Clinical Study Protocol

Study Title: Evaluation of the Calypso Knee System for Symptom Relief in Subjects with Medial Knee Osteoarthritis

Short Title: Calypso Knee System Clinical Study
Protocol No: CP0001 (Formerly CLIN102837)
Revision: **F**

[redacted]

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Investigator Protocol Signature Page

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I agree to conduct the investigation in accordance with the Calypso Knee System Clinical Study Protocol.

_____

Investigator Signature Date

_____

Investigator Name (please print or type)

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PROTOCOL SUMMARY

Protocol Title:	Evaluation of the Calypso Knee System for Symptom Relief in Subjects with Medial Knee Osteoarthritis Short Title: Calypso Knee System Clinical Study
Protocol Number:	CP0001 (formerly CLIN102837)
Study Objective:	A pivotal study to evaluate the safety and effectiveness of the Calypso Knee System when used in subjects with symptomatic osteoarthritis of the medial compartment of the knee.
Study Design:	Prospective, multicenter clinical study comparing the Calypso Knee System to the cohort of subjects treated with High Tibial Osteotomy (HTO) from a recent non-randomized trial (GOAL study).
Intended Use:	The Calypso Knee System is intended to treat symptoms of pain and loss of knee function in subjects with a diagnosis of osteoarthritis in the medial compartment of the knee.
Device Description:	[redacted]

Staged Enrollment:	[redacted]
Sample Size and Number of Sites:	80 subjects will be enrolled in this study at up to 10 investigational sites located in the U.S.
Patient Population:	Male or female subjects age 25 to 65 years, with a diagnosis of medial knee osteoarthritis and study knee pain with an overall WOMAC pain score ≥ 40 (scale 0-100).
Inclusion/ Exclusion Criteria:	**Radiographic criteria (Inclusion #6 and Exclusion #3, 4, 5) will be assessed by an independent core laboratory per the Radiographic Evaluation Protocol (CLIN102792) as part of the screening process.** **Inclusion Criteria** Subjects enrolled in the study must meet all of the following criteria: 1. Subjects age 25 to 65 years at time of screening 2. Body Mass Index (BMI) of < 35 3. Weight < 300 lbs 4. WOMAC pain ≥ 40 5. Knee flexion ≥90^{o} and ≤ 140^{o} 6. Clinical symptoms (such as pain primarily localized to the medial aspect of the study knee and generally exacerbated by weight bearing) and radiographic evidence, using a weight-bearing fixed flexion view, of osteoarthritis in the study knee as defined as KL grade of 1-4* 7. Failed at least 6 months of non-operative treatment defined as at least one of the treatments per *AAOS Treatment of Osteoarthritis of the Knee; Evidence based guideline 2nd Edition 2013* **Exclusion Criteria** Subjects will be excluded from the study if any of the following conditions apply: ***Knee Osteoarthritis*** 1. Radiographic evidence of large, defined as > Grade 2^{+}, marginal osteophytes in the medial compartment of the study knee 2. Bony erosion 3. Clinical symptoms or radiographic evidence of osteoarthritis in the: a. Lateral compartment of the study knee defined as KL grade of > 2* b. Patellofemoral compartment of the study knee defined as KL grade > 3* 4. Clinical symptoms or radiographic evidence of osteoarthritis at the contralateral knee that would preclude activity of daily living, stair climbing, stair descending,

	or requires the use of an assist device* 5. Mechanical axis alignment (Hip-Knee-Ankle) < -16^{o} (varus) or > 0^{o} (valgus) OR anatomic axis alignment < -10^{o} (varus) or > 6^{o} (valgus) as measured on a Long Standing AP X-ray view* 6. Hyperextension >5^{o} 7. Flexion contracture > 10^{o} 8. Insufficiency of the cruciate and collateral ligaments, which would preclude stability of the Calypso Knee System 9. Pathologic ligamentous (Lachman > 1) or meniscal instability 10. Previous knee surgeries: a. Lateral meniscectomy, patellar surgery, osteotomy, prior knee implant, or knee joint replacement of the study knee b. Joint modifying surgery in the study knee within 12 months of index procedure (e.g., ligament reconstruction, meniscus repair, cartilage transplantation, microfracture, etc.) c. Arthroscopic surgeries in the study knee within 3 months of index procedure for joint lavage, meniscectomy, chondral debridement, and loose body removal ***Joint or Bone Complications/Comorbidities*** 11. Active infection, sepsis, osteomyelitis or history of septic arthritis in any joint 12. Rheumatoid arthritis, other forms of inflammatory joint disease or autoimmune disorder 13. Paget's disease or metabolic disorders which may impair bone formation 14. Osteomalacia or osteonecrosis (known or suspected) 15. Known or suspected rapidly destructive OA (RDO) as determined by the investigator[++] 16. Charcot's joint disease 17. Osteoporosis Self-Assessment Tool (OST) score of < 4 for women or < 6 for men AND a T-score less than -1.0 based on a DEXA scan of the proximal femur (preferred) or lumbar spine. All subjects with an OST score < 4 for women or < 6 for men will undergo a DEXA scan to determine the bone mineral density T-score. 18. Steroid treatment (oral or IV), medication use that affects bone metabolism (such as chemotherapy) or radiotherapy within 6 months of index procedure 19. Bone malignancy (active or history) ***Other Complications/Comorbidities*** 20. Allergy or hypersensitivity to cobalt, chromium, iron, or nickel metals (suspected or documented) 21. Life expectancy estimated to be less than 5 years (i.e., malignancies, end stage liver, kidney, cardiac failure) 22. Co-morbidities that could impact study participation or results: a. Neurological disorders affecting gait b. Neuropathic pain or fibromyalgia, restless leg syndrome, complex regional pain syndrome or Reflex Sympathetic Dystrophy (RSD) or pain requiring

	chronic pain management c. Severe neurosensory deficits, muscular atrophy, neuromuscular disease d. Immunologically suppressed or immunocompromised patients such as HIV e. Diabetes mellitus requiring daily insulin therapy f. Radicular symptoms associated with lumbar spine pathology g. Significant psychiatric disorders (e.g., major depression, anxiety disorders, bipolar disorder, and schizophrenia) h. Substance and alcohol dependence and abuse (meeting standard diagnostic criteria described in the Diagnostic and Statistical Manual of Mental Disorders DSM-V) ***General Conditions*** 23. Pregnancy or planning to become pregnant 24. Subjects unable to give voluntary written informed consent to participate 25. Subjects who are currently involved in any investigational drug or device trial or have been enrolled in such trials within 3 months of index procedure 26. Other factors that the investigator feels would interfere with the participation and completion of the study such as: a. Unable to understand the clinical investigation or cooperate with investigational procedures b. Planned relocation or unable to return for required follow-up visits c. Active litigation for musculoskeletal injuries or disorders d. Active workers compensation or Labor & Industries claim for musculoskeletal injury or disorder *Radiographic analysis will be provided by an independent imaging core laboratory to support the investigator in confirming inclusion/exclusion criteria prior to enrollment. [+]Altman RD, Gold GE Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage. 2007;15 Suppl A:A1-56 (pg. 42-49). [++]Hart G, Fehring T, Rapidly destructive osteoarthritis can mimic infection. Arthroplasty Today. 2016; 2(1):15-18.
Primary Endpoint:	24 month composite endpoint demonstrating non-inferiority of the Calypso Knee System to HTO data. A subject is a responder if all of the following components are met at 24 months: • Clinically significant improvement of at least 20% from baseline on the WOMAC pain questions in the KOOS Knee questionnaire with a change of ≥10 points • Clinically significant improvement of at least 20% from baseline on the WOMAC function questions in the KOOS Knee questionnaire with a change of ≥10 points • Freedom from the following device-related serious adverse events: ○ deep infection requiring surgical intervention (Both arms) ○ damage to adjacent neurovascular or ligament structures necessitating reconstruction (Both arms) ○ non-union (HTO only) • Maintenance of implant integrity as evaluated by radiographic assessment NOTE: A subject will be considered a non-responder if they have a conversion to

	arthroplasty or loss of implant integrity of the Calypso Knee System at 24 months.
Secondary Endpoints:	Secondary endpoints demonstrating superiority of the Calypso Knee System to HTO data for each of the following: **Recovery:** 1. Time to full weight bearing **Early WOMAC Pain and Function:** 2. Percent change from baseline to 3 months on the WOMAC pain in the Knee injury and Osteoarthritis Outcome Score (KOOS Knee Survey) 3. Percent change from baseline to 3 months on the WOMAC function in the Knee injury and Osteoarthritis Outcome Score (KOOS Knee Survey) **Durability of WOMAC Pain and Function:** 4. Percent change from baseline to 24 months on the WOMAC pain in the Knee injury and Osteoarthritis Outcome Score (KOOS Knee Survey) 5. Percent change from baseline to 24 months on the WOMAC function in the Knee injury and Osteoarthritis Outcome Score (KOOS Knee Survey)

Additional Observations:	**Safety Observations:**
	• Knee Range of Motion (ROM)
	  ○ Measured passively defined as degrees of flexion and extension
	• Adverse Events by type, over time, severity, seriousness, and relatedness
	• Secondary surgical interventions by type of surgical intervention (revision, removal, re-operation (includes conversion to arthroplasty) supplemental fixation, other intervention)
	• Metal ion levels
	• In the event of a Calypso Knee System removal, the following assessments will be evaluated:
	  ○ Radiographic evaluations
	  ○ MRI assessment as available
	  ○ Calypso Knee System (implant) retrieval analysis
	  ○ Histology
	  ○ Metal Ion levels
	  ○ Arthroplasty conversion data, if applicable
	Effectiveness/Other Observations:
	• Patient reported knee outcome measures and activity (KOOS Knee Survey, KSS, Subject Activity and Satisfaction, SF-12 Health Survey)
	• Investigator reported KSS

Statistical Analyses:	**Primary Statistical Analysis** The primary objective is to establish that the Calypso Knee System is non-inferior to HTO on a responder analysis combining pain, function, specified device-related SAEs, and implant integrity. A subject is considered a responder if he/she meets all success criteria that comprise the definition of the composite end-point at 24 months. **Secondary Statistical Analysis** Secondary Statistical Analysis will only be conducted upon a successful primary analysis of non-inferiority. Analysis of secondary objectives will take a hierarchical

	approach. These analyses will be conducted sequentially, starting from the first objective with progression towards the fifth objective. Each subsequent objective is only analyzed when all of the previous analyses are successful at demonstrating superiority.
	Additional Observations Analysis
	Traditional confidence intervals and p-values will be reported for these analyses, as applicable.
	• Knee Range of Motion (ROM) – evaluation using Calypso Knee System at baseline compared to 24 months
	• Adverse Events by type over time, severity, seriousness, and relatedness. AEs will be tabulated and summarized as counts and percentages. AEs will also be cross-tabulated according to:
	  ○ Severity;
	  ○ Unanticipated Adverse Device Effect (UADE)
	  ○ Seriousness (Serious Adverse Event (SAE), Non-serious AE);
	  ○ Device-Relatedness (Unrelated, Possibly Related, Probably Related, Definitely Related);
	  ○ Procedure-Relatedness (Unrelated, Possibly Related, Probably Related, Definitely Related).
	• Secondary surgical interventions by type of surgical intervention (revision, removal, re-operation (includes conversion to arthroplasty) supplemental fixation, other intervention)
	• Changes in patient reported knee outcome measures and activity (KOOS Knee Survey, KSS, Subject Activity and Satisfaction, SF-12 Health Survey) as compared to baseline
	• Changes in Investigator reported KSS

Study Duration:	All subjects included in this study will return for follow-up visits at 6 weeks and 3, 6, 12, 18, and 24 months, then annually through 5 years.
References:	CLIN102840: Calypso Knee System Metal Ion Protocol LBL102812: Calypso Knee System, Instructions for Use - Product Insert LBL102811: Calypso Knee System Instruments, Instructions for Use - Product Insert CLIN102845: Calypso Knee System Surgical Technique Guide CLIN102792: Calypso Clinical Study Radiographic Evaluation Protocol CLIN102799: Calypso Clinical Study Informed Consent CLIN102852: Calypso Clinical Study Implant Retrieval Protocol CLIN102838: Calypso Knee System Rehabilitation Guideline CLIN102842: Calypso Clinical Study Investigator's Agreement CLIN103113: Statistical Considerations and Preliminary Propensity Score (PS) Design Memorandum CLIN102839: Calypso Clinical Study Surgeon Training CLIN102853: Calypso Clinical Study Monitoring Plan CLIN102859: Calypso Clinical Study CEC Charter

PRINCIPAL CONTACTS

	Name, Address and Contact
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Study Sponsor Contact	Rose S. Weinstein Director, Clinical Affairs Moximed Inc. Tel. (510) 887-3375 Fax. (510) 880-7179 E-mail: rsweinstein@moximed.com
Study Statistician	[redacted]
Medical Monitor	[redacted]
Data Management	[redacted]
Clinical Events Committee (CEC)	[redacted]
Imaging Core Lab	[redacted]
Metal Ion Core Lab	[redacted]
Implant Retrieval Analysis Core Lab	[redacted]
Histology	[redacted]

ABBREVIATIONS

Table 1 Abbreviations

AE	Adverse Event
AT	As Treated Patient Population
BMI	Body Mass Index
CA	Competent Authority
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CFR-PEEK	Carbon-fiber reinforced polyetheretherketone
CoCr	Cobalt Chrome
CRF	Case Report Form
CWO	Closed Wedged Osteotomy
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HA	Hyaluronic acid, sodium hyaluronate, hyaluronan
IA	Intra-articular
ICF	Informed Consent Form
IDE	Investigational Device Exemption
HTO	High Tibial Osteotomy
ITT	Intent to Treat
ISO	International Organization for Standardization
IRB	Institutional Review Board
KOOS Knee Survey	Knee injury and Osteoarthritis Outcome Score Knee Survey
KL (or K&L)	Kellgren and Lawrence
KSS	Knee Society Score
LOCF	Last Observation Carried Forward
MDD	Medical Device Directive
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
OMERACT-OARSI	Outcome Measures in Rheumatology-Osteoarthritis Research Society International
OUS	Outside of the United States
OWO	Open Wedge Osteotomy
PHI	Personal Health Information
PD	Protocol Deviation
PI	Principal Investigator
PP	Per Protocol Patient Population
PA	Posterior-Anterior
PCU	Polycarbonate-urethane
QA	Quality Assurance
QOL	Quality of Life

RDO	Rapidly Destructive OA
SAE	Serious Adverse Event
SD	Standard Deviation
SF-12 Health Survey	Short Form Health Survey-12
TKA	Total Knee Arthroplasty
TKR	Total Knee Replacement
UADE	Unanticipated Adverse Device Effect
UKA	Unicompartmental Knee Arthroplasty
USA	United States of America
WOMAC	Western Ontario and McMaster Universities Arthritis Index

1.0 STUDY PURPOSE

1.1 Introduction and Background

[redacted]

Load Bearing and Joint Mechanics

[redacted]

1.1.1 Current Conservative Care

[redacted]

[redacted]

[redacted]

1.1.2 Education

[redacted]

1.1.3 Weight loss

[redacted]

1.1.4 Exercise

[redacted]

1.1.5 Physical Therapy

[redacted]

1.1.6 Knee Braces and Orthotics

[redacted]

1.1.7 Pharmacologic Approaches

[redacted]

1.1.8 Current Surgical Treatment Options

[redacted]

[redacted]

High Tibial Osteotomy

[redacted]

Joint Unloading with External Joint Distraction

[redacted]

Knee Arthroplasty

[redacted]

[redacted]

1.1.9 Conclusions

[redacted]

1.2 Rationale for This Study

[redacted]

[redacted]

1.3 Device Name

For purposes of this study, "investigational device" or "study device" refers to the Calypso Knee System.

1.4 Description of the Device

[redacted]

Figure 2. Calypso Knee System with cross-section of Absorber on the right

[redacted]

[redacted]

1.4.1 Mechanism of Action

[redacted]

The components of the Calypso Knee System are described in Table 2 below.

Table 2 Calypso Knee System Implant Components

[redacted]

1.5 Intended Use Statement

The Calypso Knee System is intended to treat symptoms of pain and loss of knee function in subjects with a diagnosis of osteoarthritis in the medial compartment of the knee.

1.6 Prior Clinical Investigation

[redacted]

[redacted]

[redacted]

2.0 PROTOCOL

2.1 Study Objective

The Calypso Clinical study is a pivotal study to evaluate the safety and effectiveness of the Calypso Knee System when used in subjects with symptomatic osteoarthritis of the medial compartment of the knee.

2.1.1 Study Design Overview

The Calypso Clinical Study is a prospective, multicenter clinical study comparing the Calypso Knee System to the cohort of subjects treated with High Tibial Osteotomy (HTO) from a recent non-randomized trial (GOAL study). A total of 80 subjects will be enrolled in this study at up to 10 investigational sites located in the U.S. using a staged enrollment.

[redacted]

The subject population for this study is male or female subjects age 25 to 65 years, with a diagnosis of medial knee osteoarthritis and study knee pain with an overall WOMAC pain score ≥ 40 (scale 0-100).

All subjects included in this study will return for follow-up visits at 6 weeks and 3, 6, 12, 18, and 24 months, then annually through 5 years.

At each follow-up visit, safety and effectiveness data will be collected. Subjects will be interviewed to determine if adverse events (AEs) were experienced since the previous follow-up visit. A complete orthopaedic knee assessment will be performed at baseline for all subjects and again during each follow-up visit. All subjects will be required to complete the KOOS Knee Survey and KSS to evaluate function, pain, and quality of life at each follow-up visit.

Radiographic evaluations will be performed at pre-op, prior to discharge, 6 weeks, 3 months, 6 months, 12 months, 18 months, 24 months and annually thereafter through 5 years for all subjects. Radiographic evaluations will also be performed within 60 days prior to any planned Calypso Knee System removal.

MRI evaluations will be performed at the pre-procedure and at 2 and 5 year follow-up visits.

2.2 Study Scope and Participating Institutions

[redacted]

2.3 Patient Population

[redacted]

[redacted]

[redacted]

[redacted]

2.3.1 Inclusion/Exclusion Criteria

Radiographic criteria (Inclusion #6 and Exclusion #3, 4, 5) will be assessed by an independent core laboratory per the Radiographic Evaluation Protocol (CLIN102792) as part of the screening process.

Inclusion Criteria

Subjects enrolled in the study must meet all of the following criteria:

1. Subjects age 25 to 65 years at time of screening
2. Body Mass Index (BMI) of < 35
3. Weight < 300 lbs

4. WOMAC pain ≥ 40
5. Knee flexion ≥90^{o} and ≤ 140^{o}
6. Clinical symptoms (such as pain primarily localized to the medial aspect of the study knee and generally exacerbated by weight bearing) and radiographic evidence, using a weight-bearing fixed flexion view, of osteoarthritis in the study knee as defined as KL grade of 1-4*
7. Failed at least 6 months of non-operative treatment defined as at least one of the treatments per *AAOS Treatment of Osteoarthritis of the Knee; Evidence based guideline 2nd Edition 2013*

Exclusion Criteria

Subjects will be excluded from the study if any of the following conditions apply:

Knee Osteoarthritis

1. Radiographic evidence of large, defined as > Grade 2^{+}, marginal osteophytes in the medial compartment of the study knee
2. Bony erosion
3. Clinical symptoms or radiographic evidence of osteoarthritis in the:
    a. Lateral compartment of the study knee defined as KL grade of >2*
    b. Patellofemoral compartment of the study knee defined as KL grade > 3*
4. Clinical symptoms or radiographic evidence of osteoarthritis at the contralateral knee that would preclude activity of daily living, stair climbing, stair descending, or requires the use of an assist device*
5. Mechanical axis alignment (Hip-Knee-Ankle) < -16^{o} (varus) or > 0^{o} (valgus) OR anatomic axis alignment < -10^{o} (varus) or > 6^{o} (valgus) as measured on a Long Standing AP X-ray view*
6. Hyperextension > 5^{o}
7. Flexion contracture > 10^{o}
8. Insufficiency of the cruciate and collateral ligaments, which would preclude stability of the Calypso Knee System
9. Pathologic ligamentous (Lachman > 1) or meniscal instability
10. Previous knee surgeries:
    a. Lateral meniscectomy, patellar surgery, osteotomy, prior knee implant, or knee joint replacement of the study knee
    b. Joint modifying surgery in the study knee within 12 months of index procedure (e.g., ligament reconstruction, meniscus repair, cartilage transplantation, microfracture, etc.)
    c. Arthroscopic surgeries in the study knee within 3 months of index procedure for joint lavage, meniscectomy, chondral debridement, and loose body removal

Joint or Bone Complications/Comorbidities

11. Active infection, sepsis, osteomyelitis or history of septic arthritis in any joint
12. Rheumatoid arthritis, other forms of inflammatory joint disease or autoimmune disorder
13. Paget's disease or metabolic disorders which may impair bone formation
14. Osteomalacia or osteonecrosis (known or suspected)
15. Known or suspected rapidly destructive OA (RDO) as determined by the investigator^{+}
16. Charcot's joint disease
17. Osteoporosis Self-Assessment Tool (OST) score of < 4 for women or < 6 for men AND a T-score less than -1.0 based on a DEXA scan of the proximal femur (preferred) or lumbar spine. All subjects with

an OST score < 4 for women or < 6 for men will undergo a DEXA scan to determine the bone mineral density T-score.

18. Steroid treatment (oral or IV), medication use that affects bone metabolism (such as chemotherapy) or radiotherapy within 6 months of index procedure
19. Bone malignancy (active or history)

Other Complications/Comorbidities

20. Allergy or hypersensitivity to cobalt, chromium, iron, or nickel metals (suspected or documented)
21. Life expectancy estimated to be less than 5 years (i.e., malignancies, end stage liver, kidney, cardiac failure)
22. Co-morbidities that could impact study participation or results:
    a. Neurological disorders affecting gait
    b. Neuropathic pain or fibromyalgia, restless leg syndrome, complex regional pain syndrome or Reflex Sympathetic Dystrophy (RSD) or pain requiring chronic pain management
    c. Severe neurosensory deficits, muscular atrophy, neuromuscular disease
    d. Immunologically suppressed or immunocompromised patients such as HIV
    e. Diabetes mellitus requiring daily insulin therapy
    f. Radicular symptoms associated with lumbar spine pathology
    g. Significant psychiatric disorders (e.g., major depression, anxiety disorders, bipolar disorder, and schizophrenia)
    h. Substance and alcohol dependence and abuse (meeting standard diagnostic criteria described in the Diagnostic and Statistical Manual of Mental Disorders DSM-V)

General Conditions

23. Pregnancy or planning to become pregnant
24. Subjects unable to give voluntary written informed consent to participate
25. Subjects who are currently involved in any investigational drug or device trial or have been enrolled in such trials within 3 months of index procedure
26. Other factors that the investigator feels would interfere with the participation and completion of the study such as:
    a. Unable to understand the clinical investigation or cooperate with investigational procedures
    b. Planned relocation or unable to return for required follow-up visits
    c. Active litigation for musculoskeletal injuries or disorders
    d. Active workers compensation or Labor & Industries claim for musculoskeletal injury or disorder

*Radiographic analysis will be provided by an independent imaging core laboratory to support the investigator in confirming inclusion/exclusion criteria prior to enrollment.

[+]Altman RD, Gold GE Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage. 2007;15 Suppl A:A1-56 (pg. 42-49).

[++]Hart G, Fehring T, Rapidly destructive osteoarthritis can mimic infection. Arthroplasty Today. 2016; 2(1):15-18.

2.4 Study Endpoints

2.4.1 Primary Endpoint

The primary endpoint is a 24 month composite endpoint demonstrating non-inferiority of the Calypso Knee System to HTO data. A subject is a responder if all of the following components are met at 24 months:

- Clinically significant improvement of at least 20% from baseline on the WOMAC pain questions in the KOOS Knee questionnaire with a change of ≥10 points
- Clinically significant improvement of at least 20% from baseline on the WOMAC function questions in the KOOS Knee questionnaire with a change of ≥10 points
- Freedom from the following device-related serious adverse events:
    - deep infection requiring surgical intervention (Both arms)
    - damage to adjacent neurovascular or ligament structures necessitating reconstruction (Both arms)
    - non-union (HTO only)
- Maintenance of implant integrity as evaluated by radiographic assessment

NOTE: A subject will be considered a non-responder if they have a conversion to arthroplasty or loss of implant integrity of the Calypso Knee System at 24 months

Details of the radiographic assessment for implant integrity may be found in the Radiographic Evaluation Protocol (CLIN102792).

2.4.2 Secondary Endpoints

Secondary endpoints demonstrating superiority of the Calypso Knee System to HTO data for each of the following:

Recovery:

1. Time to full weight bearing

Early WOMAC Pain and Function:

2. Percent change from baseline to 3 months on the WOMAC pain in the Knee injury and Osteoarthritis Outcome Score (KOOS Knee Survey)
3. Percent change from baseline to 3 months on the WOMAC function in the Knee injury and Osteoarthritis Outcome Score (KOOS Knee Survey)

Durability of WOMAC Pain and Function:

4. Percent change from baseline to 24 months on the WOMAC pain in the Knee injury and Osteoarthritis Outcome Score (KOOS Knee Survey)
5. Percent change from baseline to 24 months on the WOMAC function in the Knee injury and Osteoarthritis Outcome Score (KOOS Knee Survey)

2.4.3 Additional Observations

Safety Observations:

- Knee Range of Motion (ROM)
    - Measured passively defined as degrees of flexion and extension
- Adverse Events by type, over time, severity, seriousness, and relatedness

- Secondary surgical interventions by type of surgical intervention (revision, removal, re-operation (includes conversion to arthroplasty) supplemental fixation, other intervention)
- Metal ion levels
- In the event of a Calypso Knee System removal, the following assessments will be evaluated:
    - Radiographic evaluations
    - MRI assessment as available
    - Calypso Knee System (implant) retrieval analysis
    - Histology
    - Metal Ion levels
    - Arthroplasty conversion data, if applicable

Effectiveness/Other Observations:

- Patient reported knee outcome measures and activity (KOOS Knee Survey, KSS, Subject Activity and Satisfaction, SF-12 Health Survey)
- Investigator reported KSS

2.5 Measures to Increase Validity and Minimize Bias

[redacted]

2.6 Study Duration

All subjects included in this study will return for follow up visits at 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months post index procedure. Evaluation of the primary endpoint will be completed on all subjects at 24 months post procedure. Follow-up visits will continue annually for a total of 5 years.

3.0 STUDY PROCEDURES

3.1 Informed Consent

[redacted]

3.2 Enrollment Procedure

[redacted]

3.3 Patient Assessments

3.3.1 Patient Screening (Pre-Op Visit)

- [redacted]

Table 3 Imaging Assessment Schedule

[redacted]

3.3.2 Surgical Procedure

[redacted]

[redacted]

[redacted]

Treatment Procedures

[redacted]

- [redacted]

3.3.3 Concomitant Procedures

[redacted]

- [redacted]

[redacted]

3.3.4 Post Procedure Care (Discharge)

[redacted]

[redacted]

[redacted]

- [redacted]

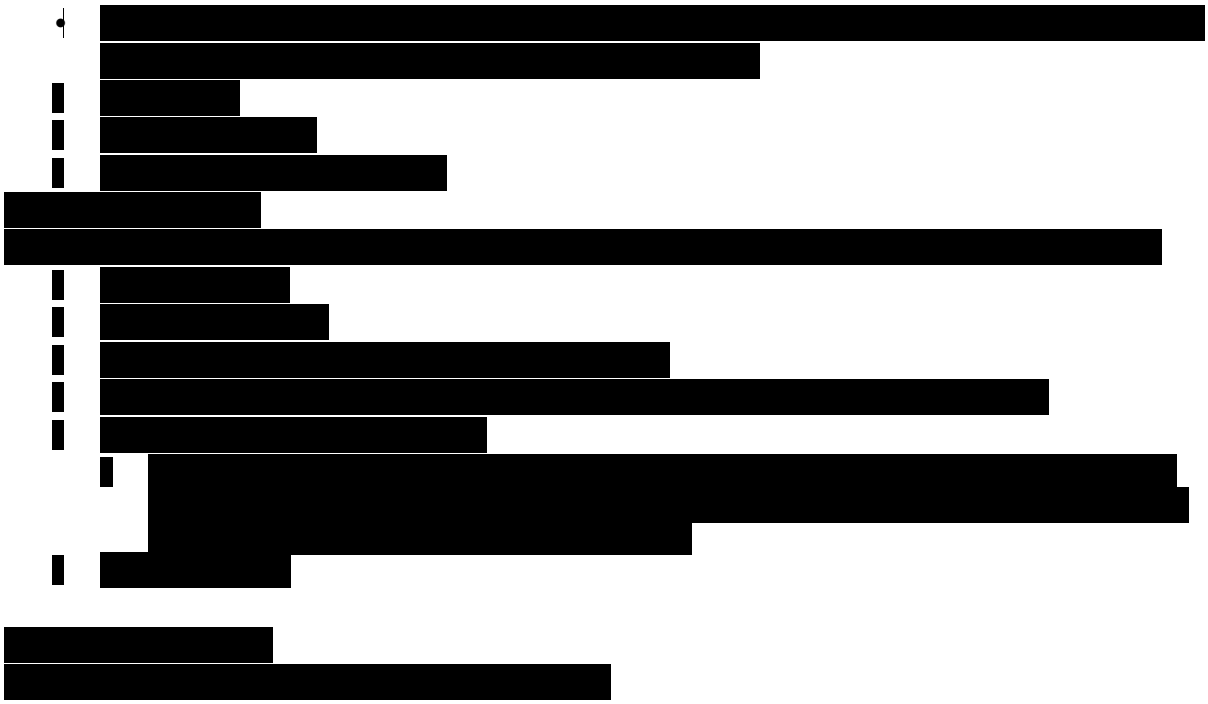
3.3.5 Post procedure and post-operative rehabilitation recommendations

[redacted]

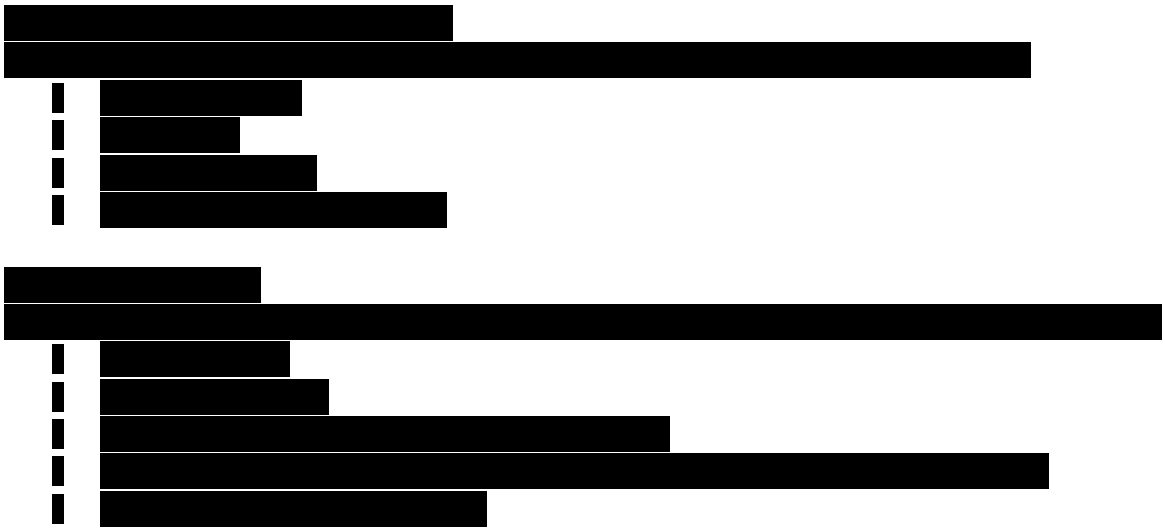
3.3.6 Post Procedure Follow Up Assessments

All subjects included in this study will return for follow up visits at 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months post index procedure and annually for 5 years post procedure.

3.3.6.1 6 week follow-up (±14 days)



3.3.6.2 3 and 6 month Follow-Up (±31 days)



[redacted]

3.3.6.3 1 year, 18 months, 2, 3, 4, and 5 Year Follow-up (± 60 days)

[redacted]

Table 4 Calypso Knee System Clinical Study Schedule of Events

[redacted]

3.4 Calypso Knee System Implant Removal

[redacted]

3.5 Termination of Subject Participation

[redacted]

[redacted]

[redacted]

- Subject Lost to Follow-Up: Unable to locate subject despite at least three documented attempts to notify the subject via telephone or e-mail, and by certified mail. A subject will not be considered lost to follow-up until the last scheduled follow-up visit (60 month (5 years) study time point).
- Subject Withdraw Consent: The subject requests to terminate his/her involvement in the study, therefore withdrawing his/her consent to participate in the study (the investigator must thoroughly document the reasons for termination). Attempts will be made to retrieve any follow-up data, prior to the time point at which voluntary consent was withdrawn, when available, in particular regarding possible AEs at the time of study discontinuation.
- Subject Withdrawn by Investigator: Subjects who are withdrawn by the Investigator for any reason prior to study completion.
- Subject Death: If possible, an autopsy and/or death certificate should be obtained in order to document the cause of death.

All serious device-related adverse events will be followed until resolution, stabilization or 30 days after the last subject enrolled has completed the study, whichever occurs first.

4.0 SAFETY REPORTING

[redacted]

4.1 Adverse Events

[redacted]

[redacted]

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

1. **Unrelated:** The adverse event is determined to be solely caused by the underlying disease, disorder or condition of the subject, or attributable solely to other extraneous causes (unrelated to the device, device malfunction, or the procedure).
2. **Possibly related:** The adverse event has onset within a clinically relevant temporal relationship to exposure to the device or procedure, and is plausibly at least partially caused by or aggravated by the use of the device, device malfunction, or the procedure. It must also meet one of the following criteria: (1) follows a known or easily foreseen pattern of response to device use or procedure and (2) is not fully attributable to the underlying disease, disorder or condition of the subject, or attributable to other extraneous causes.
3. **Probably related:** The adverse event has onset within a clinically relevant temporal relationship to exposure to the device or procedure, and is more likely than not to be at least partially caused by or aggravated by the use of the device, device malfunction, or the procedure. It must also meet both of the following criteria: (1) follows a known or easily foreseen pattern of response to device use or procedure; and (2) is not fully attributable to the underlying disease, disorder or condition of the subject, or attributable to other extraneous causes. In addition, if the adverse effect is reversible upon reoperation or device exchange, and such a procedure is done, the effect disappears or lessens in severity within the expected time interval.
4. **Definitely related:** The adverse event is clearly caused by the use of the device, device malfunction, or the procedure. It must meet all following criteria: (1) has a clear temporal relationship between device exposure and onset of the event; (2) follows a known pattern of response to device use or procedure; and (3) is not reasonably attributable to the underlying disease, disorder or condition of the subject, or attributable to other extraneous causes. In addition, if the adverse effect is reversible upon reoperation or device exchange, and such a procedure is done, the effect disappears or lessens in severity within the expected time interval.

[redacted]

[redacted]

[redacted]

4.2 Anticipated Adverse Events

The following AEs and symptoms may be associated with the Calypso Knee System and/ or surgical procedure:

[redacted]

[redacted]

[redacted]

[redacted]

4.3 Subsequent Surgical Interventions of the Knee

[redacted]

- **Revision:** A revision is a procedure that adjusts or in any way modifies or removes *part* of the original implant configuration with or without replacement of a component. A revision may also include adjusting the position of the original configuration. This may include removing a component of the device and only replacing that single component.
- **Removal:** A removal is a procedure where all of the original system configuration is removed with or without replacement due to, for example, mechanical failure of the device, pain or infection.
- **Re-operation:** A reoperation is any surgical procedure that does not include removal modification, or addition of any components to the system (e.g., drainage of a hematoma at the surgical site).
- **Supplemental fixation:** A supplemental fixation is a procedure in which additional instrumentation not under study in the protocol is implanted.
- **Other interventions:** This category includes other surgeries of the study knee that the subject incurs while enrolled in the study that seemingly are unrelated to the implanted device.

4.4 Device Malfunction

All device malfunctions of the Calypso Knee System must be reported within 24 hours of the knowledge of the event in the EDC system.

5.0 STATISTICAL ANALYSIS PLAN

Refer to the Statistical Considerations and Preliminary Propensity Score (PS) Design Memorandum (CLIN103113) for the Calypso Clinical Study for primary and secondary endpoint study analysis, analysis population, sample size and power, evaluation of missing data, and baseline covariates against endpoint success rates.

5.1 Additional Outcomes

Safety Observations:

- Knee Range of Motion (ROM)
    - Measured passively defined as degrees of flexion and extension
- Adverse Events by type, over time, severity, seriousness, and relatedness
- Subsequent surgical interventions of the knee by type of surgical intervention (revision, removal, re-operation (includes conversion to arthroplasty) supplemental fixation, other intervention)
- Metal ion levels
- In the event of a Calypso Knee System removal, the following assessments will be evaluated:
    - Radiographic evaluations
    - MRI assessment as available
    - Calypso Knee System (implant) retrieval analysis
    - Histology
    - Metal Ion levels
    - Arthroplasty conversion data, if applicable

Effectiveness/Other Observations:

- Patient reported knee outcome measures and activity (KOOS Knee Survey, Activity Questionnaire, SF-12 Health Survey, Patient Satisfaction)
- Investigator reported KSS

5.2 Baseline Variables

Demographic and baseline variables will be summarized. Sample sizes, means, standard deviations and ranges will be presented for all continuous variables.

5.3 Follow-Up and Reporting

All subjects enrolled and devices used in the clinical study will be accounted for in the final report. All reasons for exclusion from analysis will be carefully documented. Similarly, for all subjects and devices included in an analysis population, the measurements of all important variables must be accounted for at all relevant time points. Additional information that is available on subjects screened for entry but not enrolled will also be summarized.

Subjects with early termination will be identified and a descriptive analysis of them provided, including the reasons for their loss to follow-up and known treatment outcome.

Subjects requiring removal of the Calypso Knee System will continue to participate in follow-up through the duration of the study. These subjects will take part in all protocol required follow up examinations, test, and the completion of questionnaires.

6.0 STUDY MANAGEMENT

6.1 Sponsor Ethical and Regulatory Considerations

[redacted]

General Duties

[redacted]

[redacted]

Selection of Clinical Sites

[redacted]

[redacted]

Site Training

[redacted]

[redacted]

Investigator Training

[redacted]

Subject Confidentiality

[redacted]

Data Management

[redacted]

Record Retention

[redacted]

[redacted]

6.2 Investigator Responsibilities

[redacted]

[redacted]

6.2.1 IRB Approval and Informed Consent

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.2.2 Data Collection and Reporting

[redacted]

6.2.3 Data Completion and Submission

[redacted]

6.2.4 Device Accountability

[redacted]

6.2.5 Source Documents

[redacted]

- [redacted]
- [redacted]

[redacted]

6.2.6 Regulatory Filing

[redacted]

6.2.7 Audits/Inspections

[redacted]

6.3 Clinical Events Committee (CEC)

An independent Clinical Events Committee (CEC) will be established to adjudicate all serious adverse events

[redacted]

6.4 Medical Monitoring

[redacted]

6.5 Protocol Deviations

[redacted]

[redacted]

7.0 RISK ANALYSIS

7.1 Potential Risks

[redacted]

Surgical Risks

[redacted]

1. **Risks associated with general surgery include:**

[redacted]

- [redacted]

2. **Risks associated with knee surgery include:**

- [redacted]

- [redacted]

[redacted]

3. **Risks associated with Calypso Knee System:**

- [redacted]

[redacted]

Risks Associated with Radiographs

[redacted]

[redacted]

Risks Associated with MRI

[redacted]

Reproductive Risks

[redacted]

Metal Ion Blood Draw Risks

[redacted]

Allergy Risks

[redacted]

7.2 Minimizing Study Risks

[redacted]

- [redacted]

7.3 Benefit-Risk Summary

[redacted]

[redacted]

7.4 Anticipated Changes during the Investigation

There are no known anticipated changes of the Calypso Knee System during the investigation.

8.0 MONITORING PLAN

[redacted]

[redacted]

Site Qualification/Initiation Visits

[redacted]

[redacted]

Interim Monitoring Visits

[redacted]

[redacted]

[redacted]

Site Close Out Visit

[redacted]

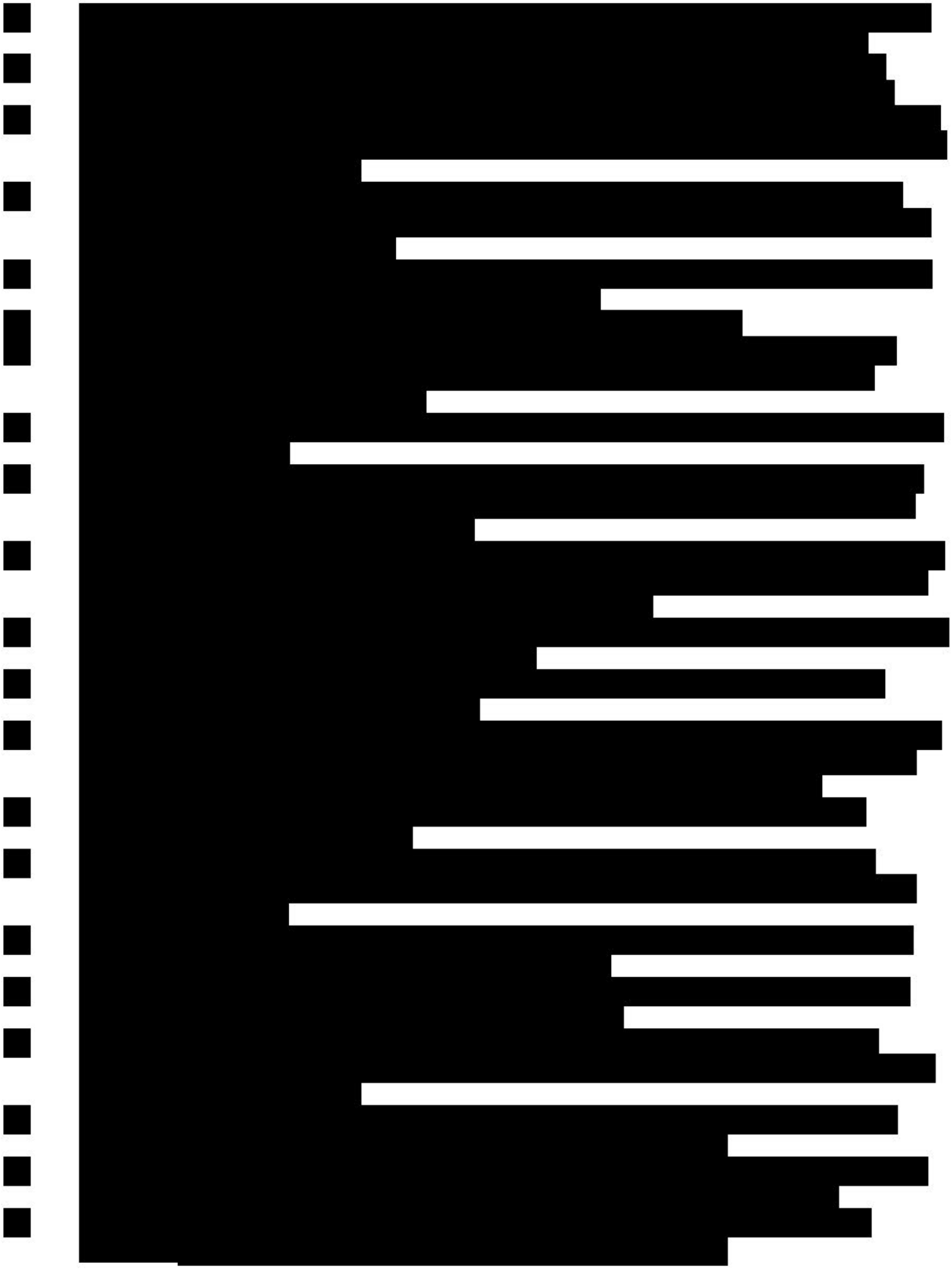
Qualifications of Study Monitor

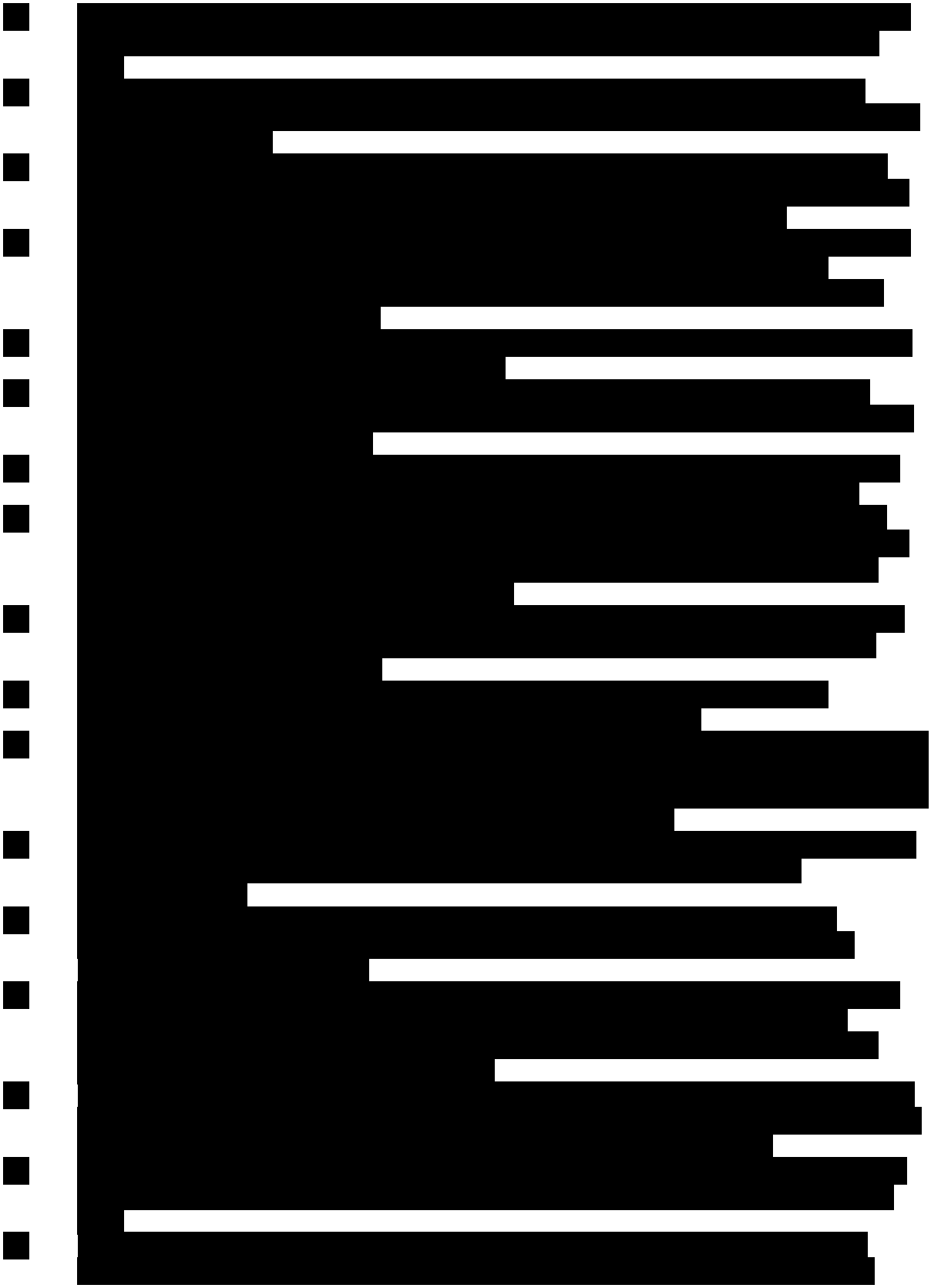
[redacted]

9.0 REFERENCES

1. [redacted]

17. [redacted]





APPENDIX A: DEFINITIONS

ANALGESIC

A pain-relieving effect with no loss of consciousness

BLEEDING COMPLICATION

A procedure related hemorrhagic event that requires a transfusion or surgical repair.

BURSITIS

Bursitis is an inflammation of the native bursae that can result in irritation and pain.

CELLULITIS

A superficial, spreading infection of the skin and subcutaneous tissue, usually following lacerations and surgical wounds. The most common causative organism is penicillin sensitive streptococci. Cellulitis is characterized by signs of inflammation (local pain, tenderness, swelling and erythema). The border between involved and uninvolved skin is usually indistinct and systemic illness characterized by fever, chills, malaise and toxicity is frequently present.
http://www.who.int/surgery/publications/en/SCDH.pdf

DEEP VEIN THROMBOSIS

Deep vein thrombosis (DVT) is a blood clot that forms in a vein deep in the body.
Http://www.nhlbi.nih.gov/health/dci/diseases/dvt/dvt_whatis.html

DEVICE MALFUNCTION

The failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. (21 CFR Part 803)

DIABETES MELLITUS

A condition caused by insufficient production of insulin resulting in abnormal metabolism of carbohydrates, fats and protein. Diabetes mellitus is defined as symptoms of hyperglycemia (thirst, polyuria, weight loss, visual blurring) and a casual plasma glucose concentration of ≥200 mg/dl; or a fasting plasma blood glucose concentration of ≥126 mg/dl; or a 2-hour post load glucose ≥200 mg/dl during an oral glucose tolerance test as described by the World Health Organization (WHO).

ENROLLED
Subjects who sign informed consent and undergo an anesthesia start time for purposes of receiving the Calypso Knee System.

HEMATOMA
A localized mass of extravasated blood that is relatively or completely confined within an organ or tissue, a space, or a potential space that measures four centimeters or greater in diameter at the vascular access site, or those requiring transfusion or necessitating prolonged hospitalization.

HEMORRHAGE
An escape of blood through ruptured, or unruptured vessel walls.

KNEE SCARRING, ARTHROFIBROSIS, OR PERIPROSTHETIC LOCAL ADHESIONS
A process of fibrosis or proliferation of fibrotic tissue as part of the healing process. May occur about the knee joint, intra-articular or extra-articular or present as periprosthetic local adhesions. Arthrofibrosis is a term typically used when the knee scarring is excessive and limiting ROM.

LIFE THREATENING
The subject is or subject was, in the view of the investigator, at immediate risk of death from the adverse event as it occurred. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

LOCAL INFLAMMATION
A local protective tissue response to injury or destruction of tissues, which serves to destroy, dilute, or wall off both the injurious agent and the injured tissues. The classical signs of acute inflammation are pain, heat, redness, swelling, and loss of function. http://medical-dictionary.thefreedictionary.com/systemic+inflammation+response+syndrome+(SIRS)

MISSED ENROLLMENT
Subjects who do meet inclusion/exclusion criteria but were in the screening process when enrollment closed.

NEURALGIA
Pain in one or more nerves that occurs without stimulation of pain receptor (nociceptor) cells. Neuralgia pain is produced by a change in neurological structure or function rather than by the excitation of pain receptors that causes nociceptive pain. http://en.wikipedia.org/wiki/Neuralgia

PATIENT REPORTED OUTCOME MEASURES (PROMS)

- **KOOS:** The Knee injury and Osteoarthritis Outcome Score (KOOS) Knee Survey is a disease-specific, measure of 5 subscales; Pain, other Symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec) and knee related Quality of life QOL. The last week is taken into consideration when answering the questions. KOOS Knee Survey contains the full and original version of the Western Ontario and McMasters University Osteoarthritis Index (WOMAC) and thus WOMAC scores can be calculated from the KOOS Knee questionnaire. It is estimated to take about 10 minutes to complete the KOOS Knee questionnaire. http://www.koos.nu/
- **KSS:** Knee Society Score[87] is a standard clinical evaluation system for reporting results for subjects undergoing knee implant surgery and is both subject and physician derived (Scuderi et al). The new Knee Society Scoring System, copyrighted in 2011, is a validated system that combines an objective physician-derived component with a subjective patient-derived component. The objective knee score, completed by the surgeon, includes an assessment of alignment, ligament stability, and ROM along with deductions for flexion contracture or extensor lag. Given the diverse activity profiles of many contemporary subjects, the functional component of the score was improved to include a subject specific survey, which evaluates features such as standard activities of daily living, subject-specific sports and recreational activities (function), subject satisfaction, and subject expectations. Portions of the original Knee Society Clinical Rating System have been integrated into the new version to maintain the integrity of the prior version of the Knee Society score.
- **SF-12:** SF-12® Health Survey is a registered trademark of Medical Outcomes Trust. It is a short form of SF-36 in which it is 12 questions from each of the 8 concepts from SF-36 – split into physical health and mental health.
- **Subject Activity and Satisfaction:** Moximed generated questionnaire to capture level of subject activity and subject satisfaction post index procedure.
- **WOMAC:** The Western Ontario and McMaster Universities Arthritis (WOMAC) Index is self-administered, validated assessment of the three dimensions of pain, disability and joint stiffness in knee and hip osteoarthritis using a battery of 24 questions. http://www.auscan.org/womac/index.htm

PHYSICIAN REPORTED OUTCOME MEASURES

- **KSS:** Knee Society Score[87] is a standard clinical evaluation system for reporting results for subjects undergoing knee implant surgery and is both subject and physician derived (Scuderi et al). The new KSS survey has recently been validated by the Knee Society. It is both physician and subject derived. The objective knee score, completed by the surgeon, includes an assessment of alignment, ligament stability, and ROM along with deductions for flexion contracture or extensor lag. Subjects then record their VAS score of pain walking on level ground and on stairs or inclines satisfaction, functional activities, and expectations. Given the diverse activity profiles of many contemporary subjects, the functional

component of the score was improved to include a subject specific survey, which evaluates features such as standard activities of daily living, subject -specific sports and recreational activities, subject satisfaction, and subject expectations. Portions of the original Knee Society Clinical Rating System have been integrated into the new version to maintain the integrity of the prior version of the Knee Society score.

- **Pain:** Moximed generated questionnaire to capture confounding factors, type, location, and scale of pain.

PERONEAL NERVE INJURY

Damage to the peroneal nerve leading to loss of movement or sensation in the foot and leg. Injury may result in a loss of sensation, muscle control, muscle tone, and eventual loss of muscle mass because of lack of nervous stimulation to the muscles.
http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001795/

SCREEN FAILURE

Subjects who sign informed consent but failed to meet one or more of the Inclusion/Exclusion criteria.

SOFT TISSUE IRRITATION

Superficial Tissue Irritation An inflammatory condition of superficial layers of the skin as a result of an aseptic irritant, such as skin reaction to suture or dressings.

Periprosthetic Soft Tissue Irritation An inflammatory condition of the tissues about the implant resulting from aseptic tissue irritation. Fluid may accumulate in the periprosthetic tissues possibly resulting in the tissue swelling, localized tenderness, pain and/or joint motion is restriction.

SYNOVITIS

An inflammatory condition of the synovial membrane of the knee joint as the result of aseptic trauma, often caused by extreme or excessive activity on the joint. The knee joint is swollen, tender, and painful; and motion is restricted

SURGICAL SITE INFECTION[90]

Superficial Infection (skin and subcutaneous tissue) occurs after the operation *and* infection involves only skin or subcutaneous tissue of the incision *and* at least *one* of the following:

1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat *and* superficial incision are deliberately opened by surgeon, *unless* incision is culture-negative.

4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

Do *not* report the following conditions as SSI:

1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).
2. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).

Deep Incisional Infection (deep soft tissue, fascia and muscle)

Infection occurs if infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision *and* at least *one* of the following:

1. Purulent drainage from the deep incision but not from the space component of the surgical site.
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the subject has at least one of the following signs or symptoms: fever (>38ºC), localized pain, or tenderness, unless site is culture-negative.
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

Notes:

1. Report infection that involves both superficial and deep incision sites as deep incisional SSI.
2. Report an organ/space SSI that drains through the incision as a deep incisional SSI.

Organ or Space Infection

Infection occurs if no implant is left in place or if implant is in place and the infection appears to be related to the operation *and* infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation *and* at least *one* of the following:

1. Purulent drainage from a drain that is placed through a stab wound‡ into the organ/space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

Wound infections have been subdivided according to the following clinically related subgroups:

- **Aetiology:** In a primary infection, the wound is the primary site of infection, whereas a secondary infection arises following a complication that is not directly related to the wound;
- **Time:** An ***Early*** infection presents within 30 days of a surgical procedure, whereas an infection is described as ***Intermediate*** if it occurs between one and three months afterwards and ***Late*** if it presents more than three months after surgery;
- **Severity:** a wound infection is described as ***Minor*** if there is a discharge without cellulitis or deep tissue destruction, and ***Major*** if the discharge of pus is associated with tissue breakdown, partial or total dehiscence of the deep fascial layers of the wound, or if systemic illness is present.