Clinical Investigational Plan

Zimmer Knee Creations SCP® Observational Cohort Follow-Up Study

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Sponsor:
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1. Protocol Synopsis

Study Title	Zimmer Knee Creations SCP® Observational Cohort Follow-Up Study
Study Nickname	SCP® Observational Study
Study Design	Multi-center patient outcome observational cohort
Sponsor	Zimmer Knee Creations
Protocol Number	KC.CR.I.AM.16.3
Protocol Version	2
Number of Sites	Approximately 30
Number of Patients	Approximately 1000
Inclusion Criteria	1. Surgeon considers patient appropriate for SCP® procedure. 2. Patient has agreed to undergo the SCP® procedure or has already undergone the procedure. 3. Subject is willing and able to sign a written consent form. 4. The subject has the mental capacity and the willingness to contribute follow-up outcome data. 5. Patient is willing and able to complete outcome forms in person or by phone, email or regular mail.
Evaluation Parameters	1. Detailed Patient Demographic Information 2. Work/disability status 3. Operative details 4. Safety (i.e. adverse events) 5. Visual Analog Scale (VAS)—Knee Pain 6. International Knee Documentation Committee (IKDC) Subjective Knee Form 7. VR-12 Health Survey 8. Secondary Surgical Intervention

2. Description of SCP® Procedure

Subchondroplasty® (SCP®) is a procedure performed on subjects who have bone marrow lesion(s) (BML). BMLs are subchondral defects in the bone and the SCP procedure allows surgeons to place AccuFill® calcium phosphate (CaP) (bone void filler) at the defect site. SCP is performed on the subchondral bone of the knee utilizing an arthroscopic/percutaneous approach. Using standard arthroscopic surgery techniques, skin incisions are made for the insertion of arthroscopic instrumentation. Other arthroscopic procedures in the knee are performed per the surgeon's operative plan for each subject. Using fluoroscopic guidance, the surgeon locates the BML and one or more AccuPort cannulas are drilled into the bone. Through the cannula, calcium phosphate bone void filler is injected into the bone marrow lesion until the edematous region is

filled. The calcium phosphate fills the edematous void (defect) and hardens within the BML. The calcium phosphate is resorbed over time and replaced with natural bone.

3. Study Design

This is a multi-center patient outcome observational cohort study intended to collect data on the short- and long-term safety and effectiveness of the SCP procedure. This observational cohort will become a repository of data reflecting patient experiences with the SCP procedure over time. Detailed patient demographic information (e.g., age, gender, location of defect, severity of symptoms, etc.) will be collected to determine the most suitable SCP patient population(s). The study duration is expected to be 10 years.

3.1 Study Population

The SCP Observational Cohort study will enroll either patients undergoing SCP or patients who have already had the SCP procedure for the treatment of BMLs where bone void filler is placed at the site of the BML (defect).

3.2 Study Sites

The study will be conducted at up to 30 sites. All will be trained on the SCP Observational Cohort study.

3.3 Sample Size

As an observational cohort study there is no upper subject enrollment limit. Every patient undergoing the SCP procedure will be invited to participate in the study. The study goal is to collect data for approximately 1000 patients and evaluate demographics and outcomes data.

4. Study Procedures

4.1 Subject Eligibility

Enrollment will be based on the treating physician's standard of care and the following criteria:

1. Surgeon considers patient appropriate for SCP procedure.
2. Patient has agreed to undergo the SCP procedure or has already undergone the procedure.
3. Subject is willing and able to sign a written consent form.
4. The subject has the mental capacity and the willingness to contribute follow-up outcome data.
5. Patient is willing and able to complete outcome forms in person or by phone, email or regular mail.

4.2 Subject Enrollment

All patients considered for the SCP procedure by the investigator or who have had the SCP procedure will be invited to participate in the study. Patients expressing an interest in participation will proceed with the informed consent process. No study activities will be performed prior to patient signature of the informed consent form. If the patient does not sign the informed consent, the patient will still undergo the SCP procedure, but they will not be included in the observational cohort study. Should a patient not undergo SCP, the patient will not be enrolled in the observational cohort study and will be reported as a screen fail. The enrollment status for each patient considered in the study will be appropriately documented on a screening log.

4.3 Subject Informed Consent

Patients will provide written consent to be included in the SCP study. The informed consent form will conform to 21 CFR Part 50, Protection of Human Subjects. Each patient must read, have an opportunity to have any questions addressed, and sign this form prior to being enrolled in the study.

The investigator or appropriate study staff's signature on the consent form will document that the informed consent process included the following items:

- The subject was provided adequate time to read and review the consent form prior to signing it.
- The subject was given an opportunity to ask any questions he/she had concerning the study.
- The subject understands what their expectations are for participating in the study.
- The information in the consent form was provided in a language the subject understands.
- The subject signed the consent form prior to enrollment in the observational cohort study.
- The subject received/will receive a copy of the signed and dated consent form.

4.4 Data Collection

This section is applicable to individuals who have undergone screening, have signed an Informed Consent Document, and have otherwise been found eligible to participate in this study. This section details the pre-operative, operative, and post-operative management of Subjects.

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. The follow-up data to be collected as part of this study will be mailed or emailed to study

subjects by their study doctor at the selected time points (6 weeks, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years). The patient will fill out the evaluation forms and then mail the forms back to their study doctor or complete them online. These forms may also be completed by phone with study staff; however an approved phone script must be used. Additionally, if the subject returns to the physician's office during a follow-up time point, the evaluation forms may be completed in person.

Zimmer Knee Creations will work with an electronic data capture (EDC) system developed to track all patient data for this observational cohort study. The EDC firm will complete the necessary diligence to ensure any platform selected meets the technical, reporting, data management, storage and security needs of the firm. Data collected on the CRFs will be included in the study database.

4.4.1 Preoperative Procedures

Prior to surgery, the data in Table 1 must be collected for each enrolled Subject.

Table 1: Preoperative Data Collection

Form 1—Medical History	
Evaluation	**Details of Evaluation**
Enrollment Checklist	Authorized medical personnel will verify subject eligibility.
Patient Demographics	Authorized medical personnel will collect basic demographics from the preoperative time period.
Knee Related History	Authorized medical personnel will collect previous/current treatments and previous/current medications (prescription drugs) for the affected knee, as well as previous surgical treatments.
Concomitant Medical Conditions	Authorized medical personnel will collect medical conditions from the preoperative time period.
Current Medications	Authorized medical personnel will collect current medications (prescription drugs) not related to the affected knee.

Form 2—Pre-Operative Clinical Evaluation	
Evaluation	**Details of Evaluation**
VAS—Knee Pain	Each of the questionnaires should be completed by the Subject. It typically takes 5-10 minutes per questionnaire to complete.
Length of Painful Symptoms	
Work/Disability Status	
IKDC	
VR-12 Health Survey	

4.4.2 Operative Procedures

The surgical process is to follow site standard of care.

Data collected during the operative procedure of the Subject is listed in Table 2.

Table 2: Operative Data Collection

Form 3—Surgical Evaluation & Details	
Evaluation	**Details of Evaluation**
Imaging Evaluation	Baseline MRI and Standing Alignment X-Ray dates.
Standing Alignment	Patient's standing alignment.
Bone Marrow Edema Location	Surgeon must indicate locations of bone marrow edema on MRI.
Surgical Procedure Details	Description of Subject's operative procedure including such items as findings and treatments, operative times and diagnoses.
Adverse Event (if applicable)	Description of adverse events occurring during the operative procedure, *if applicable.*

4.4.3 Postoperative Procedures

Immediate post-operative management is at the discretion of the surgeon and support staff and should follow each Site's standard of care.

Data collection for this study will occur post-operatively at 6 weeks, 3 months, 6 months, 1 year, 2 years, 3 years, 4 years and 5 years. The post-operative visit data listed in Table 3 must be collected for each enrolled Subject either in person or by email, mail or telephone.

Table 3: Postoperative Data Collection

Form 4—Post-Operative Evaluation	
Evaluation	**Details of Evaluation**
VAS—Knee Pain	Each of the questionnaires should be completed by the Subject. It typically takes 5-10 minutes per questionnaire to complete.
Medications	
Surgical/Non-Surgical Procedures	
Work/Disability Status	
IKDC	
VR-12 Health Survey	
Adverse Event (if applicable)	**Only AEs which are possibly or definitely related to the device or procedure will be reported to the sponsor.** **Serious AEs must be reported as soon as possible and within 24 hours after the investigator first learns of the event**. The Sponsor is subsequently responsible for reporting as required. *See Adverse Event Reporting in Section 5.*
End of Study/ Withdrawal	At any time during the study a Subject may withdraw. Subject withdrawal must be documented and provided to the Sponsor.

4.5 Data Analysis

Please note that detailed patient demographic information (age, gender, location of defect, severity of symptoms, etc.) will be collected and analyzed to identify suitable candidates for SCP and to perform covariate analyses on the post-operative clinical outcomes for the study population.

5. Adverse Event Reporting

5.1 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. 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 and/or is confirmed by the improvement of the effect upon discontinuation of the clinical use of the device, and/or the effect is not reasonably explained by the Subject's clinical state.

Relationship to study device or procedure should be rated as follows:

1. **None** (definitely not related): there is no relationship between study device or procedure and the event.
2. **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.
3. **Definite** (definitely related): the relationship between study device or procedure and event does exist and is confirmed upon further investigation by the investigator.

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

AEs are reported beginning from time of surgery until Subject participation has ended (study completed or Subject withdrawn). AEs must be followed to resolution or until the study completion or Subject withdrawal.

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.

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

The following categories of AE severity are to be used:

1. **Mild:** awareness of a sign, symptom or event that is easily tolerated and transient in nature with minimal or no impairment to normal activity.
2. **Moderate:** moderate symptoms that are poorly tolerated, sustained, interfere with normal activity and require medical attention.
3. **Severe:** symptom(s) require intervention, and the activities of daily living are significantly altered.

5.2 Serious Adverse Events

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

1. Results in death
2. Is a life-threatening illness or injury
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability/incapacity, or
5. Is a congenital anomaly/birth defect
6. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or function.
7. Other serious (Important Medical Events). Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

For the purpose of this protocol, **any surgical intervention** is considered a serious adverse event. In case of death, all possible information available, such as autopsy or other post-mortem findings should be provided.

SAEs must be reported to the Sponsor as soon as possible and within 24 hours after the investigator first learns of the event. SAEs are reported to the respective Institutional Review Board (IRB) or Ethics Committee (EC), as per their respective requirements by the site.

6. 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 considered Lost to Follow-Up and exited from the study under the conditions described in section 7.2. There should be at least three documented attempts to contact the subject to obtain follow-up data with any combination of an email reminder via OBERD, a phone call or an IRB approved subject follow-up letter.

7. Discontinuation of Subject Participation

7.1 End of Study/Withdrawal

Study participation may be discontinued through surgical revision (Partial, Total Knee Arthroplasty or total removal of AccuFill), withdrawal of consent, investigator decision or death. 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. This form should be sent to the Sponsor upon completion and placed in the subject's binder.

7.2 Lost to Follow-Up

If the subject does not complete the required questionnaires through the five year time point and the Investigator or Study Coordinator has attempted to contact that subject at least three times via email reminder through OBERD, 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 should have documentation of the attempts to contact the subject. The final attempt to contact the subject will be performed by certified mail and the receipt will be placed in the subject's file. An end of study form must be completed, sent to the Sponsor and also placed in the subject's file.

Should a subject who previously chose to withdraw their consent wish to re-enter the study, a new signed Informed Consent Document will be required. The site may resume follow-up visits as long as they are within the designated visit window.

8. Protocol Adherence

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. A log of the violations will be kept within the site's regulatory binder and sent to the Sponsor when any violations have occurred.

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.

Protocol deviations will **not** be collected for this study nor added to the protocol violation log. 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.

9. Ethical Considerations

9.1 IRB Approval

IRB approval will be obtained prior to patient enrollment at each site. The revocable informed consent form will conform to 21 CFR Part 56, Institutional Review Boards.

9.2 Protection of Patient Confidentiality

All HIPAA requirements for subject confidentiality will be maintained.

Only approved study personnel shall have access to the patient records. None of the specific patient data will be disclosed to persons or organizations not involved in the research. Reports generated will not identify individual patients in any way.

In addition to protection of patient privacy rights, Zimmer Knee Creations will use due diligence to restrict access to this study platform and patient outcomes. Zimmer Knee Creations will maintain exclusive responsibility for study administration and oversight.

Zimmer Knee Creations will complete the development of this observational cohort program; provide training and continuing education on proper methods for data collection, entry and reporting; and oversee compliance with patient privacy rights including HIPAA.

10. Subject Stipends or Payments

Subjects will receive stipends based on each site's respective budget and informed consent form.