A multi-center, prospective, randomized study comparing surgical and economic parameters of Total Knee Replacement performed with single-use Efficiency instruments with patient-specific technique (MyKnee®) versus traditional metal instruments with conventional surgical technique.

Study Protocol

Protocol #: Efficiency-20161119

Sponsor: Medacta USA, Inc.

1 INTRODUCTION

1.1 Study Rationale

Total knee arthroplasties are a common procedure in the United States (US), designed to relieve pain and improve the quality of life in patients with advanced knee osteoarthritis. Age and obesity are major risk factors for osteoarthritis and as the US population continues to age and body mass index (BMI) levels increase, the incidence of total knee arthroplasties will increase as well.[1] In 2013, total knee arthroplasties were occurring at a rate of greater than 500,000 procedures per year and are expected to increase to 3.48 million by 2030.[2] Costs for total knee arthroplasties currently exceed $11 billion in the US alone.[1]

With the numbers of total knee arthroplasties continuing to increase, efforts are being made to cut procedural costs. One way this can be achieved is by decreasing operative times. The utilization of single-use instruments can decrease the time spent preparing for and cleaning after the surgery, thereby decreasing patient turnover time. Single-use instruments are common in ophthalmology, cardiothoracic surgery and urologic surgery, but have yet to experience much of a crossover into lower extremity surgery, including total joint arthroplasty. Mont *et al.* studied 400 procedures using single-use instruments for total knee arthroplasty, concluding that single-use instruments showed promising benefits and after further study, could play a role in increasing operating room efficiency. [2] Siegel *et al.* found that total operating room time during total knee arthroplasty was on average 30 minutes shorter for single-use instruments and saved between $480 and $600 per case. [3] The same study also suggested that single-use instrumentation may also decrease the risk of infection. There is controversy regarding some manufacturers' claims of improved clinical outcomes, surgical efficiency and decreased costs with patient-specific cutting blocks.[4] It is evident that not all patient-specific instruments from different manufacturers are equivalent, and each needs to be studied individually. This study is being conducted to evaluate the total knee replacement instrument options for a single manufacturer.

1.2 Study Treatment

The GMK single-use (Efficiency) instruments are made of medical-grade composite technopolymers that give high fatigue and abrasion resistance in addition to form versatility. The single-use instruments are shipped from the manufacturer in pre-sterilized packaging, eliminating the need to use the hospital Central-Sterile processing equipment. The reproducible sterility may potentially reduce the infection risk.

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[1] Losina E, *et al.* Cost-effectiveness of Total Knee Arthroplasty in the United States: Patient Risk and Hospital Volume. *Arch Intern Med* (2009); 169(2):1113-1122.

[2] Mont MA, *et al*. Single-Use Instruments, Cutting Blocks, and Trials Increase Efficiency in the Operating Room During Total Knee Arthroplasty: A Prospective Comparison of Navigated and Non-Navigated Cases. *J Arthroplasty* (2013); 28(7):1135-1140.

[3] Siegel Gw, *et al*. Cost Analysis and Surgical Site Infection Rates in Total Knee Arthroplasty Comparing Traditional vs. Single-Use Instrumentation. *J Arthroplasty* (2015); 30: 2271-2274

[4] Lachiewicz, PF, Henderson, RA: Patient-specific Instruments for Total Knee Arthroplasty. J Am Acad Orthop Surg, 2013: 21:513-518.

MyKnee® patient-specific cutting blocks allow the surgeon to realize his pre-operative 3D planning, based on CT or MRI images of the patient's knee. The blocks are created based on the individual patient's anatomy, his/her mechanical axis, and the surgeon's preferred reconstruction goals. The innovative concept combines the following features giving potential benefits to both the surgeon and the patient:

- Accurate bony cuts and therefore implant positioning
- No intramedullary canal violation
- Up to 60% reduction of surgical steps for bone resection and related time
- Up to 66% reduction of time and cost in washing, assembling and sterilization procedures
- Interactive 3D web planning

1.3 Study Objectives

The objectives of this study are to compare economic factors and the rate of adverse events between two types of instrumentation used for total knee replacement:

- Single-use Efficiency Instruments with Patient Specific Technique (MyKnee®)
- Traditional Metal Instruments with Conventional Surgical Technique

The data obtained from this study could be useful for surgeons, facilities, and payors to help determine appropriate instrumentation in total knee arthroplasties.

Primary Objective:

- To compare the time-saving parameters associated with the two procedures with respect to parameters such as OR preparation time, intra-operative time (OR efficiency), OR clean-up time and sterilization costs.

Secondary Objectives:

To compare the following surgical and clinical outcomes between the two study groups

- To compare correction of alignment after total knee replacement via long standing AP hip-knee-ankle x-rays.
- To compare the accuracy of tibial slope angle on a lateral knee x-ray
- To compare the number of trays sent to sterilization
- To compare the volume of estimated blood loss during the procedure
- To compare the drop in post-operative (day 1) hemoglobin and total volume of transfusions (allogeneic and/or autologous)
- To compare the occurrence of adverse events
- To compare the waste weight at the end of each surgery, considering separately those recyclable and those not recyclable.
- To compare the rate of intraoperative and post-operative complications
- To compare the rate of successful use of MyKnee® cutting blocks (i.e. the incidence of surgical cases where the surgeon did not need to abort the use of MyKnee intra-operatively and default to the use of standard cutting blocks.

The cost-per-minute value based on hospital estimates will be used to calculate an overall cost-savings total.

2 STUDY DESIGN

The study is a multi-center, prospective, randomized study comparing surgical and economic parameters of Total Knee Replacement performed with single-use Efficiency instruments with patient-specific technique (MyKnee®) versus traditional metal instruments with conventional surgical technique. The objective is to evaluate the impact of single-use instrumentation versus traditional metal instruments in reducing overall surgical costs and improving mechanical axis alignment. The timing of routine surgical phases will be measured, including the pre-operative preparation time, intra-operative phase, OR clean-up time and sterilization phase in 300 adult patients undergoing total knee replacement. AP and lateral x-rays will be utilized to assess the implant's mechanical axis alignment and tibial slope after discharge to the completion of the 6 week visit. Additionally, other parameters will be recorded including blood loss, post-op day 1 hemoglobin drop, adverse events, number of trays sent to sterilization, and total waste weight at the end of each procedure, considering separately those recyclable and those not recyclable. To ensure that the minimum of 300 patients is met, 342 patients will be randomized into two treatment cohorts in a 2:1 ratio.

Group A: **Single-Use Efficiency Instruments with Patient Specific Technique (Efficiency/MyKnee®**)
Patients randomized to Group A will undergo surgery utilizing single-use Efficiency Instruments with patient-specific technique (MyKnee® patient-matched cutting blocks)

Group B: Traditional Metal Instruments with Conventional Surgical Technique (Conventional TKA)
Patients randomized to Group B will undergo conventional surgical technique utilizing traditional metal instrumentation and traditional cutting blocks (Metal)

Additional demographic information will be collected to describe the study population and to document whether the two treatment groups are clinically comparable. Data collected will include: age, gender, BMI, race/ethnicity, smoking history, and employment status, in addition to pre-operative knee history/diagnosis and degree of pre-operative knee malalignment and Kellgren-Lawrence grade.

3 PATIENT RECRUITMENT AND SAMPLE SIZE

The study participants will be recruited from the patients receiving care with one of the study investigators or their practice partners. Participating clinicians and their staff will be notified of this protocol and will be asked to refer patients undergoing total knee arthroplasty.

342 patients will be enrolled and randomized with 2:1 ratio, MyKnee/Efficiency (n = 228) : Conventional/Metal (n = 114).

3.1 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the study prior to enrollment and randomization. Subjects must meet all inclusion criteria and none of the exclusion criteria to be eligible for the study.

3.1.1 Inclusion Criteria

In order to be eligible for participation in this study, the patient must meet all of the following inclusion criteria:

1) Age 18 to 75 years
2) BMI ≤ 40
3) Undergoing unilateral total knee arthroplasty due to osteoarthritis (primary or post-traumatic OA)
4) Able and willing to give consent and to comply with study requirements, including follow up visit at 6 weeks

3.1.2 Exclusion Criteria

The subject must be excluded from participating in the study if the subject meets any of the following exclusion criteria:

1) Pregnant women or those seeking to become pregnant. Pregnancy test is administered prior to surgery as part of routine care by the hospital / surgery center for all female patients of childbearing potential
2) Is participating in another clinical study
3) Has inflammatory arthritis
4) Has knee avascular necrosis
5) Has severe deformity, defined as greater than 15 degrees varus or valgus relative to the mechanical axis.
6) Has retained hardware in the knee that requires removal or interferes with TKA procedure

3.2 Study Procedures

Patients who are undergoing a unilateral total knee arthroplasty and meet all of the inclusion/exclusion criteria will be approached to participate in the study. If consent is obtained the study coordinator will be notified. The coordinator will randomize the patients in a 2:1 ratio to one of the two treatment cohorts (i.e., total knee arthroplasty utilizing Efficiency instruments with patient specific technique (MyKnee®) or total knee arthroplasty with traditional metal instruments with conventional surgical technique respectively).

Preoperatively, subjects randomized to Group A (Efficiency/MyKnee®) will undergo a pre-operative CT scan or MRI as standard of care. The investigator will perform appropriate pre-operative planning which enables the custom manufacturing of the MyKnee® cutting blocks that will be delivered to the surgical facility. Subjects randomized to Group B (Conventional TKA) will undergo imaging required for preoperative planning as deemed standard of care by the investigator.

At the next visit all subjects will undergo the total knee arthroplasty procedure utilizing the assigned instrumentation. Timing of various operative and sterilization phases will be recorded. Following the procedure, the patient will undergo X-rays after discharge to the completion of the 6 week visit to examine the alignment of the implant.

3.2.1 **I**

nformed Consent

Individuals who agree to participate in this study will be asked to provide formal written informed consent. A signed copy of the informed consent form will be given to the patient, and the original will be maintained in the patient file.

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/EC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

3.2.2 **R**

andomization

Patients will be randomized using a computer generated blocked randomization with 2:1 allocations to the single-use Efficiency instruments (and MyKnee) versus traditional metal instruments (conventional TKA) groups. The randomization will be performed separately for each site.

In case the investigator decides not to include the patient after randomization, this patient will be treated as withdrawn although a randomization has been performed. The reason for withdrawal must be documented in the patient file. The used randomization number cannot be used again. For the next patient, the following randomization number will be used.

3.2.3 P

rotocol Deviations

Protocol deviations will be recorded and will capture the date of deviation, associated study visit, and type of deviation. Types of deviations are as follows:

- Consent procedures
- Inclusion/exclusion criteria
- Study procedures
- Serious adverse event / unanticipated adverse device effect (SAE/UADE) reporting
- Randomization procedures
- Visit schedule / window
- Other (site will be requested to specify)

3.3 Evaluation Parameters

Time of Operative Phases

The time of the following pre-operative, operative and sterilization phases will be recorded (hh:mm:ss):

1. Surgery Room Preparation and Clean-up Phase
    a. Instrument preparation for surgery from stock to Operative Room (OR)
    b. Surgical table preparation
    c. Instrument collection after surgery for sterilization

2. Intra-operative Phase
    a. Patient OR time
    b. Skin-to-skin time
    c. Femoral and tibial resection times
    d. Tourniquet time

3. Sterilization Phase
    a. Instrument transportation to the sterilization unit
    b. Instrument reception
    c. Instrument cleaning before sterilization
    d. Instrument decontamination before sterilization
    e. Instrument sterilization
    f. Instrument collection after sterilization
    g. Instrument transportation to stock

Additional Operative Parameters

1. Estimated blood loss (cc)
2. Drop in post-operative hemoglobin (measured at Day 1 or discharge if patient does not stay overnight)
3. Total volume of transfusions (allogeneic and/or autologous)

4. Number of trays sent to sterilization
5. Waste weight at the end of each surgery; recyclable and non-recyclable (grams)

Radiographic Parameters

Each subject will undergo the following radiographic assessments pre-operatively and at 6 weeks post-operatively.

- Long standing (hip to ankle) AP x-ray to assess the mechanical axis alignment
- Standard lateral x-ray to assess tibial posterior slope

Subjects randomized to Group A (Efficiency/MyKnee®) will also undergo a preoperative CT or MRI.

Accuracy will be determined by the difference between the final position on the post-operative x-rays and the surgeon's intended position (usually 0 degrees of mechanical axis on AP, and recreation of tibial slope on the lateral x-ray).

Adverse Events

All operative and post-operative adverse events, whether voluntarily reported by the patient or observed by the investigator, will be recorded in the patient's study records.

3.4 Study Visits

Each subject will attend 3 study visits. Each visit will have specified activities as described below.

Visit 1: Baseline (-1 to -90 days prior to surgery)

The baseline visit will occur to screen subjects, confirm study eligibility, complete the informed consent process, and enroll and randomize the subject.

- Informed consent
- Randomize patients meeting inclusion/exclusion criteria
- Collect demographics data, pre-operative knee history/diagnosis and employment status
- Visual Analog Scale (VAS) for knee pain
- Long standing AP and lateral x-rays to assess pre-operative mechanical axis alignment and posterior tibial slope. X-rays obtained within 6 months prior to surgery are acceptable for the baseline visit. The investigator may repeat x-rays if needed for clinical or imaging quality reasons.
- Complete CT scan or MRI for pre-operative planning and selection of cutting blocks (Group A Only)

Visits 2: Operative (Day 0-Discharge)

The following activities will be performed at each surgery visit.

- For all female patients of child bearing potential, pregnancy test will be administered prior to surgery as part of routine care by the hospital or surgery center.
- Surgery using instrumentation per randomization assignment
- Adverse event assessment
- Transfusion summary
- Bloodwork for hemoglobin assessment (measured at Day 1 or discharge if patient does not stay overnight)

Visit 3: 6 Weeks (± 3 weeks)

The following activities will be performed at the post-operative/discharge visit.

- Long standing AP x-ray to assess mechanical axis alignment
- Standard lateral x-ray to assess tibial slope
- Visual Analog Scale (VAS) for knee pain
- Adverse event assessment

Activity	Baseline	Operative	6 Weeks(±3)
Informed Consent	X		
Baseline Details	X		
- Medical History	X		
- Eligibility Criteria	X		
- Demographics	X		
CT Scan or MRI for Pre-Operative Planning*	X*		
Randomization	X		
Visual Analog Scale (VAS) for knee pain	X		X
Pregnancy Test		X	
Operative Details		X	
- Timing for Pre-Operative Phase		X	
- Timing for Intra-Operative Phase		X	
- Timing for Sterilization Phase		X	
- Other Operative Parameters		X	
Adverse Events		X[1]	X[1]
Long Standing and Lateral Knee X-Rays	X		X

[1]If applicable
*Group A (Efficiency/MyKnee®) Only

3.5 Case Report Forms

Case Report Forms (CRFs) are to be completed for all subjects.

All data is collected on study source documents and entered into the Case Report Forms by the Study Coordinator or delegated designee. All data will be reviewed for consistency and correctness with the protocol by the Investigator (or designee) and the Clinical Research Associate (CRA). All discrepancies requiring verification via an examination of the source documents will be sent to the study site for resolution or resolved during monitoring visits. During monitoring visits, the CRA will review all data, evaluate for completeness and have the site enter missing information and/or resolve errors. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee.

3.6 Study Documents

The following documents will be required by each site prior to activation:

- Signed protocol signature page
- Signed and dated written approval from the IRB of the protocol, informed consent form, and any applicable recruiting materials
- Signed investigator's agreement
- Financial disclosure form
- Signed and dated Delegation of Authority log
- Curriculum Vitae and medical licenses of applicable study staff

4 STATISTICAL ANALYSIS PLAN

The Sponsor will evaluate for non-inferiority based on economic factors and the rate of adverse events between the two groups. The Sponsor may conduct additional post-hoc analyses of the study data after study completion. These analyses may be done for the purposes of publication or in conjunction with additional data that may be available to Sponsor from other sources.

4.1 Data Analysis

The objectives of this study are outlined in Section 1.3. For purposes of this study, economic outcomes of interest include the peri-operative time, intra-operative time (OR efficiency), and sterilization times as quantitative values. These outcomes will be subsequently used in comparative cost analyses. The secondary objectives are to assess the accuracy of mechanical axis alignment and posterior tibial slope after total knee replacement, additional operative parameters, and adverse events.

Descriptive statistics, specifically means will be used to summarize the peri-operative, intra-operative and sterilization time data.

The primary objective will be met by comparing mean values of each of the time-saving parameters. The null hypotheses of no differences in mean values between re-usable and single-use devices will be tested using separate t-tests for two independent groups for each endpoint. A p-value of less than 0.05 will be considered significant for each endpoint. Endpoints with statistically significant differences are expected to contribute to expected cost differences to be determined in subsequent analyses.

Descriptive analyses as well as similar two-sample comparisons will be used to evaluate secondary measures.

4.2 Sample Size Analysis

Sample size for this study was determined on the basis of device group differences observed in the Mont et al 2013 study for four (related) but important health care utilization endpoints. The table below summarizes the data in Table 2 of Mont et al, but also provides a summary of the comparisons between single-use and re-usable pooling over whether or not navigation was employed. These data were used to approximate the expected effect size (standardized mean difference) comparing between single-use vs re-useable instruments. The sample sizes required for a two sample t-test to obtain 80%, 85%, and 90% power as a function of the observed pooled effect sizes were determined. The effect sizes were derived from the reported mean differences and p-values. The maximum sample size per group required to achieve at least 80% statistical power to reject the null hypothesis of equal group mean was determined across the four outcomes summarized in Table 2. For the 2:1 allocation between the single-use Efficiency instruments with MyKnee versus traditional metal instruments, this sample size was 200:100 or total N=300. This value was increased by 14% to N=342 to account for uncertainty in the estimated effect sizes, to account and to allow for additional analyses of economic outcomes. Therefore, 228 and 114 patients will be randomly allocated into single-use Efficiency instruments and traditional metal instruments arms respectively.

Sample Size Analysis for Main Effect of Traditonal vs Single-Use Devices

		Traditional		Single-Use				Analysis				
Outcome	Navi.	patients	Mean	patients	Mean	Mean Differnce (d)	p-value	SD from means and p-value	Effect Size = d/SD	N total 2:1 (80%)	N total 2:1 (85%)	N total 2:1 (90%)
Instrument Set-up Time	No	96	36.61	95	33.56	3.050	0.002	6.82	0.447			
	Yes	97	39.00	100	35.96	3.040	0.042	10.49	0.290			
	Comb.	193	37.42	195	34.43	2.985		8.66	0.345	300	340	400
Instrument Cleanup	No	96	16.43	95	13.59	2.840	0.001	5.96	0.476			
	Yes	97	24.96	100	20.09	4.870	0.011	13.44	0.362			
	Comb.	193	20.50	195	16.75	3.752		9.72	0.386	240	275	320
Combined	No	96	53.04	95	47.15	5.890	0.001	12.37	0.476			
	Yes	97	63.96	100	56.05	7.910	0.001	16.87	0.469			
	Comb.	193	57.92	195	51.18	6.737		14.63	0.460	180	195	225
Surgical Episode Time	No	96	100.58	95	97.11	3.470	0.100	14.58	0.238			
	Yes	97	128.51	100	119.61	8.900	0.001	18.98	0.469			
	Comb.	193	113.43	195	107.54	5.893		16.79	0.351	290	330	385

5 BENEFIT / RISK PROFILE

5.1 Potential Benefits

Results of this study will be helpful in evaluating the impact of single-use instrumentation versus traditional metal instruments on overall surgical cost reduction and improving mechanical axis alignment improvement when using patient-matched cutting blocks. The study will provide the initial data to understand the health economic impact of the Efficiency single-use instrumentation when using MyKnee® patient-matched cutting blocks.

5.2 Possible Risks

It is not expected that the possible risks will increase with the instrumentation options. All risks are anticipated with total knee replacement surgery and surgery in general. The following risks and discomforts may occur and are considered anticipated in connection with total knee arthroplasty procedures at the time of the operation:

- Complication from Anesthesia
- Allergic Reaction
- Hemorrhage (Bleeding)
- Immunologic Response
- Deep Vein Thrombosis
- Pulmonary Embolism
- Vascular Damage
- Nerve Damage
- Fat Emboli Syndrome

The following risks and discomforts may occur with reusable or single-use instrumentation:

- Instrument Breakage
- Instrument Malfunction
- Retention of foreign body

6 ADVERSE EVENTS

6.1 Adverse Event Definition

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. For the purposes of this study, AE's will include any complications that may be routinely observed with total knee arthroplasty, such as infection, prosthesis loosening, etc. AE's will be noted within the research database whenever the Investigator is aware of them.

Adverse event collection will begin from the time of first incision. All medical events and conditions that occur prior to this time point are to be captured as pre-existing conditions in the patient's medical history. Adverse event collection will conclude at the completion of the final follow-up visit.

Observed and reported adverse events shall be recorded in the patient's study records and on the Adverse Event Form within 48 hours of the site becoming aware of each event, and must include the following information at minimum:

- Event Description
- Date of Onset
- Date of Resolution
- Severity (mild, moderate, severe)
- Seriousness
- Relationship to surgery (definitely, probably, possibly, unlikely, not related)
- Relationship to instrumentation (definite, probable, possible, unlikely, not related)
- Event treatment (e.g., none, non-drug therapy, medications, surgery)
- Outcome

Significant new information and updates will continue to be captured in the patient's records as they become available. The investigator will follow each subject who experiences an AE until the event resolves or no further improvement is expected. If the AE has not resolved by the time of the subject's completion, the AE will be listed as ongoing at the time of subject discontinuation.

6.2 Assessment of Severity

The severity of the adverse event is classified as mild, moderate or severe.

- Mild: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.

- Moderate: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.

- Severe: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

6.3 Relationship to Surgery/Instrumentation

The investigator will evaluate the relationship of the adverse event to the research intervention according to the following definitions. The term "treatment-related," as it pertains to adverse events, means that the event was or may have been attributable to the treatment, or that the treatment was or may have been a factor in an event, including those occurring as a result of malfunction, poor manufacture, inadequate labeling, or improper design.

- Definitely

The adverse event is clearly related to the research intervention: the adverse event has a temporal relationship to the administration of the research intervention, follows a known pattern of response, or is otherwise logically related to the intervention, and no alternative cause is present.

- Probably

The adverse event is likely related to the research intervention: the adverse event has a temporal relationship to the administration of the research intervention, follows a known or suspected pattern of response, or is otherwise logically related to the intervention, but an alternative cause may be present.

- Possibly

The adverse event may be related to the research intervention: the adverse event has a temporal relationship to the administration of the research intervention, follows a suspected pattern of response, or is otherwise logically related to the intervention, but an alternative cause is present.

- Unlikely

The adverse event is doubtfully related to the research intervention: the adverse event has a temporal or other relationship to the administration of the research intervention, but follows no known or suspected pattern of response, and an alternative cause is present.

- Not Related

The adverse event is clearly NOT related to the research intervention: the adverse event has no temporal or other relationship to the administration of the research intervention, follows no known or suspected pattern of response, and an alternative cause is present.

6.4 Serious Adverse Events

A serious adverse event (SAE) is any adverse event that:

- Results in death;
- Is life-threatening; the subject was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient;
- Results in hospitalization (initial or prolonged);
- Results in disability or permanent damage; the event resulted in a substantial disruption of the person’s ability to conduct normal life functions;
- Results in a congenital anomaly or birth defect;

- Requires intervention to prevent permanent impairment or damage; medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure.
- Results in any other serious, important medical events; the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes.

In case of Serious Adverse Events (SAE), the Investigator must notify the Sponsor or its representative using the Adverse Event Form as soon as possible but at most within 24 hours **of** becoming aware of the event using the contact information below.

Sponsor Contact: Mukesh Ahuja
E-mail: mahuja@medacta.us.com
Fax: (312) 546-6881

The Investigator should provide additional information on the SAE by updating the information on the Adverse Event Form and CRF as updates become available. The Sponsor may also ask for additional clinical reports including redacted source documents to be provided by the Investigator to assist in the assessment of the event. Significant new information and updates should continue to be submitted promptly to the Sponsor and entered on the Adverse Event CRF as they become available, and the Investigator should follow the SAE until it is resolved or no further improvement is expected.

New SAEs will only be documented for each patient until the last study-related clinic visit.

6.5 Unanticipated Adverse Device Effects

An UADE is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device/product, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol or application, or any other unanticipated serious problem associated with a device/product that is related to the rights, safety, or welfare of subject. Adverse events that might reasonably occur because of placement or attempted placement of the product or during follow-up are identified through a risk assessment and summarized in the Instructions for Use.

If Medacta determines that a UADE presents an *unreasonable risk* to study subjects, Medacta will:

- terminate the investigation, or the parts of the investigation presenting that risk, within 5 working days after making the “unreasonable risk” determination, or within 15 working days of receiving notice of the UADE
- immediately investigate and evaluate the adverse effect,
- report the results of the investigation to all reviewing IRBs and to all participating investigators within 10 working days after Medacta receiving notice of the UADE, and
- resume the study, if appropriate, as specified by the IRB.

6.6 Adverse Event Reporting

Adverse events should be reported to the overseeing IRB per the board's specified reporting requirements. The CRA or Sponsor's representative will review each IRB's reporting requirements with the site.

7 ETHICAL AND LEGAL ASPECTS

7.1 Institutional Review Board (IRB)

This trial can only be undertaken after full approval has been obtained through the IRB or Ethics Committee (EC). The approval(s) must cover the protocol and addenda, if applicable, as well as the Informed Consent Form, product brochure and manufacturer information (if applicable).

During the trial the following documents will be sent to the EC/IRB for their review:

- Changes to the product brochure and manufacturer information
- Reports of all Adverse Events that are rated serious, unexpected and associated with the study product and meet IRB reporting requirements.
- All protocol amendments and revised Informed Consent Forms (if any).

For any protocol amendments that increase subject risk, the amendment and applicable Informed Consent Form revisions must promptly be submitted to the EC/IRB for review and approval prior to implementation of the change(s).

Reports on, and reviews of the trial and its progress will be submitted to the EC/IRB by the Investigator at intervals stipulated in their guidelines.

At the end of the trial, the Investigator will notify the EC/IRB about the trial completion.

7.2 Good Clinical Practice

This trial will be conducted in accordance with the current ICH-GCP-guidelines as specified for medical devices in ISO 14155.

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

7.3 Informed Consent

Prior to entry in the study, the investigator must explain to potential subjects or their legal representatives the trial and the implications of participation. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not impact on the care the subject will receive for the treatment of his/her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that

competent authorities may access their records and authorized Sponsor's persons without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations. By signing the Informed Consent Form (ICF) the subject or legally acceptable representative is authorizing such access.

The subject will be given sufficient time to read the informed consent form and to ask additional questions. After this explanation and before entry to the trial, consent should be appropriately recorded by means of the subject's dated signature. After having obtained the consent, a copy of the Informed Consent must be given to the subject.

7.4 Confidentiality, Compliance, and Data Management

Provisions for maintaining and insuring (1) the confidentiality of data, subject records, and investigator information, (2) compliance with financial disclosure requirements, law, audit, debarment, (3) quality management system, (4) data management are set forth in the executed contract between Sponsor and participating clinical centers.

All HIPAA requirements for subject confidentiality will be maintained. All summary data shared beyond the Sponsor, Sponsor's representatives and the patients' clinical team will be de-identified. Such summary data will not contain any of the identifiable protected health information (PHI) listed below:

Data that includes any of the following identifiers are considered identifiable health information:

- Name
- Social Security number
- Medical Record Number
- Address by Street Location
- Address by Town/City/Zip Code
- Date of Birth
- Admission or Discharge Date
- Date of Death
- Telephone Number
- Fax Number
- Electronic E-Mail Address
- Web URLs
- Internet Protocol (IP) Address
- Health Plan Beneficiary Number
- Account Number
- Certificate/License Number
- Vehicle Identification Number and Serial Number, including License Plate Number
- Medical Device Identifiers and Serial Numbers
- Biometric Identifiers (finger and voice prints)
- Full Face Photographic Image
- Any Other Identifier likely to identify the subject

8 SUBJECT DISCONTINUATION / WITHDRAWAL

Consent to participate in this study is completely voluntary. Consent may be withdrawn at any time, if desired by the study participant or the investigator may choose to discontinue the subject. Reasons for discontinuation of a patient from the clinical study may be (1) insufficient cooperation of the patient (non-compliance); (2) technical or administrative reasons (e.g., change of investigator or move of patient or cancelled/postponed surgery outside of window); or (3) death. To formally withdraw consent to participate in this study, the participant will need to notify their treating physician.