

Protocol Number: ESC-16-001

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A Prospective, Multicenter, Randomized Controlled Study to Evaluate the Wound Closure Efficiency of [REDACTED] Knotless Tissue Control Device [REDACTED] Compared to Conventional Sutures in Total Knee Arthroplasty (TKA)

Protocol Number: ESC-16-001

Approval:

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COMPLIANCE STATEMENT

This study will be conducted in compliance with the Declaration of Helsinki as well as all applicable local regulations.

INVESTIGATOR SIGNATURE

I have read, understood, and agree to:

- Ensure that the requirements for obtaining informed consent are met;
- Conduct the study in accordance with this protocol, including applicable local laws and regulations;
- Maintain the confidentiality of all information received or developed in connection with this protocol;
- Report all serious adverse events as soon as possible, but no later than 24 hours after becoming aware of the event;
- Adhere to the publication policy, as stated in the Clinical Study Agreement, for data collected during this study; and
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting the above commitments.

I will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the EC all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without Sponsor and EC approval of an amended protocol, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligation of clinical investigators and all other pertinent requirements of the Sponsor and government agencies.

Investigator Signature

Date

Printed Name of Investigator

SYNOPSIS

Title:	A Prospective, Multicenter, Randomized Controlled Study to Evaluate the Wound Closure Efficiency of [REDACTED] [REDACTED] Knotless Tissue Control Device [REDACTED] Compared to Conventional Sutures in Total Knee Arthroplasty (TKA)
Protocol Number:	ESC-16-001
Regulatory Status:	Post-Marketing All wound closure products used in the study are legally market in China and should be used within their approved indications.
Indication:	[REDACTED] Device is indicated for use in soft tissue approximation where the use of absorbable sutures is appropriate.
Objectives:	The primary objective of this prospective, randomized controlled study is to evaluate the wound closure efficiency of [REDACTED] compared to conventional sutures in patients undergoing TKA. For the purpose of this study, wound closure efficiency is defined as the total time required to close the surgical incisions in patients undergoing TKA procedures using [REDACTED] compared to those using traditional sutures. Secondary objectives will include the evaluation of differences in overall surgical procedure time, operating room (OR) time, length of stay, procedure costs, quality of life measures including pain, and range of motion (ROM). In addition, the difference in the safety profiles for both wound closure procedures will be evaluated through the analysis of the incidence of wound complications including dehiscence, wound infections, and other adverse events.

Endpoint:	<p>Primary Efficacy Endpoints: The primary endpoint will be the total time required to close the surgical incisions between treatment groups. The time to close each surgical incision is defined as the time in minutes between placement of the first suture throw in the deep tissue and the completion of intradermal layer closure (capturing the suturing time only).</p> <p>Secondary Efficacy Endpoints:</p> <ol style="list-style-type: none"> 1. Duration of procedure; 2. Overall OR time; 3. Length of stay between surgery and discharge; and 4. TKA related QoL assessments: <ol style="list-style-type: none"> a. Knee pain; b. Health-related quality of life (EQ-5D-3L); <p>Secondary Safety Endpoints:</p> <ol style="list-style-type: none"> 1. The incidence of surgical site infection (SSI) following surgery as defined by CDC criteria; 2. ASEPIS score (only for subjects with confirmed SSI); 3. Acute Inflammatory Response Evaluation (AIRE) score; 4. Incidence of wound separation or dehiscence requiring intervention; 5. Incidence of delayed wound healing events; and 6. Incidence of adverse events (AEs) and serious adverse events (SAEs) associated with wound closure;
Study Design:	<p>This is a multicenter, single blind, prospective, randomized controlled study in patients undergoing elective TKA and meeting the study's eligibility criteria. Eligible patients will be randomized on 1:1 basis to have the surgical incision closed with either [REDACTED] or conventional sutures. Wound closure and surgical procedure times will be determined perioperatively. Patients will remain blinded to the type of sutures utilized for closure of the incision.</p>
Number of Subjects (Planned):	184 subjects (92 per arm)
Duration of Study	<p>Enrollment is anticipated to require approximately 8 months. The duration of the study is therefore expected to be approximately 9 months from the date of the first patient enrolled to the last patient taking into account the 4-6 weeks follow-up period.</p>
Diagnosis/Criteria for Inclusion:	<ol style="list-style-type: none"> 1. Patient is ≥ 18 years and < 80 years of age; 2. Patient with osteoarthritis is scheduled to undergo elective unilateral TKA; 3. Patient is willing to participate in the study, comply with study requirements, follow-up schedule, and give written informed consent; and 4. Patient agrees not to schedule any additional elective surgical procedures until participation in this study is complete.

Diagnosis/Criteria for Exclusion:	<ol style="list-style-type: none"> 1. Female patient who is pregnant or lactating at the time of screening; 2. Patient has a Body Mass Index (BMI) > 40 kg/m²; 3. Patient is not able to walk independently (inability to walk at least 10 consecutive meters without a walking aid); 4. Patient has had a surgical intervention during the past 30 days for treatment of painful joint or its underlying etiology; 5. Patient has had previous open surgeries on the affected joint other than arthroscopy; 6. Patient has active infectious collagen diseases (i.e. scleroderma) or any other condition that would interfere with wound healing; 7. Patient is allergic to poly (p-dioxanon), IRGACARE®* MP (triclosan) or D&C Violet No. 2; 8. Patient has diabetes with poor control, defined as fasting plasma glucose (FPG) ≥ 10.0 mmol/L; 9. Patient has a history of immunosuppressive drug use, including steroids, within the last 6 months; 10. Patient has undergone chemotherapy or radiation within the last 6 months prior to study enrollment or is scheduled to do so during the study period; 11. Patient has known personal or family history of keloid formation or hypertrophy; 12. Patient has other dermatologic conditions known to impair wound healing; 13. Patient is participating in any other investigational drug (within 30 days or 5 half-lives of an investigational drug) or device study; 14. Patient has any physical or psychological condition which would impair study participation; and 15. Patient is judged unsuitable for study participation by the investigator for any other reason.
Study Product:	<div style="background-color: black; width: 200px; height: 1.2em; display: inline-block;"></div> Knotless Tissue Control Device

Statistical Methods:	<p>All efficacy endpoints will be summarized descriptively by treatment group. The continuous variables will be summarized descriptively by number of subjects, mean, standard deviation, minimum, and maximum. Categorical data will be summarized descriptively by frequencies along with the associated percentages.</p> <p>In addition, for the primary efficacy endpoint, a one-sided 97.5% confidence interval for the difference in treatment group means (Mean [REDACTED] closure time minus the Mean closure time for conventional suture) will be constructed using the t-distribution.</p> <p>The primary efficacy endpoint will be analyzed using the mITT and Per-Protocol analysis sets. The ITT analysis will be considered as the primary analysis. All secondary efficacy endpoints will be analyzed using the mITT analysis set.</p> <p>All secondary safety endpoints will be summarized descriptively by treatment group for the Safety analysis set using available data. The continuous variables will be summarized descriptively by number of subjects, mean, standard deviation, minimum, and maximum. Categorical data will be summarized descriptively by frequencies along with the associated percentages. No inferential statistics will be generated for the secondary safety endpoints.</p>
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SCHEDULE OF EVENTS

Event	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Baseline/ Screening ^a	Randomization	Procedure	Post-Op through Discharge ^b	30-42 days ^c (post procedure)
Informed consent	X				
IWRS/IVRS ^d		X			
Inclusion/Exclusion Criteria	X	X			
Urine/blood pregnancy test	X				
Demographics	X				
Medical/Surgical history	X		X		
Physical examination ^e	X			X	X
Knee pain VAS	X			X	X
EQ-5D-3L	X			X	X
Concomitant medications ^f	X	X	X	X	X
Length of stay ^g				X	
Health Economic Data Collection				X	
Procedural data ^h			X		
Adverse events			X	X	X
Wound complication assessment			X	X	X
SSI/ASEPSIS score ⁱ				X	X
AIRE score				X	X
Study completion					X

- a. To be performed within 30 days of surgery.
- b. Physical examination, knee pain VAS, EQ-5D-3L and AIRE score will be collect on 3-5 days after surgery.
- c. Unless withdrawn from the study, subject's status will be confirmed at the time of in-person visit at 30-42 days following surgery. If possible, an in-person visit will be scheduled to confirm status for patients withdrawn prematurely from the study for any reason.
- d. Interactive web response system/ Interactive voice response system.
- e. The physical examination at baseline/screening visit includes height, weight and ROM of knee, and the post-procedure physical examination only includes ROM of knee.
- f. Including pain medications and antibiotics (except for anesthesia medications).
- g. Defined as time between procedure and discharge.
- h. Procedure time, overall OR time, intra-operative device failure rates, operating room resource utilization (if applicable), and anesthesia method (e.g., general or lumbar anesthesia).
- i. ASEPSIS score will be applied only after SSI confirmed.

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PROTOCOL-SPECIFIC ACRONYMS AND ABBREVIATIONS

Acronyms/Abbreviations	Terms
ADE	Adverse Device Effect
AE	Adverse Event
AIRE	Acute Inflammatory Response Evaluation
ASADE	Anticipated Serious Adverse Device Effect
BMI	Body Mass Index
CDC	Centers for Disease Control
CFDA	China Food and Drug Administration
CFR	Code of Federal Regulations
CHU	Complaint Handling Unit
EC	Ethics Committee
eCRF	Electronic Case Report Form
ESC	████████ Surgical Care
EDC	Electronic Data Capture
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
ICD	Informed Consent Document
mITT	modified Intent-to-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
OR	Operating Room
PI	Principal Investigator
PP	Per-Protocol
QoL	Quality of Life
ROM	Range of Motion
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard of Care
SSI	Surgical Site Infection
TKA	Total Knee Arthroplasty
TSA	Topical Skin Adhesive
USP	United States Pharmacopeia
VAS	Visual Analogue Scale

1.0 Introduction

1.1 Knee Joint Disorder and TKA

The knee joint is a complicated structure bound by a host of tendonous and ligamentous structures prone to acute and chronic injury. Since the hyaline cartilage covered weight bearing surfaces are separated by menisci, body weight, impact and trauma gradually draw them together over time. Once the joint space is compromised by meniscal thinning, hyaline surfaces come into contact with one another, degenerative processes begin and osteoarthritis develops. Other types of disease that may affect the knee include rheumatoid arthritis, post-traumatic arthritis, osteonecrosis and cancer. Irrespective of the underlying degenerative process, pain and decreased range of motion begin to impact the patients' quality of life. Gradually, fewer daily activities are performed and systemic and mental healths are affected.

First performed in the 1960's, total knee arthroplasty (TKA) is a historically successful procedure that removes diseased portions of the knee joint and replaces them with prosthetic implants. Although there are many causes of knee joint deterioration, the primary indication for a patient to undergo TKA is to address the pain and loss of joint function secondary to advanced osteoarthritis.

Over the past 20 years, due to ageing, development of diagnostic and surgical technologies, as well as the continuous improvement of surgical instruments, the number of TKA surgery continues to grow over time [1, 2]. And the number could still continue growing rapidly in the next two decades [3-5], and further increasing the burden of health-care institutions. Currently, interrupted suture was still in use to close surgical incision during the operation. In comparison to the traditional continuous suture technique, interrupted suture may in some degree improve the suture strength for the surgical incision, in order to meet the need of early function exercise. However, interrupted technique has a relatively low suture efficacy, thus may prolong the suturing and operation time, when compared to the continuous technique. Reducing the operation time is associated with reduced risk of incisional complications, especially surgical site infection [6], which as a result, can be catastrophic for the TKA surgery outcome. [REDACTED] have a unique barbed design, which, theoretically, allows physicians to perform highly efficient continuous suture, and to improve operation efficiency. By reducing the operation time, the new product can achieve the same safety and effectiveness as compared with the interrupted suture technique [5, 7-10].

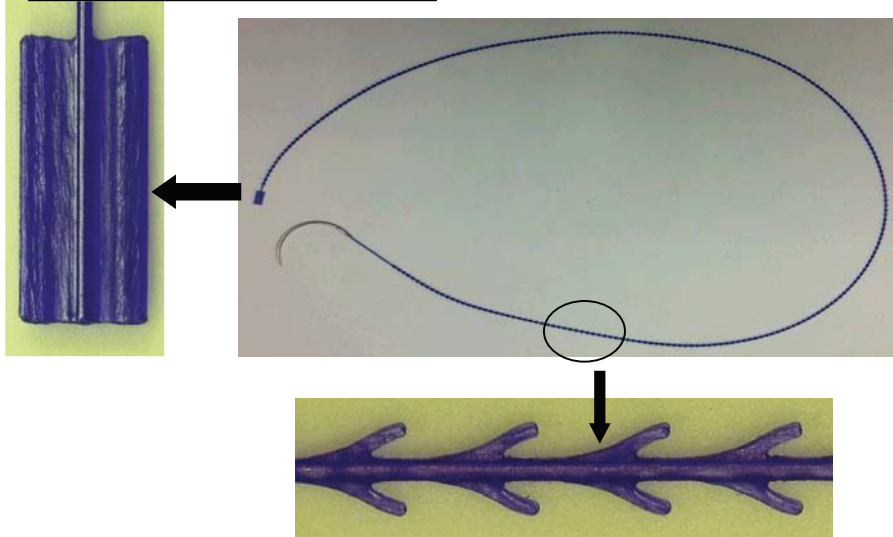
This study was designed to verify that [REDACTED] can improve the operation efficacy, can reduce the suturing and operation time as well as meet the clinical demand for suture safety, as compared to traditional interrupted suture technique during TKA surgery.

1.2 Study Device Description

[REDACTED] is an antibacterial (polydioxanone) monofilament, synthetic absorbable device prepared from polydioxanone (p-dioxanone). The device contains IRGACARE®1 MP (triclosan), a broad spectrum antibacterial agent. [REDACTED] monofilament is dyed with D&C Violet No. 2. [REDACTED] consists of an absorbable thread with unidirectional anchors, equipped with a surgical needle at one end and a fixation tab at the other (Figure 1). The anchors and fixation tab design allows for tissue approximation without the need to tie surgical knots. The cross-sectional area of the [REDACTED] core is comparable to the cross-sectional area of a United States

Pharmacopeia (USP) suture with the same designation, i.e., 0, 1, 2-0, 3-0. [REDACTED] straight tensile strength is stronger than the knot tensile strength for a USP polydioxanone suture of the equivalent size. Polydioxanone has been found to be non-allergenic, non-pyrogenic, and to elicit only a slight tissue reaction during absorption.

Figure 1: [REDACTED] (with Anchor and Fixation Tab Enlargements)



2.0 Study Objectives

The primary objective of this prospective, randomized controlled study is to evaluate the wound closure efficiency of [REDACTED] compared to conventional sutures in patients undergoing TKA. For the purpose of this study, wound closure efficiency is defined as the total time required to close the surgical incisions in patients undergoing TKA procedures using [REDACTED] compared to those using traditional sutures. Secondary objectives will include the evaluation of differences in overall surgical procedure time, operation room (OR) time, length of stay, procedure costs, quality of life measures including pain, and range of motion (ROM). In addition, the difference in the safety profiles for both wound closure procedures will be evaluated through the analysis of the incidence of wound complications including dehiscence, wound infections, and other adverse events.

2.1 Primary Endpoints:

The primary endpoint will be the total time required to close the surgical incisions between treatment groups. The time to close each surgical incision is defined as the time in minutes between placements of the first suture throws in the deep tissue to the completion of Intradermal layer closure (capturing the suturing time only).

2.2 Secondary Efficacy Endpoints:

1. Duration of procedure: defined as the time in minutes elapsed from first incision to the skin closure.

2. Overall operating room (OR) time: defined as the time in minutes from anesthesia to exiting the OR;
3. Length of stay between surgery and discharge.
4. TKA related QoL assessments:
 - a. Knee Pain: pain at rest and pain during mobilization is measured using a 10 centimeter Visual Analogue Scale (VAS) in which patient is asked to describe degree of pain with 0 being no pain and 10 being the worst pain.
 - b. Health-related Quality of Life (EQ-5D-3L): patient is asked to confirm his/her health state by selecting the most appropriate level for each of the following 5 dimensions. Refer to Table 1.
 - Mobility
 - Self-care
 - Usual activities
 - Pain/discomfort
 - Anxiety/depression

Table 1: EQ-5D-3L

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- | | |
|---|--------------------------|
| I have no problems in walking about | <input type="checkbox"/> |
| I have moderate problems in walking about | <input type="checkbox"/> |
| I am unable to walk about | <input type="checkbox"/> |

Self-care

- | | |
|---|--------------------------|
| I have no problems washing or dressing myself | <input type="checkbox"/> |
| I have moderate problems washing or dressing myself | <input type="checkbox"/> |
| I am unable to wash or dress myself | <input type="checkbox"/> |

Usual Activities (i.e work, study, housework, family or leisure activities)

- | | |
|--|--------------------------|
| I have no problems doing my usual activities | <input type="checkbox"/> |
| I have moderate problems doing my usual activities | <input type="checkbox"/> |
| I am unable to do my usual activities | <input type="checkbox"/> |

Pain/Discomfort:

- | | |
|------------------------------------|--------------------------|
| I have no pain or discomfort | <input type="checkbox"/> |
| I have moderate pain or discomfort | <input type="checkbox"/> |
| I have extreme pain or discomfort | <input type="checkbox"/> |

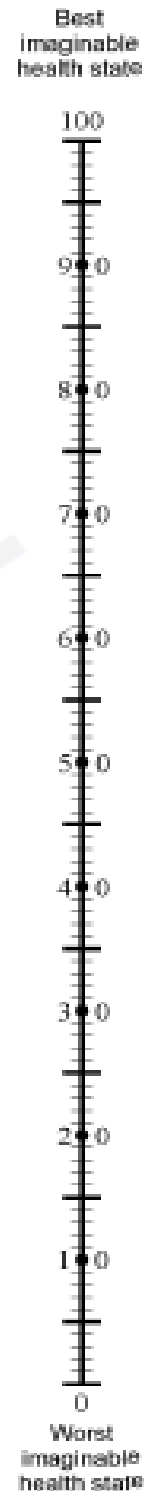
Anxiety/Depression

- | | |
|--------------------------------------|--------------------------|
| I am not anxious or depressed | <input type="checkbox"/> |
| I am moderately anxious or depressed | <input type="checkbox"/> |
| I am extremely anxious or depressed | <input type="checkbox"/> |

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked **100** and the worst state you can imagine is marked **0**.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own
health state
today



2.3 Secondary Safety Endpoints:

The following data will be summarized by treatment group. The continuous variables will be summarized descriptively by number of subjects, mean, standard deviation, minimum, and maximum. Categorical data will be summarized descriptively by frequencies along with the associated percentages.

1. The incidence of SSI following surgery as defined by:

a. CDC criteria^[11]:

1) Superficial incisional SSI:

Infection occurs within 30 days after the operation and infection involves only skin or subcutaneous tissue of the incision and at least one of the following:

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

Do not report the following conditions as SSI:

- Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration);
- Infection of an episiotomy or new born circumcision site;
- Infected burn wound;
- Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).

Note: Specific criteria are used for identifying infected episiotomy and circumcision sites and burn wounds.

2) Deep incisional SSI:

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to, be related to the operation and infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision and at least one of the following:

- Purulent drainage from the deep incision but not from the organ/space component of the surgical site;
- A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever ($>38^{\circ}\text{C}$), localized pain, or tenderness, unless site is culture-negative;
- An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination;
- Diagnosis of a deep incisional SSI by a surgeon or attending physician.

Notes:

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

3) Organ/Space SSI:

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year 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:

- Purulent drainage from a drain that is placed through a stab wound into the organ/space;
- Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space;
- 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;
- Diagnosis of an organ/space SSI by a surgeon or attending physician.

No confirmatory culture will be required unless deemed by the physician per local standard of care to provide appropriate treatment to subject.

- b. ASEPIS Score (only for patients with confirmed SSI): assesses severity of wound infection using numerical scoring (as opposed to the CDC's absence or presence of SSI and type). The ASEPIS Wound Score evaluates wound characteristics and additional treatments as predictors of infection that may develop once the subject leaves the hospital. These include the presence of serous exudates, erythema, purulent exudates, separation of deep tissues, antibiotics, drainage of pus, wound debridement, isolation of bacteria, and requirement for inpatient stay. Surgeons assess each parameter and provide a numerical score based upon objective criteria of wound appearance and clinical consequences of the infection. Extra points were added for antibiotic treatment of SSI (10 points), drainage of pus under local anesthesia (5 points), debridement of the wound under general anesthesia (10 points), isolation of bacteria from the wound (10 points), and an inpatient stay of more than 14 days (5 points). An overall score, ranging from 0 to 100, is then calculated to define wound severity according to the proportion of the wound affected by each of these characteristics^[12, 13]. Refer to Table 2:

2. Use Acute Inflammatory Response Evaluation (AIRE) score measuring inflammatory tissue reaction. Of note, an AE will be reported when the score is >1. Refer to Table 3^[14, 15];
3. Incidence of wound separation or dehiscence requiring intervention;
4. Incidence of delayed wound healing events;
5. Incidence of wound closure related adverse events and serious adverse events;

Table 2: ASEPSIS Score

Wound Characteristic	Proportion of Wound Affected					
	0	<20	20-39	40-59	60-79	>80
Serous Exudate	0	1	2	3	4	5
Erythema	0	1	2	3	4	5
Purulent Exudate	0	2	4	6	8	10
Separation of Deep Issue	0	2	4	6	8	10
Points are scored for daily wound inspection.						
Additional Treatment			Points			
Antibiotics			10			
Drainage of Pus under local anesthesia			5			
Debridement of Wound (General Anesthesia)			10			
Serous Discharge*			Daily 0-5			
Erythema*			Daily 0-5			
Purulent Exudate*			Daily 0-10			
Separation of Deep Tissues*			Daily 0-10			
Isolation of Bacteria			10			
Stay as In-patient Prolonged Over 14 Days			5			
*Given scores on 5 of 7 days and the highest weekly score used.						
Category of Infection						
Total Score**			Definition			
0-10			Satisfactory Healing			
11-20			Disturbance of Healing			
21-30			Minor Wound Infection			
31-40			Moderate Wound Infection			
>40			Severe Wound Infection			
**Total Score calculated adding scores for individual wound characteristics and additional treatment.						

Table 3: Acute Inflammatory Response Evaluation (AIRE) Score

Score	Erythema	Oedema	Pain	Temperature
0	None observed	None observed	None	None
1	Slight blanching redness along incision closure line	Slight increase in tissue firmness (turgor)	Pain at site with pressure	Slightly warmer compared to adjacent skin
2	Moderate redness extending < 2 mm	Pitting of skin around incision with mild pressure	Pain at site with touch	Definitely warmer compared to adjacent skin
3	Intense redness extending > 2 mm	Tense firmness of skin around incision	Continuous pain	Radiating heat at incision site

3.0 Investigational Plan

3.1 Overall Study Design and Plan-Description

This is a multicenter, single blind prospective, randomized controlled study in patients undergoing elective TKA and meeting the study's eligibility criteria. Eligible patients will be randomized on 1:1 basis to have the surgical incision closed with either [REDACTED] or conventional sutures. The plan is to randomize at least 92 subjects for each of the two groups into this study in about 8 sites. Wound closure and surgical procedure times will be determined perioperative. Patients will remain blinded to the type of sutures utilized for closure of the incision.

3.2 Study Population

3.2.1 Inclusion Criteria

Subjects satisfying the following criteria will be considered eligible for enrollment in this study:

1. Patient is ≥ 18 and < 80 years of age;
2. Patient with osteoarthritis is scheduled to undergo elective unilateral TKA;
3. Patient is willing to participate in the study, comply with study requirements, follow-up schedule, and give written informed consent; and
4. Patient agrees not to schedule any additional elective surgical procedures until participation in this study is complete.

3.2.2 Exclusion Criteria

Subjects meeting any of the following criteria will not be eligible for enrollment:

1. Female patient who is pregnant or lactating at the time of screening;
2. Patient has a Body Mass Index (BMI) $> 40 \text{ kg/m}^2$;
3. Patient is not able to walk independently (inability to walk at least 10 consecutive meters without a walking aid);
4. Patient has had a surgical intervention during the past 30 days for treatment of painful joint or its underlying etiology;
5. Patient has had previous open surgeries on the affected joint other than arthroscopy;
6. Patient has active infectious collagen diseases (i.e. scleroderma) or any other condition that would interfere with wound healing;
7. Patient is allergic to poly (p-dioxanon), IRGACARE®* MP (triclosan) or D&C Violet No. 2;
8. Patient has diabetes with fasting plasma glucose (FPG) $\geq 10.0 \text{ mmol/L}$;
9. Patient has a history of immunosuppressive drug use, including steroids, within the last 6 months;
10. Patient has undergone chemotherapy or radiation within the last 6 months prior to study enrollment or is scheduled to do so during the study period;
11. Patient has known personal or family history of keloid formation or hypertrophy;
12. Patient has other dermatologic conditions known to impair wound healing;
13. Patient is participating in any other investigational drug (within 30 days or 5 half-lives of an investigational drug) or device study;
14. Patient has any physical or psychological condition which would impair study participation; and
15. Patient is judged unsuitable for study participation by the investigator for any other reason.

3.2.3 Removal of Subjects from Study

In accordance with the current revision of the Declaration of Helsinki, a subject has the right to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or the institution. Should a subject (or subject's legally authorized guardian/representative) decide to withdraw, 1) all data collected up to the point of withdrawal will be considered for analysis; and 2) all efforts will be made to collect and report the final visit observations as thoroughly and timely as possible. The primary reason for early withdrawal will be recorded in the electronic case report form (eCRF), as such:

Adverse Event

When the subject experiences an AE and the PI or Medical Monitor believes it is in their best interest to discontinue participation in the study, the subject will be withdrawn from the study.

Withdrawal of consent

Any method of contact with the subject in which they state they no longer want to participate in the study specific activities constitutes withdrawal of consent for participation in the study. When possible, the reason for withdrawal will be documented.

Site Termination or Study Termination

A study site or the entire study may be terminated. When this occurs, all subjects currently enrolled at the site will be withdrawn and documented as early terminations. Reasons for site or study termination may include, but are not limited to the following:

- Administrative Concerns (e.g., inadequate subject enrollment, Investigator/institution non-compliance, change of business strategy, etc.);
- Safety Issues, including those due to non-compliance, which substantially affect the risk to benefit ratio of the study subjects at a site or for the study as a whole; or
- Regulatory Body Mandate(s).

Death

- When possible, the cause of death will be documented.

Other

- Either deep or intermediate layer can't be closed by one [REDACTED] suture;
- PI believed the incision is not suitable to be closed by absorbable suture (e.g., the tissue where prolonged (beyond six weeks) approximation of tissue under stress is required).

3.3 Study Procedure

3.3.1 Procedure Description

TKA Surgical Procedure:

It is suggested that no more than two surgeons at each would investigative site perform the wound closure procedure of TKA to minimize bias and variability. The TKA procedure will be performed per each institutional requirements or specific guidelines with a median incision^[16-20]. The length of incision is recommended to be no longer than 15 cm.

Wound Closure Procedure:

The wound closure will be performed at genuflex position.

For patients randomized to receive barbed sutures, the deep layer and the intermediate layer will be repaired and closed by using one [REDACTED] suture respectively. The

ratio of incision length to suture length for both layers is recommended to be no higher than 1:3. For patients randomized to receive conventional sutures, [REDACTED] sutures will be used to close the deep and the intermediate layers with interrupted suturing manner. Then for both groups, [REDACTED] sutures will be used to close the intradermal layer and the [REDACTED] Skin Closure System, a topical skin adhesive (TSA) will be applied to the skin surface to tissue approximation. Please find the details in Table 4,5.

Table 4: Wound closure procedure and devices in barbed suture group

Layer	Suture Material	Suture Technique	Code
Deep layer	[REDACTED]	Continuous	[REDACTED]
Intermediate layer	[REDACTED]	Continuous	[REDACTED]
Intradermal layer	[REDACTED]	Continuous	[REDACTED]
Skin layer	[REDACTED]	N/A	[REDACTED]

Table 5: Wound closure procedure and devices in control group

Layer	Suture Material	Suture Technique	Code
Deep layer	[REDACTED]	Interrupted	[REDACTED]
Intermediate layer	[REDACTED]	Interrupted	[REDACTED]
Intradermal layer	[REDACTED]	Continuous	[REDACTED]
Skin layer	[REDACTED]	N/A	[REDACTED]

The sutures and TSA will be used per the Instructions for Use [21-24]. Surgeons must be familiar with surgical procedures and techniques involving absorbable sutures as risk of wound dehiscence/separation may vary with the site of application and the suture material used. Consequently, surgeons must consider the in vivo performance when evaluating the eligibility of potential subjects for enrollment into the study. The use of an absorbable suture may be inappropriate in elderly, malnourished, or debilitated patients, or in patients suffering from conditions which may delay wound healing.

Postoperative Care:

Postoperative care will be performed per institutional requirements ROM exercises will be performed adhering to institutional requirements and specific guidelines regarding postoperative care. Patient status is monitored closely until discharge. Thrombolytic therapy beyond discharge can be continued prophylactically per institutional requirements or not. Changes in concomitant medications including analgesics will be recorded throughout inpatient stay.

Other – Health Economic Data Collection

In order to estimate the costs characteristics and influence factors, the following costs data will be collected if available:

Overall fee: Total fees, hospital stay fees, self-paid amount, etc

Comprehensive medical services costs, including general medical service charges, general treatment procedure fees, and nursing costs, etc.

Diagnosis fees, including pathological diagnosis fee, imaging diagnosis fee, clinical diagnosis fee, and laboratory diagnosis fee, etc.

Treatment fees, including non-operation treatment fee (clinical physical treatment fee), operation costs (anesthetic fee, procedure costs)
Rehabilitation fee, including rehabilitation costs, etc.
Medicines fee, including traditional Chinese medicine, western Chinese medicine, antibiotic fees, etc.
Blood and blood products costs, including fees of blood, blood coagulation products, etc.
Medical supplies costs, including fees of disposal medical supplies for examination, fees of disposal medical supplies for treatment, and disposal medical supplies for surgery, etc.
The other costs, if applicable.

3.3.2 Blinding

Blinding practices for this study will include the following:

Patients: Patients will be informed of the 1:1 randomization between the different suturing material and technique, but will remain blinded as to which implant they actually received until after they have completed all study follow-up.

Implanting surgeon: It is not possible to blind the implanting physician due to the different suturing technique and products.

Medical Records: All medical records (source documents) documenting the implant procedure through hospital discharge and all follow-ups will not be blinded because the devices used will be described in the operation record.

Monitors: Monitors will not be blinded because the detachable labels provided with the product identify the product and may be used in the study device accountability records and patient research file for the purpose of device accountability and source document validation.

3.3.3 Subject Compliance

Study personnel will make preemptive contact with subjects as necessary to ensure compliance with the follow-up schedule.

3.4 Study Procedures

Screening

Subjects will be consented prior to any actual study-specific screening procedures being conducted. Subjects will be considered enrolled into the study upon satisfaction of the following criteria:

- Completion of the informed consent process and signing the ICD;
- Verification of the eligibility criteria (Sections 3.2) by the PI and authorized investigators. The verification must be conducted by the PI and/or authorized investigators prior to randomization.

Screening Failures

Screened subjects who are not enrolled will be considered screen failures. For subjects who are determined to be screen failures, only the following data will be recorded on the eCRF:

- Informed consent date;

- Demographic information (age, race, gender, and ethnicity);
- Reason for screening failure.

Randomization

Randomization will occur if the patient meets all inclusion criteria and does not meet any exclusion criteria.

Each case will be randomized to one of two groups in a 1:1 ratio. The only difference between the groups will be the suturing material and technique. The plan is to randomize at least 92 subjects for each of the two groups. A central randomization will be used in this study so that the study team cannot guess the upcoming assigned group.

3.4.1 Visit 1 – Screening/Baseline Visit

The following screening activities will occur prior to the study procedure (performed within 30 days of surgery):

- The subject must be given ample time to review and sign the ICD;
- Collection of demographic information (year of birth, race, gender, ethnicity, education, occupation);
- Review and collection of medical/surgical history
- Review/collection of inclusion/exclusion criteria and determination as to whether the subject is eligible for participation (retrospective data, per site SOC, is permitted to determine eligibility);
- Urine/blood pregnancy test;
- Date of hospital admission;
- Knee Pain VAS
- EQ-5D-3L
- Physical Examination, including height, weight and ROM of knee; and
- Concomitant medications (including pain and antibiotics) from the admission;

3.4.2 Visit 2 – Randomization

The following must be obtained prior to the surgical procedure:

- Interactive web response system/ interactive voice response system
- Confirm inclusion and exclusion criteria
- Concomitant medications including pain and antibiotics

3.4.3 Visit 3 – Surgical Procedure

3.4.3.1 Pre-procedure

The following must be obtained prior to the surgical procedure:

- Update to medical/surgical/ history
- Concomitant medications including pain and antibiotics

3.4.3.2 Intraoperative

Data collected during procedure:

- Procedure time:
 - The time in minutes and seconds by a calibrated stopwatch between placement of the first suture throws in the deep tissue to the completion of intradermal layer closure. Total operation time: defined as the time in minutes beginning with first incision to skin closure.
- Overall operating room (OR) time: defined as the time in minutes from anesthesia to exiting the OR;
- Device usage data
 - The code and quantity of wound closure device, including suture and TSA
- Operating room resource utilization;
- Intra-operative device failure rates;
- Anesthesia method;
- Wound Complication Assessment;
- Concomitant medications including pain and antibiotics (except for anesthesia medications)..;
- Adverse Events (Concomitant medication usage associated with AEs will also be captured)

3.4.4 Visit 4 – Post-Op through Discharge

The following must be obtained in this visit.

- Knee pain VAS
- ROM
- EQ-5D-3L
- Concomitant medications including pain and antibiotics
- Wound Complication Assessment
- Adverse Events (Concomitant medication usage associated with AEs will also be captured)
- SSI
- AIRE
- Length of stay: defined as time between procedure and discharge.
- Health Economic Data Collection

3.4.5 Visit 5 – 30-42 Days

Between 30 and 42 days post procedure; the following must be conducted/obtained:

- Knee pain VAS
- ROM
- EQ-5D-3L
- Concomitant medications including pain and antibiotics
- Wound Complication Assessment

- Adverse Events (Concomitant medication usage associated with AEs will also be captured)
- SSI
- AIRE

4.0 Data Management and Integrity

4.1 Data Completion and Record Keeping

4.1.1 Source Documents

Source documents are documents on which information regarding subjects is first recorded, including printed, optical, or electronic documents. Investigator subject files or hospital records generally are the basis of source document information. This includes but is not limited to, original subject files; hospital/clinic records; original recordings /tracing; digital images from automated instruments; radiographs; device accountability records; photographic negatives; and records kept at the investigation site, at the laboratories and at other departments involved in the clinical investigation.

Source documents must be retained by the Investigator as part of the subject's permanent medical record. The information in the source documents is used to complete the eCRFs. All information captured on the eCRFs should be completely and accurately supported in source documentation. Any additional information relevant to the study should be included in the source documents. In particular, any deviations from the study protocol or procedures should be recorded in the source documents. The Investigator will retain originals of all source documents, subject consent forms, and study data.

4.1.2 Electronic Data Capture

An electronic data capture (EDC) system will be utilized by study site personnel to transfer study data from source records (medical records and/or source document worksheets) onto common eCRFs. This system is a web-based, secure electronic software application (Medidata® Rave, 79 Fifth Avenue, 8th Floor, New York, New York, 10003). This system was designed and is developed and maintained by Medidata in a manner that is compliant with national and international GCP data protection/data privacy and electronic record/electronic signature (e.g., 21 CFR Part 11) regulatory requirements. The EDC system will be used to facilitate the collection of all study data at the site. Designated site personnel will be responsible for entering patient data into the EDC system. All external and Sponsor internal users will be trained on the EDC application at a level dependent on their planned function. An EDC digital User Manual will be available under the help menu within the Medidata® Rave website to assist in the collection and entry of source data into the electronic casebook.

A 24/7/365 Help Desk Support line (per Medidata web site) staffed by the outsourced vendor will also be available to respond to site-monitor questions.

4.1.3 Data Collection

Each EDC eCRF will be completed by the PI or PI's designee. Every effort should be made to respond to all monitoring and/or data management questions on each eCRF as completion of the data is required by the protocol. A unique ID number will identify each subject. The subject's unique ID number will be visible on each eCRF. At no time should the subject name appear on the eCRFs.

All data should be recorded accurately and completely. The Investigator is responsible for reviewing and approving each completed eCRF. Assurance of overall review and approval

will be documented by the Investigator electronically signing each subject's electronic casebook.

4.1.4 Data Correction

Required data corrections to eCRFs will be prompted via automated electronic edit checks and/or queries manually created by Sponsor reviewers. The change(s), individual making the change(s), and time the change(s) were made to the eCRFs will be automatically captured in the audit trail within Medidata® Rave.

4.1.5 Data Privacy

The collection, use, and disclosure of all personal data, including subject health and medical information, are to be maintained in compliance with applicable personal data protection and security laws and regulations that govern protected health information and the informed consent given by each study subject. When collecting and processing such personal data, appropriate measures are to be taken to maintain the confidentiality of patient health and medical information and to prevent access by unauthorized persons.

4.1.6 Record Retention, Inspection, and Custody

The PI must maintain all documentation related to the study for at least ten years after site closure (per applicable local regulation) and until they receive Sponsor notification. The PI will allow representatives of the Sponsor, the China Food and Drug Administration (CFDA), or other government regulatory agencies to inspect all study records, eCRFs, and corresponding portions of the subject's office and/or hospital medical records at regular intervals during the study. These inspections are to verify adherence to the protocol, integrity of the data being captured on the eCRFs, and compliance with applicable regulations.

Subject medical records will be maintained in a confidential manner. Study reports will not identify subjects by name.

If custody of the records is transferred, notice of such a transfer should be given to the Sponsor no later than 10 working days after the transfer occurs.

4.2 Medical Dictionary Coding

Medical dictionary coding of verbatim AE, Serious Adverse Event (SAE), and concomitant prescription medications terms captured on eCRFs will be performed using a coding thesaurus algorithm. The Medical Dictionary for Regulatory Activities and World Health Organization Drug Dictionary will be used after data entry and query resolution, via auto-encoding and interactive coding processes.

4.3 Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel prior to the study, and periodic monitoring visits by the Sponsor. The Sponsor will review eCRF's for accuracy and completeness during on-site monitoring visits and after their return to the Sponsor; any discrepancies will be resolved with the Investigator or designees, as appropriate. The data will be entered into the clinical study database and verified for accuracy.

4.3.1 Monitoring

This study will be monitored by the Sponsor to ensure:

- The rights and well-being of the subjects are protected;
- Reported study data is accurate, complete, and verifiable from source documents; and
- The conduct of the study is in compliance with the currently approved protocol/amendment(s), and with applicable local regulatory requirements.

The extent and nature of monitoring will be predetermined and based on considerations such as the objective, design, complexity, and endpoints of the study and mutually agreed to by the Sponsor and investigators. Monitors will comply with established written standard operating procedures as well as procedures (i.e., monitoring plan) specified by the Sponsor for monitoring this study. These monitoring procedures are characterized in the monitoring plan for this study.

4.3.2 Regulatory Requirements

This study will be conducted in accordance with ICH Harmonized Tripartite Guideline for Good Clinical Practice (1996), the Declaration of Helsinki (2008), as well as any other applicable local regulatory requirements.

4.4 Protocol Deviations

A deviation (any activity conducted outside the parameters established by the study protocol) can be identified from a number of sources. Potential sources include, but are not limited to: a member of the Investigator's staff, a Sponsor representative during monitoring visits, or a member of the data management or statistical groups when entering or analyzing data. Regardless of the source, it is crucial to document the deviation. The PI will report protocol deviations to the IRB as required by the IRB procedures.

4.5 Statistical Methods Planned in the Protocol and Determination of Sample Sizes

4.5.1 Statistical and Analytical Plans

The Data Management and Biostatistics groups of Global Surgery Clinical Development will be responsible for the analysis of data from this protocol. A comprehensive and detailed Statistical Analysis Plan (SAP) will be finalized prior to database lock and will supplement the statistical design and analysis described in this section.

4.5.2 Determination of Sample Size

The proposed sample size of 92 patients per arm (184 total) is considered adequate to test the hypothesis that [REDACTED] can reduce the time for incision closure compared to conventional sutures. Based upon a review of the literature, the mean incision closure time was assumed to be [REDACTED] minutes for conventional sutures, being calculated as a weighted (based on number of subjects) mean of the means observed in the studies reviewed. The studies reported incision closure times ranging between 14.4 to 26.5 minutes [5, 7-10]. It is expected that the [REDACTED] can reduce the incision closure time by [REDACTED]% compared to conventional sutures; therefore, the assumed mean closure time for [REDACTED] is [REDACTED] minutes. The standard deviations observed in the reviewed literature range from 3.43 to 8.5 minutes for the conventional sutures; the standard deviation for this study was conservatively assumed to be [REDACTED] minutes in both groups for several

reasons, such as the lack of data for [REDACTED] and that this patient sample may be older and with larger BMI. The distribution of incision closure time is assumed to be normal.

The statistical hypotheses for the primary endpoint are as follows:

- H_0 : Mean Barbed \geq Mean conventional suture tested against the alternative hypothesis
- H_a : Mean Barbed $<$ Mean conventional suture;

Where:

- The assumed mean time to incision closure in conventional group is [REDACTED] minutes;
- The mean time to closure in [REDACTED] is [REDACTED] minutes;
- The assumed standard deviations in the two groups are both 8.

Based upon these assumptions, a total seventy seven (77) evaluable subjects per arm will achieve 90% power to detect a difference of [REDACTED] minutes (expected mean for [REDACTED] of [REDACTED] minutes and the conventional group of [REDACTED] minutes) with estimated group standard deviations of [REDACTED] using a one-sided two-sample t-test. The assumed one-sided significance level is 0.025.

If the higher limit of the one-sided 97.5% confidence interval for the difference in the Mean [REDACTED] time minus the Mean closure time for conventional suture is smaller than 0, then it will be concluded that [REDACTED] is considered to be superior to conventional suture. The sample size is adjusted to 92 per arm to account for a 16% withdraw rate [25-28].

4.5.3 Analysis Sets

There will be three analysis sets defined:

- Modified Intent-to-treat set (mITT set) consists of all randomized subjects who had the surgical incisions closed using the randomized suture
- Evaluable [or Per-Protocol (PP)] set consists of all mITT subjects who have no major protocol violations.
- Safety set consists of all subjects who receive surgery.

Major protocol deviations are deviations that have an impact on the primary endpoint, or that have an impact on the randomization assignment. These will be determined prior to database lock.

4.5.4 Analysis of Primary and Secondary Efficacy Endpoints

For the primary efficacy endpoint, a one-sided 97.5% confidence interval for the difference in treatment group means (Mean [REDACTED] closure time *minus* the Mean closure time for conventional suture) will be constructed using the t-distribution. If the higher limit of the confidence interval is smaller than 0, then it will be concluded that [REDACTED] is considered to be superior to conventional suture.

The primary efficacy endpoint will be analyzed using the mITT and Per-Protocol analysis sets. The mITT analysis will be considered primary analysis. All secondary efficacy endpoints will be analyzed using the mITT analysis set.

All efficacy endpoints (see section 2.1) will be summarized descriptively by treatment group. The continuous variables will be summarized descriptively by number of subjects, mean, standard

deviation, minimum, and maximum. Categorical data will be summarized descriptively by frequencies along with the associated percentages. No inferential statistics will be generated for the secondary efficacy endpoints.

4.5.5 Analysis of Secondary Safety Endpoints

The incidence of adverse events (AEs) will be assessed at the preferred term level using the Medical Dictionary for Regulatory Activities (MedDRA) for event categorization. Incidence of AEs will also be assessed by 1) onset time (intraoperative or postoperative); 2) by relationship to study surgical procedure; 3) by relationship to the; and 4) by severity.

All safety endpoints (see section 2.2) will be summarized descriptively by treatment group for the Safety analysis set using available data. There will be no missing data imputation for the safety analysis. The continuous variables will be summarized descriptively by number of subjects, mean, standard deviation, minimum, and maximum. Categorical data will be summarized descriptively by frequencies along with the associated percentages. No inferential statistics will be generated for the safety endpoints.

4.6 Statistical/Analytical Issues

4.6.1 Handling of Dropouts or Missing Data

All summaries of efficacy endpoints will be performed only on subjects who are randomized, and only observed data will be summarized. There will be no imputation for missing data or imputation of data for early terminated subjects.

4.6.2 Multicenter Studies

No adjustment for this multicenter study will be performed.

5.0 Risks and Benefits of the Study Device and Clinical Investigation

The procedure being performed with the study suture and TSA are identical to the procedure subjects would receive as part of their standard of care procedure. To date, no risks have been reported with the study device beyond standard risks associated with TKA. This study may provide benefits on free wound closure device.

6.0 Adverse Event

6.1 Definitions

6.1.1 Anticipated Adverse Events

There are immediate post-operative events that are changes from the baseline condition of the Subject, but are expected events resulting from the surgery. If these events occur, they should be recorded in the Subject's medical record and reported forward as AEs to the study sponsor.

6.1.2 Pre-existing Condition

A pre-existing condition is one that is present at the start of the study, and is to be reported as part of the subject's medical history. It must be reported as a new Adverse Event if the intensity, frequency, or the character of the condition worsens during the study treatment.

To avoid confusing pre-existing conditions with AEs during data analysis, the study sites must make all attempts to provide start dates for all baseline medical conditions. Any pre-existing condition that has worsened in intensity, frequency, or the character of the condition should be recorded on the AE eCRF as an exacerbation of the pre-existing condition and the start date will be recorded as the time when the exacerbation occurred.

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

6.1.3 Adverse Event

An AE is defined as any untoward medical occurrence, regardless of its relationship to the study device (study suture) or the study procedure (TKA). An untoward medical occurrence includes any new, undesirable medical experience or worsening of a pre-existing condition, which occurs at any point from the surgery to Final Visit.

6.1.4 Expected Morbidity/Anticipated Adverse Events

An expected morbidity/procedural complication is defined as an AE that is known to be common or usual in nature, severity, or incidence during TKA in patients with knee osteoarthritis or other diseases.

Postoperative pain and fever is expected and will not be documented as an adverse event unless the Investigator considers the pain or fever to exceed that normally anticipated following a TKA procedure.

6.1.5 Serious Adverse Event

A Serious Adverse Event (SAE) is any AE that:

- led to a death,
- led to a serious deterioration in the health of the subject that either resulted in:
 - a congenital deformity or abnormality;
 - a life-threatening illness or injury;
 - a permanent impairment of a body structure or a body function;
 - in-patient hospitalization or prolongation of existing hospitalization;
 - medical or surgical intervention to prevent life-threatening illness or injury; or
 - permanent impairment of a body structure or a body function.

Note: “Death” should not be reported as an AE. The cause of death should be reported as the AE. The only exception is “Sudden Death” when the cause is unknown.

6.1.6 Adverse Device Effect (ADE)

An Adverse Device Effect is any untoward and unintended response to a medical device. This includes any event arising from insufficiencies or inadequacies in the Instructions for Use or the deployment of the device. It also includes any event that is a result of user error.

6.1.7 Serious Adverse Device Effect (SADE)

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

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

6.1.8 Severity of Adverse Events

It is the Investigator's responsibility to assess the severity of an AE. A change in severity may constitute a new reportable AE.

The following guideline should be used to determine the severity of each adverse event:

- **MILD:** Awareness of experience, but easily tolerated. No medical intervention required.
- **MODERATE:** Enough discomfort to interfere with usual activities. Medical intervention required.
- **SEVERE:** Inability to carry out usual activities. Medical intervention (including hospitalization or prolongation of hospitalization) required.

6.1.9 Relationship of Adverse Events

It is the Investigator's responsibility to assess the relationship of an AE to the study procedure (TKA) and study device.

The following guidelines should be used in determining the relationship of an adverse event to the study device, study procedure, or other causality:

- **NOT RELATED:** The event is due to extraneous causes.
- **POSSIBLY RELATED:** The event is unlikely associated, but cannot be ruled out with certainty.
- **PROBABLY RELATED:** The event is likely associated, but another cause cannot be ruled out with certainty.
- **DEFINITELY RELATED:** The event is associated with a high degree of certainty; or
- **UNKNOWN:** The event cannot be defined by the categories listed above.

6.2 Reporting Adverse Events

Investigators are required to report all AEs experienced by subjects from the time of enrollment (defined as first incision) until the subject completes the study or terminates early. All AEs, regardless of their relatedness to the study device, must be reported in the AE eCRF. The investigator will evaluate the intensity of the event, severity of the event, and its relatedness to the study device or procedure. Any necessary medical management of the event will be recorded in the subject's medical record/source document. All AEs must be followed until resolution or until they become stable but ongoing.

The sponsor will follow CFDA's guideline to request sponsor to report the safety events including SAE/AE with timeline, which is regulated by law.

6.3 Reporting Serious Adverse Events

All of the serious adverse event must be reported to the sponsor as well as China Food and Drug Administration and local ethics committee by the site immediately (within 24 hours) after the site becomes aware of the information by entering the data into the AE eCRF.

The Sponsor will report any suspected serious adverse events to the regulatory authorities (including CFDA), within the required timeframes of five working days for SAEs that are fatal, and fifteen working days for all other SAEs. Given the observational nature of this study, the Sponsor will not monitor or enforce adherence to CFDA reporting for non-██████ products.

7.0 Product Complaints

7.1 Product Complaints Definition

A product complaint is defined as any written, electronic or oral communication that alleges

deficiencies related to the identity, labeling, quality, durability, reliability, safety, effectiveness, or performance of a device (i.e., Barbed suture) after it is release for distribution (policy of Johnson and Johnson Medical Device Quality management). A product complaint may or may not be associated with an AE/SAE.

Product complaints may include, but are not limited to:

- a) Product contamination;
- b) Defective components;
- c) Poor packaging or product mix-up;
- d) Device malfunction, which is the failure of a device to perform as intended for this study;
- e) Labeling concerns
- f) User errors.

7.2 Reporting Product Complaints

All product complaints related to the study (barbed suture/TSA/traditional suture) shall be documented throughout the clinical investigation.

Product complaints related to the study (barbed suture/TSA/traditional suture) must be reported to the Sponsor in a timely manner and no later than 24 hours after becoming aware of the event.

The Product Complaint Form must be faxed to China CHU at the following [REDACTED]
[REDACTED] One copy of the processed form should be kept on-site with the device concerned, and the device should be retained. [REDACTED] and /or [REDACTED] representatives will organize collection of the device for evaluation.

7.3 Reporting Product Complaints for Non [REDACTED] Devices

In compliance with the requirements of local regulations, describing the handling of product complaints, the study site must report all product complaints of other (non-[REDACTED] marketed products/devices used in this study (e.g., knee prosthesis).

8. References

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