A Longitudinal Outcomes Study of the Subchondroplasty® Procedure in the Foot/Ankle

Protocol No.: KC.CR.I.AM.16.2
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Version: 1.0

Study Design: Multi-Center Uncontrolled Cohort (Clinical) Study

STUDY SPONSOR:
Zimmer Knee Creations, Inc.
841 Springdale Drive
Exton, PA 19341

484-873-3343

TABLE OF CONTENTS

1.0 General Information

STUDY SPONSOR:
Zimmer Knee Creations, Inc.
841 Springdale Drive
Exton, PA 19341

ZIMMER STUDY REPRESENTATIVE

Marianne Rahme, BA, CCRP
Clinical Project Manager
Zimmer Knee Creations, Inc.
805 Springdale Drive
Exton, PA 19341
Tel: (484) 873-3343
Fax: 484-879-4288
E-mail address: Marianne.rahme@zimmerbiomet.com

Patrick D. Reischling, MBS, CCRA
Director, Clinical and Regulatory Affairs
Zimmer Knee Creations, Inc.
841 Springdale Drive
Exton, PA 19341
Tel: (720) 879-7828
E-Mail address: Patrick.reischling@zimmerbiomet.com

Monitor:

iMARC Research Inc.
22560 Lunn Road
Strongsville, OH 44149
Ph: 440-801-1540
Fax: 440-801-1542

Ethics Statement:

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH/Good Clinical Practice and applicable regulatory requirements.

2.0 Protocol Signature Page

I have read and understand "A Longitudinal Outcomes Study of the Subchondroplasty® Procedure in the Foot/Ankle" and will conduct the study in accordance with all stipulations of the signed Clinical Trial Agreement (CTA), this protocol, including all attachments and amendments, and according to applicable Food and Drug Administration regulations, HIPAA, local regulations, ICH and GCP guidelines and the policies of the reviewing IRBs and institutions where the study will take place.

Principal Investigator:

_____

(Print Name)

_____

(Signature) (Date)

_____

(Site Name)

_____

(Site Address)

3.0 Protocol Synopsis

Sponsor/Company	Zimmer Knee Creations, Inc.
Study Title	A Longitudinal Outcomes Study of the Subchondroplasty® Procedure in the Foot/Ankle
Protocol Number	KC.CR.I.AM.16.2
Implant Material	AccuFill® Bone Substitute Material
Treatment	Injection of a flowable calcium phosphate (CaP) synthetic bone-void filler into osseous defects in the bones of the Foot and/or Ankle (Subchondroplasty Procedure (SCP®)) as demonstrated by bone marrow lesions on diagnostic imaging.
Number of Study Sites	Up to 25 study sites
Study Population	Approximately 250 subjects, each with at least one bone marrow lesion (BML) in any of the bones of the foot and/or ankle who have elected to undergo or who have undergone the Subchondroplasty procedure, will be enrolled in the study.
Study Design	A post-market, multi-center, longitudinal, patient-reported outcomes study of a commercially available AccuFill bone substitute material used in the Subchondroplasty procedure of the foot and/or ankle.
Study Objectives	To collect data on the short- and long-term outcomes for subjects who are undergoing or who have undergone the Subchondroplasty procedure in the foot and/or ankle in a standard clinical setting. Outcomes to be assessed include medication usage, pain, function, health status and patient satisfaction.
Inclusion/Exclusion Criteria	Candidates must meet ALL of the following: 1) Subject has at least one bone defect such as a BML, cyst or stress fracture confirmed by diagnostic imaging. 2) Surgeon considers the patient appropriate for the SCP procedure. 3) Subject provides voluntary signature on the IRB-approved Informed Consent. 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 complete outcome forms via the internet, telephone, or regular mail. Candidates will be excluded if they meet ANY of the following:

	1) Subject is pregnant at the time of surgery. 2) Subject is incarcerated. 3) Subject is involved in active litigation related to the condition being treated.
Pre-Operative Evaluations	Initial study procedures include patient demographics, medical history, foot and ankle history, activity level, and each of the assessments and measures that will be applied longitudinally, including: • Use of pain medications • Subject-reported outcomes: o EQ-5D o Foot Function Index (FFI) o Numeric Pain Scale
Study Procedure	Each subject will undergo a Subchondroplasty® Procedure in at least one of the bones in the foot and/or in the ankle joint.
Follow-Up	• A numeric pain scale will be collected at the first post-operative visit at approximately 2 weeks • Thereafter, subjects complete self-reported outcomes measures post-operatively at 6 weeks, 3 months, 6 months, 1 year and 2 years via telephone, internet or mail. • Study coordinator will contact the subject by telephone at the above time points to inquire about any revision surgeries and adverse events.
Telephone Interviews	• Study coordinator will contact subject by telephone at 3, 4 and 5 year time points to complete the numeric pain scale, global satisfaction survey and inquire about any revision surgeries.
Post-Operative Subject Questionnaires	• Use of pain medications • Subject-reported outcomes: o EQ-5D o Foot Function Index (FFI) o Numeric Pain Scale o Subject Global Satisfaction Survey
Data Analysis	Data collected in this study will be summarized descriptively and will be the basis of study reports.

4.0 Abbreviations

AE	Adverse Event
BML	Bone Marrow Lesion
BMES	Bone Marrow Edema Syndrome
BSM	Bone Substitute Material
CaP	Calcium Phosphate
CFR	Code of Federal Regulations
CRF	Case Report Form
EDC	Electronic Data Capture
ePRO	Electronic Patient Reported Outcomes
FDA	Food and Drug Administration
FFI	Foot Function Index
HIPAA	Health Insurance Portability and Accountability Act
IFU	Instructions for Use
IRB	Institutional Review Board
MRI	Magnetic Resonance Image(ing)
NSAID	Non-steroidal Anti-inflammatory Drug
OA	Osteoarthritis
SAE	Serious Adverse Event
SCP	Subchondroplasty
TKA	Total Knee Arthroplasty
USADE	Unanticipated Serious Adverse Device Effect

5.0 Introduction

5.1 Clinical Background

Subchondral bone defects, sometimes called bone marrow lesions (BMLs), 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. Pathologists have shown that BMLs represent a healing response to trauma such as micro trabecular fractures of the subchondral bone [1]. BML defects have been highly correlated with pain symptoms in the knee [2, 3]; however, BMLs and their effect on foot/ankle pain and function have not been as thoroughly studied clinically. Moreover, because the ankle joint differs from other joints in the lower extremity with unique anatomic, biomechanical and biologic characteristics [4], so too do foot/ankle BMLs differ in prevalence, clinical presentation and clinical course [5].

Early articles in the radiographic literature are generally descriptive, characterizing the MR appearance of bone marrow lesions in the foot and ankle using a variety of pulse sequences. The etiology of these imaging features can sometimes be attributed to marrow abnormalities such as osteonecrosis, stress fracture, bone contusion, tumor, etc., [5, 6, 7, 8, 9] however not all bone marrow lesion patterns are as clear cut [5]. BMLs in the foot and ankle tend to involve multiple bones, are generally seen in younger patients and present with a clinical history of prolonged pain without a distinct history of prior trauma [5, 10, 11]. In a retrospective review of 72 patients whose MRIs of the foot demonstrated edema-like bone marrow abnormalities, Zanetti et al. concluded that edema-like patterns of unknown etiology are clinically relevant and predictors of long-lasting pain [10]. These findings were substantiated by Fernandez-Canton, et al. in a comparison of MRI imaging one year after the initial diagnosis of transient bone marrow edema syndrome (BMES) in 25 patients. Previously, BMES had been considered a benign disease that typically resolved in 3-12 months, but in this study, almost a third of the patients showed persistence of edema at one year with 8% showing no improvement, leading to the conclusion that patients experience pain for an extended period of time [8].

Treatment options for BMLs of the foot and/or ankle have been conservative in nature, including non-steroidal anti-inflammatory drugs, injections, calcium, physical therapy, extracorporeal shock therapy and activity modification [5, 8, 11]. Operative treatments can be joint sparing or joint destructive, however, considering the generally younger, physically active patient population with BMLs of the foot/ankle, a joint sparing procedure that does not preclude more extensive procedures in the future is desirable. Subchondroplasty® (SCP®) is a minimally-invasive procedure first described in 2007 to fill subchondral osseous defects associated with bone marrow lesions using an injectable bone substitute material (BSM), AccuFill® [12]. AccuFill is an injectable, self-setting, macro-porous, osteo-conductive, calcium phosphate bone graft substitute material that is intended for use to fill bony voids or gaps of the skeletal system of the extremities, spine (i.e. posterolateral spine), and the pelvis that are not intrinsic to the stability of the bony structure. These defects may be surgically created osseous defects or osseous defects created from traumatic injury to the bone. AccuFill is a bone graft substitute that resorbs and is replaced with new bone during the healing process. AccuFill has unique properties that allow it to flow through the osseous defects in trabecular bone and then set up hard at body temperature [13]. 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 [14]. The goal of this study is to track outcomes in a population undergoing SCP of the foot and/or ankle.

5.2 Product Description

The Subchondroplasty Procedure targets and fills bone defects with AccuFill BSM utilizing an arthroscopic / percutaneous approach as follows. Preoperatively, the BML bone defect is identified on 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 edematous void and hardens within the BML, and is resorbed over time and replaced with new bone during the healing process.

The Subchondroplasty procedure will be performed using two commercially available devices: AccuFill and SCP® Surgical Instrumentation.

AccuFill is an injectable, self-setting, macro-porous, osteo-conductive, calcium phosphate bone graft substitute material that is intended for use to fill bony voids or gaps of the skeletal system of the extremities, spine (i.e. posterolateral spine), and the pelvis that are not intrinsic to the stability of the bony structure. These defects may be surgically created osseous defects or osseous defects created from traumatic injury to the bone. AccuFill is a bone graft substitute that resorbs and is replaced with new bone during the healing process.

The SCP® Surgical Instrumentation is a set of manual surgical instruments used to target and deliver AccuFill to the osseous defect.

5.3 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 sites, 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 a bone void filler.

5.4 Case Studies

Miller and Dunn reported on two case studies using the Subchondroplasty procedure in the ankle. The first patient presented with chronic ankle pain and instability after suffering a severe ankle sprain four years prior and who failed conservative management with corticosteroid intraarticular injections. An MRI revealed chronic tearing of the anterior talofibular ligament, anterior tibial joint spurring and a subchondral bone marrow lesion in the medial aspect of the talar dome. The second patient presented with continued ankle pain following a previously

nonoperatively treated fibular non-union. An MRI revealed a large osteochondral lesion in the anterior-lateral aspect of the talar dome, subchondral talar edema and a chronic tear of the anterior talofibular ligament. Both patients underwent the Subchondroplasty procedure in conjunction with a modified-Bröstrom procedure. Patient One also had an anterior ankle arthrotomy and Patient Two had juvenile articular cartilage allograft delivered to the defect. At the 10 month follow-up visit, Patient One reported mild discomfort while golfing, while Patient Two returned to full activities without restrictions. Both patients state they would elect to have their procedures performed again [11].

5.5 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. (Appendix A).

2. SCP® Surgical Instrumentation – These are Class I manual surgical instruments. Per 21 CFR 888.4540, manual surgical instruments are premarket exempt.

6. 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 foot/ankle outweigh the potential risks to the subjects. Alternative treatment options may require more invasive surgical therapy to treat the painful foot/ankle, up to and including arthrodesis or arthroplasty.

6.1 Risks of surgical intervention

With any surgical procedure, there are risks of complication including those risks currently associated with surgical interventions in the foot/ankle. These risks include intra-articular adhesions (scar tissue), superficial and/or deep wound infection, nausea and/or vomiting, bleeding, ankle 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 foot/ankle.

6.2 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.

6.3 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 or foot/ankle surgeons will participate as investigators and have experienced staff to perform the study procedures.

6.4 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 bone marrow lesion of the foot and/or ankle. The justification for this study is to learn more about patient outcomes following the Subchondroplasty procedure in the foot/ankle.

7.0 Study Objectives

The purpose of this post-market clinical study is to collect data on the short- and long-term outcomes for subjects who are undergoing or who have undergone the Subchondroplasty procedure in the foot and/or ankle in a standard clinical setting. Outcomes to be assessed include medication usage, pain, function, activity levels and patient satisfaction.

8.0 Study Design

This is a post-market, multicenter, prospective, patient outcomes centered study to evaluate the on-label use of AccuFill during the Subchondroplasty procedure. Enrolled subjects will satisfy the inclusion/exclusion criteria and have at least one BML in any of the bones of the foot and/or ankle joint.

Demographics, medical history and medications will be recorded at the time of enrollment. Subjects will complete validated patient reported outcomes measures pre-operatively. Surgical details including the SCP® procedure, concomitant surgical procedures and intraoperative safety events will be recorded. Pain outcomes will be assessed at the first post-operative visit (7-21 days). Information on medication usage, pain, function, health status and subject global satisfaction will be collected post-operatively at approximately 6 weeks, 3 months, 6 months, 1 year, and 2 years. Subject global satisfaction and numeric pain scores will be collected at 3 years, 4 years and 5 years post-surgery. Screening for adverse events and revision surgeries will occur throughout the study. The target enrollment is 250 subjects.

Subjects will complete the study at 5 years or will be withdrawn if the patient undergoes revision of the Subchondroplasty site. For the purposes of this protocol, a revision will be defined as any joint arthroplasty, fusion or any bone fixation, bone grafting or bone substitute procedure on the index foot/ankle.

9.0 Subject Selection Criteria

9.1 Inclusion Criteria

Candidates must meet ALL of the following:

1) Subject has at least one bone defect such as a BML, cyst or stress fracture confirmed by diagnostic imaging.
2) Surgeon considers the patient appropriate for the SCP procedure.
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 the internet, telephone or regular mail.

9.2 Exclusion Criteria

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

1) Subject is pregnant at the time of surgery.
2) Subject is incarcerated.
3) Subject is involved in active litigation related to the condition being treated.

10.0 Study Procedures

10.1 Screening and Enrollment

Potential subjects will be screened from each investigator's patient population to determine if they meet the inclusion criteria described in Section 9.1 and none of the exclusion criteria described in Section 9.2. 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 inclusion/exclusion criteria, sign a consent form, and undergo the SCP procedure. With prior approval of the Sponsor, the site may enroll subjects who have previously undergone Subchondroplasty. The subject will sign informed consent prior to completing follow-up study questionnaires. The Study Site will maintain a Subject Enrollment Log for all enrolled subjects.

10.2 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. The Informed Consent Form must be signed prior to the collection of any protocol-specific data.

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.

If the Study Site does not have an IRB of record, a central IRB may be utilized upon approval by Zimmer Knee Creations.

10.3 Preoperative Procedures

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

10.3.1 The preoperative visit will include collection of basic demographic information, medical history, foot and ankle history and current use of prescription and over-the-counter pain medication.

10.3.2 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:

- The Foot Function Index (FFI)
- EQ-5D
- Numeric Pain Scale

10.3.3 For subjects enrolled after the completion of the Subchondroplasty procedure, basic demographic information, medical history, foot and ankle history and pre-op use of prescription and over-the-counter pain medication data should be collected, if available, from the subject's medical record. Pre-operative FFI, EQ-5D, and/or numeric pain scale should be entered if they were collected as part of the standard of care.

10.4 Subchondroplasty Procedure

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

- The preoperative MRI should be used in planning the access point, trajectory and depth of the AccuPort cannula(s) for accessing the location of the BML(s).
- AccuPorts should be placed using fluoroscopic guidance.
- Use of the SCP Navigation guide is optional.
- Appropriate volume of AccuFill should be used to adequately fill the area(s) of BML(s), per the surgical technique guide in Appendix B, 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 Surgical Documentation Case Report Forms completed during surgery to serve as source documents.

Surgical Documentation

- OR time
- SCP procedure time
- Anesthesia type
- Intraoperative adverse events
- Documentation of SCP injection
  - Type of AccuPort(s) used (end target, side target, gauge, etc.)
  - Volume of AccuFill injected for each lesion
- Lot numbers of SCP Complete Kit, AccuFill, AccuPort(s) and AccuMix used
- Documentation of treated BML(s)
- Concomitant procedures

10.5 Postoperative Procedures and Assessments

During the immediate postoperative period, the investigator's standard postoperative care procedures should be followed. All adverse events and complications are to be assessed and recorded on the **Adverse Event Form,** per Section 11.0 Adverse Event Reporting.

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

10.6 Evaluation Schedule

Patients will be enrolled at the physician's office. A numeric pain score will be collected at the first post-operative standard of care visit at approximately 7-21 days. Subjects may complete follow-up questionnaires in the office, over the telephone, or online through an EDC system at the selected time points post-operatively at 6 weeks, 3 months, 6 months, 1 year and 2 years. At the 3, 4, and 5 year time points, the study coordinator will contact the subject by telephone to remind the subject to complete the numeric pain scale, the global satisfaction survey and record any revision surgeries.

If internet access is not available, questionnaires may be mailed to study subjects by their study physician at the selected time points and mailed back to their study doctor.

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

10.6.1 Any medications or therapies used for pain relief are to be recorded, specifically the classification (acupuncture, analgesic/non-narcotic, anti-inflammatory, narcotic, etc.), and whether or not the medication/therapy usage is related to the index foot/ankle. Any hyaluronic acid or cortisone injections should be recorded.

10.6.2 The subject is to complete a series of surveys and scales regarding their clinical outcomes during the time frame indicated on the form. These scales include:

- Foot Function Index (FFI)
- EQ-5D
- Numeric Pain Scale
- Subject Global Satisfaction Survey

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 subject reported outcomes (ePRO) system. Prior to conducting the study visit, the Study Coordinator will check to confirm whether these surveys have been completed electronically or not. If time is an issue, the Study Coordinator will fax, email or mail a copy of the surveys to the subject with instructions for completion or initiate another reminder from the ePRO system. Mailed surveys will be sent with a stamped, return envelope. The subject should be instructed to return the surveys within one week. 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.

10.6.3 A Subject Stipend may be offered to the subject at the completion of each follow-up time point, if in accordance with the institution's policies.

10.7 Telephone Interviews

The Study Coordinator will schedule a call with the subject within the visit window.

During the call, the subject is to be queried regarding the occurrence of any Adverse Events and Serious Adverse Events, per Section 12.0 Adverse Event Reporting. Any adverse event that results in reoperation or revision is to be recorded as a Serious Adverse Event.

The subject is to be queried regarding any reoperations of the index foot/ankle. All reoperations are to be documented using the Surgical Reoperation Form, per Section 11.1.

The subject will be reminded to complete the online surveys. The subject can also elect to complete the surveys via the telephone or mail. 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.

The Study Coordinator is to document the phone interview in the Telephone Log, including any completion of outcome measures via the phone.

At the 3, 4 and 5 year follow-up, the Study Coordinator will inquire about Adverse Events, Serious Adverse Events and reoperations, and remind the subject to complete the Global Satisfaction Survey and Numeric Pain Scale.

Table 1. Schedule of Events

	Visit 1	**Visit 2**	**Visit 3**	**Post-Op Questionnaires**	**Post-Op Questionnaires**	**Post-Op Questionnaires**	**Post-Op Telephone Call**
Procedures	**Study Admit/ Pre-operative**	**Operative**	**SOC Post-Op Visit (7-21 days)**	**6 weeks**	**3 months 6 months**	**1 year 2 years**	**3 years 4 years 5 years**
Visit Window	≤60 days Prior to Surgery			±7 Days	±14 Days	±60 Days	±60 Days
Informed Consent	X						
Inclusion & Exclusion Criteria	X						
Demographic Form	X						
Medical History	X						
Pain Medications/Therapies	X			P	P	P	
FFI	P			P	P	P	
Numeric Pain Scale	P		X	P	P	P	X
EQ-5D	P			P	P	P	
Global Satisfaction Survey				P	P	P	X
Surgical Documentation		X					
Adverse Event or Serious Adverse Event[2]		(X)	(X)	(X)	(X)	(X)	(X)
Protocol Deviation[2]		(X)	(X)	(X)	(X)	(X)	(X)
Telephone Contact[2]				X	X	X	X
Surgical Reoperation[3]			(X)	(X)	(X)	(X)	(X)
Study Exit[4]		(X)	(X)	(X)	(X)	(X)	X

X Investigator completed forms
(X) Completed by Investigator when required
P Subject completed forms
[2] Case Report Forms to be completed if/when event occurs.
[3] Surgical Reoperation form will be completed if the investigator performs any procedure on the index foot/ankle regardless of whether the subject's change in condition is related to the initial study procedure.
[4] Study Exit form will be completed if the subject is no longer participating in the study for any reason.

11.0 Management of Intercurrent Events

11.1 Surgical Reoperation or Revision

A reoperation of the index foot/ankle or revision 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 foot or ankle. 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 foot or ankle.

The investigator is to dictate detailed operative notes that include the measures listed below, or have paper copies of the Surgical Reoperation Form completed during surgery to serve as a source document.

11.1.1 Surgical Reoperation Documentation

- Reason for surgery

- Postoperative diagnosis
- OR Time
- Anesthesia Type
- Status of the Subchondroplasty Injection Location

If the reoperation occurs due to an adverse event, the event should be documented on a Serious Adverse Event Form and the surgery documented on the Surgical Reoperation Form.

11.1.2 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 foot/ankle), the subject will be exited from the study. A Serious Adverse Event Form and Surgical Reoperation Form will be completed.

11.1.3 In the event that a reoperation occurs that does not involve revision of the BML site(s), a Serious Adverse Event Form and Surgical Reoperation Form will be completed, and the subject will continue to be followed in the study per protocol.

11.2 Postoperative Injections

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

11.3 Missed Follow-up Completion of Questionnaires

If a subject fails to complete the post-operative questionnaires at a follow-up time point, the site should continue to attempt follow-up of the subject through the five year study end point. The subject should only be exited from the study under the conditions described in section 11.7.

11.4 Protocol Amendments

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.

11.5 Unscheduled Office Visits

Investigators may see the subjects, at their professional discretion, outside of the time points described in the study protocol. If an adverse event (AE) is reported during an unscheduled visit, the AE should be documented per Section 12.0 Adverse Event Reporting. No additional data collection or Case Report Forms are required at the unscheduled visit.

11.6 Protocol Deviations and Violations

The Investigator(s) agrees to conduct the study in accordance with this protocol. For the purpose of this study, **only** violations that affect the subject's rights, safety, or welfare, or the integrity of the data will be recorded.

11.6.1 A protocol violation can be described as accidental or unintentional change to, or non-compliance with the IRB approved protocol without prior Sponsor and IRB approval. Violations generally increase risk and/or decrease benefit, affects the subject's rights, safety, or welfare, or the integrity of the data. Examples include failure to obtain valid informed consent (e.g., obtained informed consent on an unapproved consent form), loss of laptop/computer that contained identifiable and private information about subjects or not following inclusion/exclusion criteria.

Any deviations to inclusion or exclusion criteria must be submitted to Zimmer Biomet and the reviewing IRB, where applicable, for analysis and approval prior to subject enrollment.

All protocol violations 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.

11.6.2 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.

11.7 Withdrawal and Study Re-Entry

During the course of the study, it is possible that subjects will be withdrawn from the study. Factors leading to subject withdrawal may include, but are not limited to, the following:

Subject Withdrawal – A subject may voluntarily withdraw 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 any other reason per their professional opinion. The date and reason for subject withdrawal is to be documented on the **Study Exit** form.

If a subject is withdrawn or terminated due to medical safety considerations because of an adverse event, the adverse event must be followed by the investigator to satisfactory resolution or until the investigator determines the event to be chronic or clinically stable. All study data related to event is to be recorded.

Subject Lost to Follow-Up – If the subject does not complete the required questionnaires and the Investigator or Study Coordinator has attempted to contact that subject at least three times via telephone 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. A study Exit Form must be completed.

Should a subject who previously chose to withdraw or was considered lost-to-follow-up wishes 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.

Subject Death – Should a subject expire, complete the Adverse Event and Study Exit 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.

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.

12.0 Adverse Event Reporting

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

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. See Section 12.1.

In the event there is an exacerbation of the pre-existing medical condition or symptoms (due to the device or study related procedure), then an AE must be reported.

12.1 Relationship to study device or procedure

The relationship to the 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.

- 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, the investigator should obtain all the information required to complete the appropriate AE form(s). If an event occurs at an outside institution, the investigator should attempt to obtain, if possible, required AE information to report to the Sponsor.

12.2 Adverse Event Data Collection

The Adverse Event Form will collect the following:

- Description of complication
- Date of onset
- Severity/Intensity of symptoms
  - Mild: Event/symptom is transient and well tolerated by the subject.
  - Moderate: Event/symptom causes discomfort and interferes with routine activities of the subject.
  - Severe: Event/symptom interferes considerably with the routine activities of the subject or causes inability to work.
- Duration
- Relationship to surgical procedure
- Relationship to product
- Treatment
- AE Outcome

12.3 Events Followed to Resolution

Any Adverse Event considered by the Investigator to be possibly or definitely related to the Subchondroplasty procedure should be followed over the study period until resolution or until the Investigator determines the event is chronic or clinically stable.

12.4 Serious Adverse Events

A Serious Adverse Event (SAE) is described as any adverse event that is:

- Fatal;
- Life-threatening*;
- Results in permanent impairment of a body function or permanent damage to body structure; or
- Necessitates medical or surgical intervention, including hospitalization

** NOTE: the term "life-threatening" refers to an event in which the subject was at a risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*

If an AE is determined to be serious (i.e., an SAE), the Investigator(s) will determine the

relationship of the adverse event to the procedure, device, or any commercial products used during the period of the study and complete a **Serious Adverse Event Form**. Death is considered to be an outcome of an Adverse Event and documented on the Serious Adverse Event Form. The actual cause of death (rather than the term "death") should be recorded on the form. All SAEs will be followed until resolution or the Investigator judges the event to be chronic or stable.

The Investigator must report all SAEs that meet the criteria below to a Zimmer Biomet Study Representative within twenty-four (24) hours after becoming aware of the incident:

- Definitely or possibly related to the Study Procedure AND unexpected

The Investigator is responsible for notifying the IRB of all Adverse Events, including SAEs, in accordance with local regulations and institutional policies.

If an Unanticipated Serious Adverse Device Effect (USADE) is identified by the Sponsor, it will be promptly reported to concerned Investigators and regulatory authorities as required by applicable regulatory requirements. If applicable per their reporting requirements, the Investigator or Designee will report the USADE to their IRB or EC.

13.0 Assessment of Safety

All reports of Adverse Events will be entered into the study database and evaluated by the Sponsor or their designee on a regular basis throughout the study. These reports will be made available to the Investigator for preparation of IRB continuing review reports, when requested.

Individual and aggregated events will be reviewed for consistency with expected events, for both severity and rate of incidence. Individual events or trends in events that appear to impact subject safety are reviewed by Zimmer Biomet management to determine if a change in the protocol or termination of the study is warranted. These decisions will be promptly communicated to all Investigators and local IRBs.

14.0 Statistical Considerations and Methodology

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 the foot/ankle cases and may be used for reports or to support presentations or publications.

Summaries will routinely describe categorical data as counts and percentages and ninety-five percent confidence limits will generally be used to assess categorical differences. 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 to contrast differences. Routine summaries of return to function, patient outcomes measures, etc. will generally be described via the Kaplan-Meier method and these 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.

15.0 Data Management

15.1 Data Collection

Data will be recorded using an electronic data capture (EDC) platform provided by Zimmer Biomet. Zimmer Biomet personnel will provide access, training and user support to all sites. Investigative sites will be required to have broadband internet access with standard firewall protection features.

Data are 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.

15.2 Data Submission

Data will be recorded 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.

Submitted forms will undergo review by Zimmer Biomet personnel and questions or requests for corrections will be sent to the Investigator via the EDCs electronic data query system. All corrections are to be made by the site coordinator 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.

16.0 Records and Reporting

16.1 Disclosure of Health Information

The use or disclosure of all protected health information will comply with the Health Insurance Portability and Accountability Act (HIPAA). Any information provided to Zimmer Biomet will be identified only by a subject ID and date of surgery. All information will be treated with strict adherence to professional standards of confidentiality and will be filed at Zimmer Biomet under

adequate security and restricted accessibility by clinical personnel.

16.2 Auditing and Inspecting

The Investigator will permit study-related monitoring visits, quality assurance audits, and inspections by the IRB, the Sponsor, government agencies, and other local health authorities as necessary to ensure proper conduct of the study in terms of collection and recording of data and maintaining records. Representatives of Zimmer Biomet should be allowed access to relevant study materials, including source documents of data collected as part of this study.

Every precaution will be taken to protect the privacy of research subjects and the confidentiality of their personal information when using or disclosing protected health information (PHI), or when requesting PHI from others. Reasonable efforts will be made to limit the disclosures to the minimum necessary to accomplish the intended purpose of the use, disclosure, or request. Zimmer Biomet strictly complies with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy and Security Rules.

16.3 Maintenance of Records

The Investigator is to maintain a copy of all study records and source documentation, including signed Informed Consent Forms and HIPAA Authorization, for a minimum of 6 years following the last protected health information disclosure. This time period may be greater if required by reviewing IRB or institutional policies.

17.0 Materials and Supplies

17.1 Study Materials

Zimmer Biomet will provide each investigative site with Investigator Notebook 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.

17.2 Subchondroplasty Products

The AccuFill bone substitute material and Subchondroplasty Instrumentation are to be ordered through the Investigator's Zimmer Biomet Sales Representative. Specific information on the products used will be recorded on study Case Report Forms, including lot numbers.

18.0 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.

19.0 References

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