Clinical Study Protocol

Study Title: Feasibility of the Phantom Knee System in Improving Pain Relief and Function in Patients Needing Unloading of the Medial Compartment of the Knee: A Prospective, Multi-Center, Single-Arm First in Human Study

Short Title: Phantom Knee System FIH Trial
Protocol No: KINE-1406 (CLIN 102486)

VERSION 7.0, DATE: 30 May 2017

Study Sponsor: Moximed, Inc.
[redacted]

Study Manager: [redacted]
VP Regulatory and Clinical Affairs
Moximed, Inc.
[redacted]

This protocol was designed and will be conducted, recorded and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines and the International Organization for Standardization (ISO) 14155[1], as well as in accordance with all national, state, and local laws of the appropriate regulatory authorities and the Declaration of Helsinki (October 2013).

I have read and agree to abide by the requirement of this protocol.

Investigator Signature	Date
Investigator Name (please print or type)	

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PRINCIPAL STUDY CONTACTS

	Name, Address and Contact
Study Sponsor Contact	[redacted] Vice President of Regulatory and Quality Affairs Moximed Inc. [redacted]
	[redacted] Scientific Affairs Manager Europe Moximed International GmbH [redacted]
Medical Monitor	[redacted]
Imaging Core Lab:	[redacted]

1.0 PROTOCOL SYNOPSIS

Protocol Title	Feasibility of the Phantom Knee System in Improving Pain Relief and Function in Patients Needing Unloading of the Medial Compartment: A Multi-Center, Single-Arm First In Human (FIH) Study
Short Title	Phantom Clinical Trial
Protocol Number	KINE-1406
References	CLIN102485: KINE-1406: Patient Information Sheet and Informed Consent Form (Template) CLIN102064: Phantom Case Report Forms CLIN102481: Imaging Evaluation Protocol CLIN102483: Phantom Retrieval Analysis Protocol
Number of patients and Study Sites	Three sites in Poland and 1 site in South Africa have enrolled 40 patients (30 in Poland and 10 in South Africa). This version of the protocol will not enroll additional patients. This protocol revision is done for the extension of the post-operative follow up duration from 24 to 60 months.
Objective	To evaluate the improvement in pain and function following implantation of the Phantom Knee Implant System in patients needing unloading of the medial compartment of the knee
Methodology	This is a prospective, multi-center, single-arm, FIH study
Duration of Study	Patients will be asked to participate in the study and return for follow up visits for a 60 month period following implantation of the study device. *Screening Phase (N/A, screening completed):* At the screening visit, patients who agreed to participate underwent the informed consent process. Patient eligibility was determined following administration of a subset of the Pain domain questions from the KOOS questionnaire (questions P5-P9 which reflect the WOMAC pain subscore). Eligible patients were required to demonstrate a minimum WOMAC pain subscore of 40 on a scale of 0-100. *Baseline Visit (N/A, baseline visits completed):* Eligible study patients were enrolled in the study and assigned a unique study ID. Each enrolled patient completed the following questionnaire: • **Knee injury and Osteoarthritis Outcome Score** (KOOS)[2]is a disease-specific measure of 5 dimensions (pain, other symptoms,

function in daily living, function in sport and recreation and knee related quality of life). ; whereby Western Ontario and McMasters University Osteoarthritis Index[3] (WOMAC) was calculated from the KOOS questionnaire.

The investigator conducted a routine orthopedic physical exam to evaluate the patient's knee and in addition documented the following:

- Knee Society Score
- Assessment of patient's global status
- Demographic information
- Medical assessment
- Baseline imaging was acquired within 3 months prior to the surgery date. The radiographic views to be obtained at specific time points are summarized in **Table 5-1**. The details for the acquisition of X-rays and MRIs are provided in the radiographic protocol (CIP-0006) and in the MRI acquisition protocol (CIP-0007), respectively.

Procedure (N/A, procedure completed):

The Phantom Knee System was implanted under spinal or general anesthesia using direct visualization and specially designed surgical instrumentation for device placement, possibly confirmed with fluoroscopic imaging. A pre discharge X-ray of the implanted knee was obtained.

No concomitant procedures, including arthroscopy, were permitted.

Follow-up Phase:

All patients return for follow up visits within specified visit windows at 6 weeks, 3 and 6 months, and at 12, 24, 36, 48 and 60 months. Safety and performance will be assessed at each of the scheduled visits.

Performance assessments include the following patient questionnaire:

- KOOS

The investigator conducts a routine orthopedic physical exam to evaluate the knee at 6 weeks, 3, 6, 12, 24, 36, 48 and 60 months. In addition, the investigator will document the following:

- Knee Society Score
- Assessment of patient's global status
- Patients Return to Activity (up to 6 months)
- Follow-up Evaluation CRF (from 36 to 60 months)
- Adverse events and treatments, update/resolution of adverse events

Safety assessments include recording physical examination findings, and adverse events.

Radiographic images are obtained per the routine standard of care at 3, 6, and 12 months, and yearly thereafter until 60 months in accordance with the Radiographic Acquisition Protocol and the imaging schedule in **Table 5-1.**

MRIs are acquired at 24 and 60 months follow-up in accordance with the MRI Acquisition Protocol.

Any patient requiring implant removal after the 24 months follow up visit is planned to continue in the study through 24 months post explant. Patients will take part in all protocol required follow up examinations and the completion of questionnaires.

Primary Study Objective

To demonstrate that the Phantom Knee Implant System provides pain relief and improvement in function at 24 months as compared to baseline, using patients as their own controls.

Durability of the effect will be measured at each follow up time point throughout the 60 months period.

Safety will be determined using the incidence of device and/or procedure related adverse events (AEs) and physical examination findings during the 60 months post procedure. Safety outcomes will be collected over the 60 month follow up period and will be assessed at all time points throughout the study.

Secondary Study Objectives

The performance of the device and its clinical effect on the activity level of the patients will be assessed by comparing baseline patient outcomes scores to follow up scores at each visit The s*econdary objectives* of this study are:

- To demonstrate procedural success
- To determine benefits of the device by assessing patient reported symptom severity changes in KOOS score as well as by assessing changes in investigator reported symptom severity in KSS and physician assessment of patient's global status.
- Radiographic appearance of the knee and the implant at each follow up time point compared to baseline.
- Additional radiographic assessments (such as OARSI- or WORMS-based assessments) may be conducted to evaluate changes in OA grade (Kellgren-Lawrence), or individual components of OA (osteophytes, joint space narrowing, subchondral sclerosis, subchondral bone attrition) or to evaluate device integrity.

Inclusion Criteria

Eligible patients met ALL of the following inclusion criteria:

1. Male or female between 25 and 65 years of age, inclusive
2. Documented pathology of the medial compartment of the knee that requires unloading with:
    a. An ICRS score >0 as assessed by MRI or Arthroscopy older than 3 months

    Or

    b. Kellgren-Lawrence grade of ≤3 as assessed by X-ray
3. Tibial-femoral varus alignment of ≤7° as measured using mechanical axis on a long standing AP view X-ray
4. Has continued target knee pain despite 6 months of conservative

treatment prior to surgery

NOTE: 6 months of conservative treatment includes the following:

a. Lifestyle modification

b. Weight loss, if BMI >25

c. Low impact aerobic exercise

d. Quadriceps strengthening

e. Pain relievers

f. IA corticosteroid injections (≥3 months prior to study enrollment)

5. Has pain in the target knee as demonstrated by a minimum score of 40 (scale 0-100) on the KOOS pain domain questions
6. Knee flexion ≥90□ to ≤140□
7. BMI 24-35 kg/m²
8. Weight ≤ 110 kg
9. Willing and able to give and have given voluntary written informed consent to participate in this clinical investigation
10. Prepared to consent to the transfer of his/her information to third parties
11. Willing to undertake the required investigational procedures and willing to return for the required follow-up evaluations

Exclusion Criteria

Patients were excluded from this study if they did not meet the specific inclusion criteria, or if any of the following exclusion criteria was present:

1. Active infection, sepsis, osteomyelitis or history of septic arthritis in any joint.
2. Rheumatoid arthritis or other forms of inflammatory joint disease.
3. Significant OA in the lateral compartment of the study knee, defined as Kellgren-Lawrence grade of $\geq$ 2 as assessed by the investigator using X-ray.
4. Significant OA in the patello-femoral compartment of the study knee, defined as Kellgren-Lawrence grade $\geq$ 3 as assessed by the investigator using X-ray.
5. Contralateral knee has radiographic evidence of OA (KL grade>2) AND clinical findings of OA symptoms that interfere with activities of daily living or require the use of an assist device
6. Previous joint modifying surgery in the target knee within 12 months prior to planned surgery date such as ligament reconstruction or meniscus repair, cartilage transplantation, and microfracture

a) Arthroscopic surgeries for joint lavage, meniscectomy, chondral debridement, and loose body removal are excluded if within 3 months prior to planned surgery date

7. Previous lateral meniscectomy >30% of the target knee
8. Previous patellar surgery in the target knee
9. Previous osteotomy or failed knee joint replacement in the target knee

10. Tibial-femoral valgus alignment >0□ as measured using mechanical axis on a long standing AP view X-ray
11. Tibial-femoral varus alignment >7□ as measured using mechanical axis on a long standing AP view X-ray
12. Hyperextension >5□
13. Flexion deformity greater than 10□
14. Ligamentous laxity, or meniscal instability as assessed by the investigator
15. Cruciate ligament instability with Lachman test, grade 2 or higher
16. Uncontrolled diabetes mellitus
17. Current smoker or stopped <1 year prior to enrollment
18. Known or suspected diagnosis of Osteoporosis
19. Paget's Disease of the bone
20. Other metabolic disorders that may impair bone formation (must specify in records)
21. Concomitant immunosuppressive therapy
22. Known or suspected diagnosis of Osteomalacia
23. Known or suspected diagnosis of Osteonecrosis
24. Infections which may spread to the implant site from distant foci
25. Rapid joint destruction, marked bone loss or bone resorption apparent on X-ray
26. Vascular insufficiency, muscular atrophy, neuromuscular disease
27. Any significant medical condition (e.g., cancer, HIV, chronic pain management for conditions such as neuropathic pain and fibromyalgia, significant psychiatric or neurological disorders, active alcohol/drug abuse, etc.) or other factor (e.g. planned relocation, uncooperative patient) that the Investigator feels would interfere with study participation/completion
28. Pregnancy or lactation or planning to become pregnant
29. History of litigation for workers benefits for musculoskeletal injuries
30. Currently enrolled in another clinical investigation that may influence the follow-up or may confound the outcome of this study
31. Prisoners

Analysis of Primary Outcome Measure

Performance outcomes (improvement in pain and function) will be determined using KOOS, KSS, and physician assessment of patient's global status.

Safety outcomes will be determined by evaluating the type, frequency, severity, and relatedness of adverse events through the 60 month time period for all patients.

All Adverse Events (AEs) will be tabulated and summarized as counts and

percentages. AEs will also be cross-tabulated according to:

- Severity (Mild, Moderate, Severe)
- Seriousness (Serious, Non-serious)
- Device-Relatedness (Unrelated, Possibly Related, Probably Related, Definitely Related)
- Procedure-Relatedness (Unrelated, Possibly Related, Probably Related, Definitely Related)

Descriptive statistics will be reported on the above findings from this observational study.

Definition of Success

A subject will be considered a safety success if the subject does not have any unanticipated serious adverse device effects (USADEs) during the 60 months study duration.

A subject will be declared a clinical success if the following conditions are met at the 24 month follow-up:

1. Clinically significant improvement of at least 20% from baseline on the WOMAC pain questions in the KOOS questionnaire with a change of ≥10 points;
2. Clinically significant improvement of at least 20% from baseline on the WOMAC function questions in the KOOS questionnaire with a change of ≥10 points;

2.0 TABLE OF CONTENTS

1.0 PROTOCOL SYNOPSIS 3
2.0 TABLE OF CONTENTS 9
3.0 ABBREVIATIONS AND TERMS 11
3.1 List of Abbreviations and Terms 11
4.0 INTRODUCTION 12
4.1 Background 12
4.2 Current Therapeutic Approaches 12
4.3 Prior Clinical Experience 12
4.4 Rationale for This Study 13
4.5 Device Description 14
4.6 Intended Use 17
4.7 Implant Procedure 17
5.0 INVESTIGATIONAL PLAN 18
5.1 Study Design 18
5.2 Goals and Objectives of the Investigation 18
5.3 Study Hypotheses 19
5.4 Duration and Extent of Investigation 19
5.4.1 Number and Source of Subjects 19
5.4.2 Inclusion/Exclusion Criteria 19
5.4.3 Enrollment Procedure 21
5.4.4 Process for Obtaining Informed Consent 21
5.5 Patient Assessments 22
5.5.1 Screening Phase 22
5.5.2 Baseline Visit 22
5.5.3 Procedure Visit 23
5.5.4 Post-Procedural Assessments 24
5.5.5 Follow-up Requirements of Patients after Phantom Implant Removal 27
5.6 Data Analysis Plan 28
5.6.1 Performance Analysis 28
5.6.2 Safety Analysis 28
5.7 Sample Size Justification 29
5.8 Study Termination 29
5.9 Termination of Subject Participation 29
6.0 SAFETY REPORTING 31
6.1 Adverse Events 31

6.2 UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECTS 33
6.3 SUBSEQUENT SECONDARY SURGICAL INTERVENTIONS 33
6.4 DEVICE FAILURE/DEFICIENCY 34
6.5 REPORTING OF ADVERSE EVENTS 34
7.0 RISK ANALYSIS 35
7.1 POTENTIAL BENEFITS 35
7.2 POTENTIAL RISKS 35
7.3 PROCEDURAL MINIMIZATION OF RISKS 37
8.0 DATA MONITORING AND QUALITY CONTROL 39
8.1 CONFIDENTIALITY OF DATA 39
8.2 DATA COLLECTION AND REPORTING 39
8.3 REPORTING OF PROTOCOL DEVIATIONS 39
8.4 TIME WINDOWS FOR COMPLETION AND SUBMISSION OF CRFS 39
9.0 STUDY RESPONSIBILITIES 40
9.1 SPONSOR RESPONSIBILITIES 40
9.2 PRINCIPAL INVESTIGATOR RESPONSIBILITIES 41
9.3 SOURCE DOCUMENTATION 43
9.4 PROTOCOL DEVIATIONS 44
9.5 PUBLICATION POLICIES 45
9.6 MEDICAL MONITOR 45
10.0 MONITORING PLAN 46
10.1 SITE QUALIFICATION/INITIATION 46
10.2 PERIODIC MONITORING 46
10.3 SITE CLOSE OUT 47
10.4 MONITORING TRIP REPORTS AND FOLLOW UP LETTERS 48
10.5 QUALIFICATIONS OF STUDY MONITOR 48
11.0 REFERENCES 49

List of Tables

Table 4-1: Modular Component Materials 16
Table 5-1: Imaging Schedule 23
Table 5-2: Test Schedule 26

List of Figures

Figure 4-1: Illustration of Phantom Knee System 15
Figure 4-2: Illustration of Phantom Implant Design 16

3.0 ABBREVIATIONS AND TERMS

3.1 List of Abbreviations and Terms

AE	Adverse Event
BMI	Body Mass Index
CA	Competent Authority
CIP	Clinical Investigation Plan
CRF	Case Report Form
EC	Ethics Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HA	Hyaluronic acid, sodium hyaluronate, hyaluronan
IA	Intra-articular
ICF	Informed Consent Form
HTO	High Tibial Osteotomy
ICRS	International Cartilage Research Society
ISO	International Organization for Standardization
K-L	Kellgren Lawrence
KOOS	Knee Injury and Osteoarthritis Outcome Score
KSS	Knee Society Scoring System
MDD	Medical Device Directive
MRI	Magnetic Resonance Imaging
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
PA	Posterior-Anterior
PCU	Polycarbonate Urethane
PHI	Personal Health Information
PI	Principal Investigator
QA	Quality Assurance
QOL	Quality of Life
SAE	Serious Adverse Event
SD	Standard Deviation
TKA	Total Knee Arthroplasty
USADE	Unanticipated Serious Adverse Device Effect
WOMAC (LK 3.1)	Western Ontario and McMasters University Osteoarthritis Index, Likert Scale Version 3.1
WORMS	Whole-organ MRI Scoring

4.0 INTRODUCTION

4.1 Background



4.2 Current Therapeutic Approaches



4.3 Prior Clinical Experience



studies. Results from these investigations demonstrate the safety and effectiveness of the KineSpring

[redacted]

4.4 Rationale for This Study

[redacted]

[redacted]

4.5 Device Description

[redacted]

[redacted]

Mechanism of Action

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

4.6 Intended Use

[redacted]

4.7 Implant Procedure

[redacted]

5.0 INVESTIGATIONAL PLAN

5.1 Study Design

This prospective multi-center study is designed as a single-arm, observational study.

5.2 Goals and Objectives of the Investigation



5.3 Study Hypotheses

Since this is a First-in-Human trial, it is strictly observational and there is no study hypothesis.

5.4 Duration and Extent of Investigation

[redacted]

5.4.1 Number and Source of Subjects

40 subjects were enrolled from inpatient and outpatient facilities affiliated with the 4 investigative sites.

5.4.2 Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Eligible patients met ALL of the following inclusion criteria: Male or female between 25 and 65 years of age, inclusive
2. Documented pathology of the medial compartment of the knee that requires unloading with:
   - **a.** An ICRS score of >0 as assessed by wither MRI or Arthroscopy older than 3 months

     Or
   - **b.** Kellgren-Lawrence grade of ≤3 as assessed by X-ray
3. Tibio-femoral varus alignment of ≤7□ as measured using mechanical axis on a long standing AP view X-ray
4. Has continued target knee pain despite 6 months of conservative treatment prior to surgery

   NOTE: 6 months of conservative treatment includes any of the following:
   - **a.** Lifestyle modification
   - **b.** Weight loss, if BMI >25 kg/m²
   - **c.** Low impact aerobic exercise
   - **d.** Quadriceps strengthening
   - **e.** Pain relievers
   - **f.** IA corticosteroid injections (≥3 months prior to study enrollment)
5. Has pain in the target knee as demonstrated by a minimum score of 40 (scale 0-100) on the KOOS pain domain questions
6. Knee flexion ≥90^0 to ≤140□

7. BMI 24-35 kg/m²
8. Weight ≤ 110 kg
9. Willing and able to give and have given voluntary written informed consent to participate in this clinical investigation
10. Prepared to consent to the transfer of his/her information to third parties
11. Willing to undertake the required investigational procedures and willing to return for the required follow-up evaluations

Exclusion Criteria:

Patients were excluded from this study if they do not meet the specific inclusion criteria, or if any of the following exclusion criteria was present:

1. Active infection, sepsis, osteomyelitis or history of septic arthritis in any joint.
2. Rheumatoid arthritis or other forms of inflammatory joint disease.
3. Significant OA in the lateral compartment of the study knee, defined as Kellgren-Lawrence grade of ≥ 2 as assessed by the investigator using X-ray.
4. Significant OA in the patellar-femoral compartment of the study knee, defined as Kellgren – Lawrence grade of ≥ 3 as assessed by the investigator using X-ray.
5. Contralateral knee has radiographic evidence of OA (KL grade>2) AND clinical findings of OA symptoms that interfere with activities of daily living or require the use of an assist device.
6. Previous joint modifying surgery in the target knee within 12 months prior to planned surgery date such as ligament reconstruction or meniscus repair, cartilage transplantation, and microfracture
    a. Arthroscopic surgeries for joint lavage, meniscectomy, chondral debridement, and loose body removal are excluded if within 3 months prior to planned surgery date
7. Previous lateral meniscectomy >30%
8. Previous patellar surgery in the target knee
9. Previous osteotomy or failed knee joint replacement in the target knee
10. Tibial-femoral valgus alignment >0□ as measured using mechanical axis on a long standing AP view X-ray
11. Tibial-femoral varus alignment >7□ as measured using mechanical axis on a long standing AP view X-ray
12. Hyperextension >5□
13. Flexion deformity greater than 10□
14. Ligamentous laxity, or meniscal instability as assessed by the investigator
15. Cruciate ligament instability with Lachman test, grade 2 or higher
16. Uncontrolled diabetes mellitus
17. Current smoker or quit smoking <1 year prior to enrollment
18. Known or suspected diagnosis of Osteoporosis
19. Paget's Disease of the bone

20. Other metabolic disorders which may impair bone formation (must specify in records)
21. Concomitant immunosuppressive therapy
22. Known or suspected diagnosis of Osteomalacia
23. Known or suspected diagnosis of Osteonecrosis
24. Infections which may spread to the implant site from distant foci
25. Rapid joint destruction, marked bone loss or bone resorption apparent on X-ray
26. Vascular insufficiency, muscular atrophy, neuromuscular disease
27. Any significant medical condition (e.g., cancer, HIV, chronic pain management for conditions such as neuropathic pain and fibromyalgia, significant psychiatric or neurological disorders, active alcohol/drug abuse, etc.) or other factor (e.g. planned relocation, uncooperative patient) that the Investigator feels would interfere with study participation/completion
28. Pregnancy or lactation or planning to become pregnant
29. History of litigation for workers benefits for musculoskeletal injuries
30. Currently enrolled in another clinical investigation that may influence the follow-up or may confound the outcome of this study
31. Prisoners

5.4.3 Enrollment Procedure

[redacted]

5.4.4 Process for Obtaining Informed Consent

[redacted]

[redacted]

5.5 Patient Assessments

5.5.1 Screening Phase

[redacted]

5.5.2 Baseline Visit

[redacted]

[redacted]

5.5.3 Procedure Visit

[redacted]

[redacted]

5.5.4 Post-Procedural Assessments

[redacted]

[redacted]

Table 5-2: Test Schedule

	Pre-op	Intra	Post-Op	6	3	6	12	24	36	48	60	Un-
[redacted]												

5.5.5 Follow-up Requirements of Patients after Phantom Implant Removal

5.6 Data Analysis Plan

5.6.1 Performance Analysis

Performance data will be summarized using descriptive statistics.

For continuous variables, means, standard deviations, range and ninety five percent confidence intervals will be presented. Significance of changes from baseline will be assessed using the paired t-test.

For proportions, the percentage will be presented and the significance of changes from baseline will be assessed using the exact binomial test.

For categorical variables, the number and percentage in each category will be presented.

A subject meets the **clinical efficacy or clinical performance at 24 months** if the subject achieves:

1. Clinically significant improvement of at least 20% from baseline on the WOMAC pain questions in the KOOS questionnaire with a change of ≥10 points;
2. Clinically significant improvement of at least 20% from baseline on the WOMAC function questions in the KOOS questionnaire with a change of ≥10 points;

5.6.2 Safety Analysis

The safety analyses will be performed on the safety populations defined as all patients who undergo the Phantom Knee System implant procedure.

Safety outcomes will be determined by evaluating the type, frequency, severity, and relatedness of adverse events through the 60-month follow up period for all subjects. All AEs will be tabulated and summarized as counts and percentages. AEs will also be cross-tabulated according to:

- Severity (mild, moderate, severe)
- Seriousness (serious, non-serious)
- Device-relatedness (unrelated, possibly related, probably related, definite)
- Procedures- relatedness (unrelated, possibly related, probably related, definite)

If a patient has more than 1 occurrence of the same AE, he/she will be counted only once within that category in the summary tables. The most severe occurrence of an AE, as well as the most extreme relationship of the AE to the study device or implant procedure will be indicated in cases of multiple occurrences of the same AE.

The number of anticipated and unanticipated AEs that occur in the study population will be tabulated and summarized. In addition, the incidence of all types of AEs will be reviewed during the course of the study for any indications that the use of the device confers any unanticipated significant risk.

A subject will be considered a **safety success** if the subject does not have any unanticipated serious adverse device effects (USADEs) during the 60 months study duration.

5.7 Sample Size Justification

Because this is a First-in-Human study and safety is the primary endpoint, no sample size justification was required for this study design.

5.8 Study Termination

[redacted]

5.9 Termination of Subject Participation

[redacted]



6.0 SAFETY REPORTING

[redacted]

6.1 Adverse Events

An adverse event (AE) is any undesired clinical response or complication experienced by a subject. Monitoring and documenting of AEs will begin at the start of the index procedure.

All peri- and post-procedural AEs will be recorded using the Adverse Event CRF/eCRF. Data to be collected includes the description of the AE, onset and resolution dates (or whether the AE is ongoing), severity, management/treatment, outcome, and determination of the relationship to the device and/or procedure. In general, AEs should be reported and classified by the investigator using a diagnosis. The diagnosis should be confirmed through specific signs, symptoms, and (if necessary) laboratory tests.

The Investigator, on the basis of his or her clinical judgment and the following definitions, will determine the relationship and severity of the AE to the device and/or surgical procedure:

1. Unrelated: The adverse event is clearly not related
2. Possibly related: The adverse event may be related
3. Probably related: The adverse event is likely related
4. Definite: The adverse event is clearly related

An AE or an adverse device effect (ADE) may be mild, moderate, or severe.

[redacted]

For the purposes of safety reporting in this study, the definitions cited by ISO 14155:2011 will be applied:

- An **adverse event** (AE) 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 medical device.

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

Note: For users or other persons, this definition is restricted to events related to the investigational medical device.

Note: Pain in the surgically treated knee is to be expected following the procedure and is not considered an Adverse Event unless the severity or frequency of the pain has increased significantly enough to precipitate an unscheduled visit or is reported by the surgeon during a scheduled study visit.

- An **adverse device effect (ADE)** is an adverse event related to the use of a medical device, including events arising from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

  Note: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

  Note: A **serious adverse device effect** (**SADE**) is any adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

- A **Device Deficiency** is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling

  Note: a device deficiency may or may not result in an AE. If a device deficiency causes an AE or a SAE as defined above, then the consequence of the deficiency will be reported as an AE or SAE, as appropriate. However, all device deficiencies will also be documented on the Device Deficiency CRF or eCRF and tabulated separately, regardless of whether or not an adverse event results from the deficiency. Any surgical intervention for device deficiencies will also be reported as subsequent surgical interventions.

A **Serious Adverse Event (SAE)** is an adverse event that:

- led to death;
- led to a serious deterioration in health of the subject, that either resulted in:
  - a life threatening illness or injury, or
  - a permanent impairment of body structure or function, 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

Note: Planned hospitalization of a pre-existing condition, or a procedure required by the study, without serious deterioration in health, is not considered a serious AE.

Note: a device malfunction may or may not result in an AE. If a device malfunctions in a manner that causes an AE or a SAE as defined above, then the consequence of the malfunction will be reported as an AE or SAE, as appropriate. However, all device malfunctions will also be tabulated separately, regardless of whether or not an adverse event results from the malfunction. Any surgical intervention for device malfunctions will also be reported as subsequent surgical interventions.

Any SAE must be reported to the sponsor or designee by the Investigator within 1 business day of first learning about the event. A written report must be sent to the sponsor within ten working days of knowledge of the event.

- Any serious device/procedure related SAE will be forwarded to the Medical Monitor for review and determination of causality and whether the event was anticipated or unanticipated, in accordance with the risk stated in the Risk Analysis section of this protocol.

The investigator is required to notify the EC in accordance with local reporting requirements.

6.2 Unanticipated Serious Adverse Device Effects

ISO 14155:2011 (Clinical Investigation of Medical Devices – Good Clinical Practice) defines an unanticipated serious adverse device effect (USADE) as any *serious* adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the clinical investigational plan or risk analysis; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects". USADEs must be reported by the principal investigator to the sponsor and the reviewing EC, as described below:

- Investigators are required to report a USADEs to the sponsor and the reviewing Ethics Committee (EC) in accordance with applicable regulatory requirements. Events will be reported to the applicable regulatory agencies in accordance with the appropriate local regulations.
- Moximed will immediately conduct an evaluation of a USADE and report the results of the evaluation to the appropriate regulatory agency, all reviewing ECs and participating investigators within 10 working days after first notice of the effect (§§ 812.46(b), 812.150(b)(1)).

All serious reported events will be followed until resolution, stabilization or 30 days after the last patient enrolled has completed the trial, whichever occurs first.

ALL UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECTS AND SERIOUS ADVERSE EVENTS OCCURRING THROUGHOUT THE STUDY PERIOD MUST BE RECORDED ON THE ADVERSE EVENT CRF OR ECRF. RECORDING DATA ON AN ECRF WILL AUTOMATICALLY NOTIFY THE SPONSOR FOR REPORTING PURPOSES, IF USING PAPER CRFS THE SPONSOR MUST BE NOTIFIED <u>IMMEDIATELY</u> ABOUT THE EVENT.

6.3 Subsequent Secondary Surgical Interventions

[redacted]

[redacted]

6.4 Device Failure/Deficiency

[redacted]

6.5 Reporting of Adverse Events

[redacted]

7.0 RISK ANALYSIS





[redacted]

[redacted]

8.0 DATA MONITORING AND QUALITY CONTROL

8.1 Confidentiality of Data

[redacted]

8.2 Data Collection and Reporting

[redacted]

[redacted]

8.3 Reporting of Protocol Deviations

[redacted]

8.4 Time Windows for Completion and Submission of CRFs

[redacted]

[redacted]

9.0 STUDY RESPONSIBILITIES

9.1 Sponsor Responsibilities

[redacted]

[redacted]

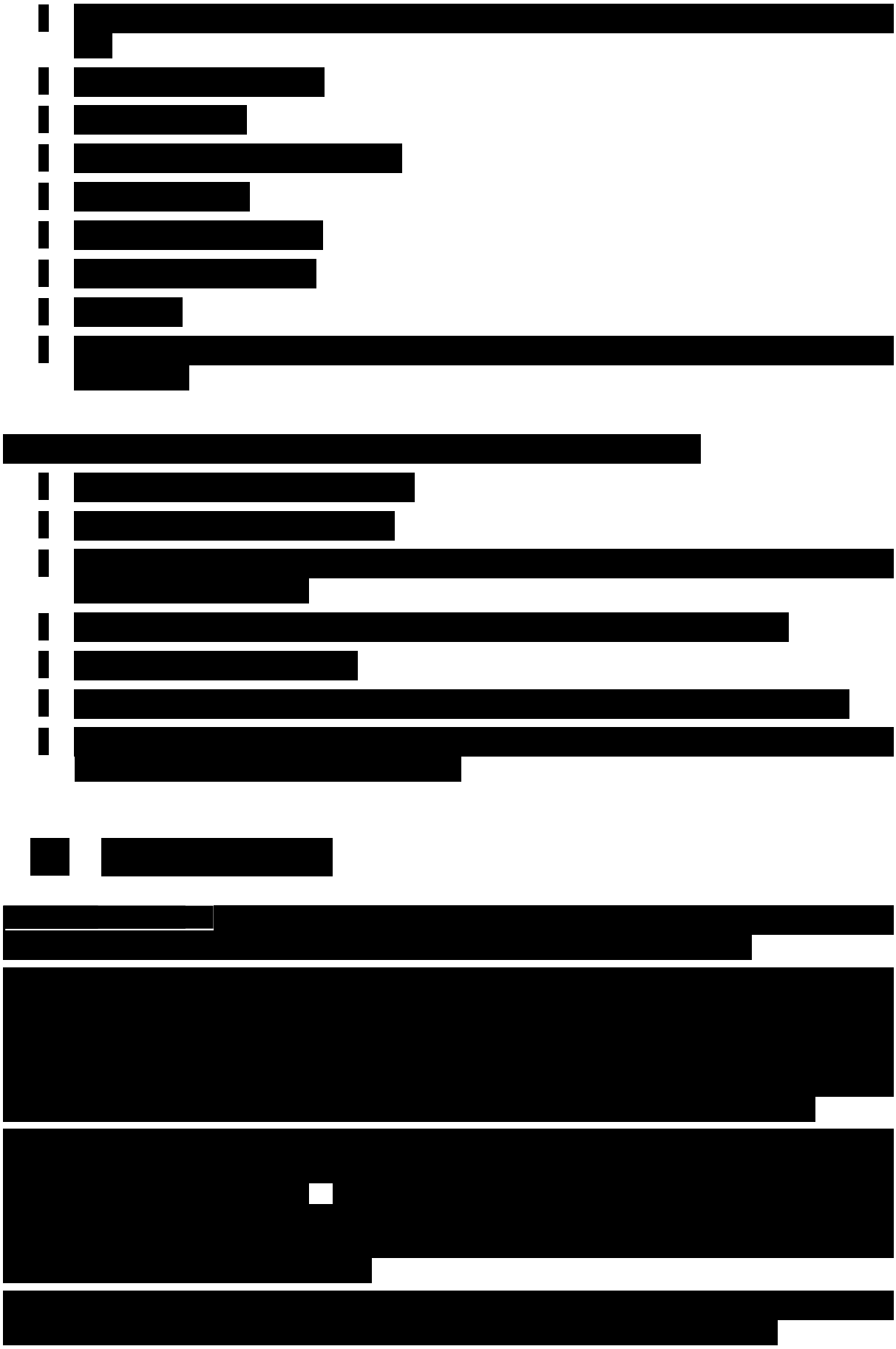
9.2 Principal Investigator Responsibilities

[redacted]

[redacted]

9.3 Source Documentation

[redacted]



9.5 Publication Policies

[redacted]

9.6 Medical Monitor

[redacted]

10.0 MONITORING PLAN

[redacted]

10.1 Site Qualification/Initiation

[redacted]

10.2 Periodic Monitoring

[redacted]

[redacted]

10.3 Site Close Out

[redacted]

10.4 Monitoring Trip Reports and Follow up Letters

[redacted]

10.5 Qualifications of Study Monitor

[redacted]

[redacted]

