report form. The completed **Adverse Event Report** case report form must be submitted to the Sponsor in a timely manner. The Investigator or Designee will also promptly provide the Sponsor with any additional requested information required for the Sponsor to comply with regulatory requirements. If applicable per their reporting requirements, the Investigator or Designee will also report applicable adverse event(s) to their IRB or EC.

The following definitions are from ISO 14155:2020.

13.1 Classification of the Event

13.1.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated

or unanticipated.

Note 1: This definition includes events related to the investigational medical device or the comparator.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices or comparators.

13.1.2 Serious Adverse Event (SAE)

A Serious Adverse Event is an adverse event that led to any of the following:

- death,
- serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function including chronic diseases, or
  - in-patient or prolonged hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, led to fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

13.1.3 Serious Health Threat

Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health of subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons.

Note 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibly of multiple deaths occurring at short intervals.

13.1.4 Adverse Device Effect (ADE)

An Adverse Device Effect is an adverse event related to the use of an investigational medical device.

Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment implantation, installation, or operation, or any malfunction of the medical device.

Note 2: This definition includes any event resulting from use error or from intentional misuse

of the medical device.

13.1.5 Serious Adverse Device Effect (SADE)

A Serious Adverse Device Effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

13.1.6 Unanticipated Serious Adverse Device Effect (USADE)

An unanticipated adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

Note 1: Anticipated serious adverse device effect (ASADE) is an effect which by nature, incidence, severity or outcome has been identified in the risk assessment.

13.1.7 Device Deficiency (DD)

A Device Deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

Note: Device Deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling.

It is important to document in the study also all device deficiencies that could have led to a medical occurrence but did not lead to an adverse event.

13.2 Causality Assessment (Relation to Device)

The relationship between the use of the medical device (including the medical - surgical procedure) and the occurrence of each adverse event shall be assessed and categorized.

During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Investigation Plan or the Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

Each adverse event will be classified according to four different levels of causality:

- None (definitely not related)
- Possibly Related (remote possibility, possibly, or probably related)
- Definitely related

The sponsor and the investigators will use the following definitions to assess the relationship of the adverse event to the investigational device, the comparator or the investigation procedure.

13.2.1 None

Relationship to the device, comparator or procedures can be excluded when the event has

no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device.

13.2.2 Possibly Related (Uncertain)

The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

13.2.3 Definitely Related

The serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt.

Note: Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related. Similarly, several routine diagnostic or patient management procedures are applied to patients regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.

13.3 Review of Reported Events

The Sponsor will review the investigator's assessment of all reported events submitted to determine and document in writing their seriousness and relationship to the study device and related procedures required by this protocol. In case of disagreement, the sponsor will consult the investigator for clarification and correction if required. If the disagreement cannot be resolved, the sponsor shall communicate both opinions to the Post Market Surveillance team for further investigation and required reporting if applicable.

13.4 Intensity of Symptoms

13.4.1 Mild

The subject is aware of the sign or symptom, but finds it easily tolerated. The event is of little concern to the subject and/or little clinical significance. The event is not expected to have any effect on the subject's overall health or well-being.

13.4.2 Moderate

The subject has discomfort enough to cause interference with or a change in usual activities. The event is of some concern to the subject's health or well-being and may require medical intervention and/or close follow-up.

13.4.3 Severe

The event interferes considerable with the subject's usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being. The event is likely to require medical intervention and/or close follow-up and may be incapacitating or life threatening. Hospitalization and treatment may be required.

Note: The term “severe” refers to the intensity of the event and can be used with any event, without regard to whether or not it meets the criteria for being classified as “serious” or “unanticipated”. For example, a subject can have a severe headache, but it is not a serious event.

13.5 Outcome Definitions

The outcome is reported in relationship to the Adverse Event, not the treatment rendered for the event (if any).

13.5.1 Recovered/Resolved

The adverse event has been resolved and/or no further treatment is required to treat the reported condition or illness.

13.5.2 Recovering/Resolving

Treatment or diagnostic studies were prescribed for the adverse event and the outcome of the adverse event is being resolved and patient is recovering, but has not completely recovered.

13.5.3 Not recovered/Not resolved

The adverse event is not yet resolved and the patient has not recovered from the adverse event.

13.5.4 Chronic, clinically stable

The adverse event will most likely never be resolved. The subject “tolerates” the illness or condition as a matter of life.

13.5.5 Death

The outcome indicates the subject died as a direct result of the reported adverse event.

14 Monitoring

Zimmer Knee Creations, Inc., as Sponsor of this clinical investigation, as well as IMARC Research, Inc. will be responsible for monitoring this study. The monitor’s duties are to aid the Clinical Investigator in the production and maintenance of complete, legible, well-organized and easily retrievable data. In addition, the Monitor will be responsible for assuring the Clinical Investigator understands the protocol and all applicable regulations. Approaches to monitoring 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 CRF entries with source documents, primarily looking at the Operative Report CRF. 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. hospital notes, appointment books, 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 Clinical Investigator will receive reasonable notification prior to each monitoring visit during the course of this clinical investigation. The monitoring frequency will be determined for each site based on factors including: the planned enrollment, the rate of enrollment, the level of experience of the clinical investigation team and the current study conduct. At each visit, the Clinical Investigator will be expected to cooperate with the Monitor for the review and verification of CRFs and any additional records as may have been previously arranged between the Clinical Investigator and the Monitor. A monitor log will be kept on site for monitor signature upon any visit completed.

This is a post-market study that does not involve investigational products or procedures, and the physical risks to the patients for participation in the study are minimal. Many assessments are standard-of-care for these patient populations and do not require special training for their use in the study. Non-standard assessments, such as patient-reported outcome measures (PROMs), are used frequently in clinical research and instructions can easily be communicated by remote methods. As such, site initiation visits may be conducted remotely for this study.

15 Risk Analysis

This study was designed to assure that the benefits and knowledge gained by studying clinical outcomes associated with Subchondroplasty for treatment of BMLs in the hip outweigh the potential risks to the subjects. Alternative treatment options may require more invasive surgical therapy to treat the painful hip, up to and including arthrodesis or arthroplasty.

15.1 General

Risks of surgical intervention

With any surgical procedure, there are risks of complication including those risks currently associated with surgical interventions in the hip. These risks include intra-articular adhesions (scar tissue), superficial and/or deep wound infection, nausea and/or vomiting, bleeding, hip pain, muscle weakness, and postoperative blood clot (hematoma). There are possibilities of wound re-opening, deep vein thrombosis (blood clot), pulmonary embolus (lung clot), vascular or nerve injury, and an allergic response to the anesthetic or medications. Some additional risks related to local anesthesia are swelling, pain, bleeding, bruising, nerve pain and loss of sensation in the skin and ligament around the hip.

Risks associated with subchondral implantation of AccuFill

Risks specific to the implantation of a bone marrow substitute may include tissue thinning over the implant site, tenderness/redness/edema, seroma/hematoma, infection, swelling/fluid collection and loss of contour. Migration, extrusion, dehiscence, fracture and sloughing of AccuFill can occur as a result of excessive trauma. Neurovascular injury may occur due to surgical trauma. A pulmonary embolism may result from using this injectable bone void filler.

Methods to minimize risk

Only appropriate subjects, who meet the include inclusion and exclusion criteria, will be recruited into the study.

Study subjects will be monitored post-operatively to assess the surgical site for any acute and chronic adverse reactions to ensure proper medical treatment can be administered. Validated and standardized outcome scales and surveys will be used to collect subjects' data. Experienced orthopedic surgeons will participate as investigators and have experienced staff to perform the study procedures.

Benefits and Justification for the Study

This is an observational study and there are no direct benefits to the subject, other than those associated with the treatment of a bone marrow lesion of the hip. The justification for this study is to learn more about patient outcomes following the Subchondroplasty procedure in the hip.

15.2 Indemnification

The indemnification provision is located in the Indemnification section of the executed clinical trial agreement.

16 Statistical Methods

16.1 Sample Size Calculation

The sample size required is based on the overall group mean improvement of the Harris Hip Score by at least the minimal clinically important differences (MCID) of 18.0 points from baseline to one year.

Based on internal Zimmer Biomet studies, assuming an improvement from baseline of 31.4 points with a standard deviation of 22.4, 80% power and alpha set at 0.05, 24 patients are needed to show the mean improvement from baseline is greater than the MCID of 18.0. Considering an attrition rate of 25%, 32 patients should be enrolled in the study. At an enrollment rate of approximately 50 subjects the study is more than adequately powered to show improvement over the MCID.

16.2 General Statistical Methods

Data collected in this study will be summarized descriptively and will be the basis of study reports. Descriptive summaries will be used to generate an overall summary of the clinical performance of the Subchondroplasty Procedure in hip cases and may be used for reports or to support presentations or publications.

16.3 Data Analysis

Summaries will routinely describe categorical data as counts and percentages. Routine summaries describing continuous data will be in the form of means, medians, standard deviations, minima and maxima; ninety-five percent confidence intervals will be used. Routine summaries of return to function, patient outcomes measures, etc. will generally be accompanied with the corresponding crude rates (expressed as percentages). Routine summaries of complication data will be in the form of frequencies and percentages. Summaries may be further

generated for strata within the study population, (e.g., males and females, different cut-points in the body mass index continuum, etc.). Subject confidentiality will be protected at all times and subject identifiers will not be included in study summaries.

17 Quality Control & Quality Assurance

The study is conducted in accordance with the Declaration of Helsinki and the ISO 14155:2020.

The Investigator will be required to permit representative(s) of the Sponsor's monitoring team to inspect all Case Report Forms and corresponding sections of the study patients office records and/or hospital original medical records. These audits will be done for quality assurance purposes, i.e. verifying adherence to the Clinical Investigation Plan and the completeness and accuracy of the data being entered on the Case Report Forms.

The Clinical Investigation Plan will be provided to all participating study centers. The Investigators will be fully trained in the proper reporting and submission of trial data prior to patient enrolment. Completed Case Report Forms will be reviewed before entering the data into a central database by the Sponsor.

The Clinical Study Manager is responsible for generating data queries for missing or unclear data if needed. It is the responsibility of the Clinical Study Manager to ensure data quality.

There are regular meetings between the Investigators and Zimmer Biomet Clinical Affairs staff. Written correspondence to all sites is used to inform the Investigators of routine study details and to update them on study status.

18 Suspension or Premature Termination of the Clinical Investigation

Zimmer Biomet may decide to suspend or prematurely terminate the clinical study at one or more investigational sites for significant and documented reasons, such as information becomes available that the risk to study subjects is higher than initially indicated.

In the case of an early termination of the study, the IRB/EC and regulatory authority(ies) should be informed in accordance with regional and/or national laws/regulations, and IRB/EC requirements. The reasons for termination should be provided and documented.

- Further follow-up of the study subjects shall proceed according to the investigator's standard of care or hospital's standard procedures.

19 Vulnerable Populations

No vulnerable patients will be included in the study.

20 Amendments / Modifications to the Clinical Investigation Plan

Any proposed amendments to this protocol must be submitted in writing and pre-approved by the Sponsor. All Sponsor-initiated protocol amendments will be documented in writing, including the date and justification for the change, and communicated in a timely manner to the

Investigators. All amendments are to be approved by the reviewing IRB prior to implementation.

21 Publication Policy

Institution or Investigators may publish, present, or use any results arising out of the performance of this Study for its or their own publication, presentation, instructional, or non-commercial research objectives provided that the publication, presentation, or use does not disclose any Confidential Information furnished by Sponsor, occurs only after completion of the Study, and contains only final Study data and analysis, unless otherwise approved by Sponsor.

Institution and each Investigator agrees that any proposed publication or presentation relating to the Study conducted under this Agreement will be submitted to Sponsor for review (not for approval or disapproval) at least thirty (30) days prior to submission for publication or presentation. In the event that the proposed publication or presentation contains patentable subject matter that needs protection, Institution and Investigators will, upon request received from Sponsor within the thirty (30) day review period, delay the publication or presentation for an additional ninety (90) days to allow Sponsor to file a patent application. Sponsor will have the right to require deletion of any Confidential Information or other proprietary information belonging to the Sponsor or information identifying Qualified Participants in the Study, unless otherwise required by law.

Notwithstanding the foregoing, to the extent the Study is part of a multi-center study, the Institution and each Investigator agree that the first publication of the results of the Study will be made in conjunction with the presentation of a joint multi-center publication of the Study results with the Investigators and institutions from all Study Sites contributing data.

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23 Appendices

A. Case Report Forms

B. Study Logs

C. Sample Informed Consent

D. Package inserts