ETHICON™ | Biosurgery

A Prospective, Randomized, Controlled Study Evaluating EVICEL® Fibrin Sealant as an Adjunct to Haemostasis During Abdominal, Retroperitoneal, Pelvic or Thoracic (Non-Cardiac) Surgery in Paediatric Patients

The Paediatric EVICEL® Soft Tissue and Parenchymal Organ Bleeding Study

Protocol Number: 400-12-006

Document	Effective Date
Original Protocol	**02 August 2013**
Amendment 1	**02 October 2013**
Administrative Change 1	**11 November 2013**
Administrative Change 2	**03 February 2014**
Amendment 2	**31 July 2015**
Amendment 3	**29 February 2016**
Administrative Change 3	**09 January 2017**
Amendment 4	**08 January 2018**

Sponsor:

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Compliance Statement

This study will be conducted in accordance with FDA Regulations (21 Code of Regulations Part 312), ICH Harmonised Tripartite Guideline for Good Clinical Practice (1996), the Declaration of Helsinki (1996), and the European Union Clinical Trial Directive (2001/20/EC, May 2001) and EU GCP Directive 2005/28/EC.

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Investigator Agreement:

I have read this protocol and agree to conduct the study as outlined herein.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the investigational product and the conduct of the study.

[redacted]

A Prospective, Randomized, Controlled Study Evaluating EVICEL® Fibrin Sealant as an Adjunct to Hemostasis During Abdominal, Retroperitoneal, Pelvic or Thoracic (Non-Cardiac) Surgery in Paediatric Patients

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Investigator Signature Date

Investigator Name (printed)

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A Prospective, Randomized, Controlled Study Evaluating EVICEL® Fibrin Sealant as an Adjunct to Hemostasis During Abdominal, Retroperitoneal, Pelvic or Thoracic (Non-Cardiac) Surgery in Paediatric Patients

SYNOPSIS

OBJECTIVES:	To evaluate the safety and effectiveness of EVICEL® Fibrin Sealant (Human) as an adjunct to achieve haemostasis during surgery in paediatric patients.
STUDY DESIGN:	This is a prospective, randomized, controlled, clinical study comparing EVICEL® to SURGICEL®, as an adjunct to haemostasis when conventional methods of controlling bleeding are ineffective or impractical during surgery in paediatric patients. At least 40 qualified paediatric subjects with an appropriate mild or moderate Target Bleeding Site (TBS) will be randomized in a 1:1 allocation ratio to either EVICEL® or SURGICEL®. Haemostasis will be assessed at 4, 7 and 10 minutes from randomization. Subjects will be followed post-operatively through hospital discharge and at 30 days (±14 days) post-surgery.
TBS DEFINITION:	The TBS is the first actively bleeding site identified in the soft tissue or a parenchymal organ with mild or moderate bleeding, where conventional methods of control are ineffective or impractical, and an alternative method is required to achieve haemostasis. The TBS must be an area that can be visualised to assess haemostasis and where EVICEL® can be applied across the whole bleeding surface in a thin layer. (Refer to investigator's brochure.)
BLEEDING SEVERITY:	**Mild Bleeding:** a TBS with a small area of capillary, arteriole or venule oozing. **Moderate Bleeding:** a TBS with a larger area of capillary, arteriole, or venule oozing that presents a significant challenge because of the larger area involved, increasing the volume of blood loss, or a TBS with bleeding that is more pronounced than oozing, that could also come from a small artery or vein, but is not massive. **Severe Bleeding (EXCLUDED FROM THIS PROTOCOL):** (arterial, venous, or mixed) that is rapidly flowing, pulsatile or spurting that in the surgeon's judgment requires rapid control to prevent haemodynamic consequences (e.g. hypovolemia, tachycardia, or hypotension) and could involve major volume loss which if not treated rapidly could be life threatening. EVICEL® should not be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial bleeding.
PROCEDURE:	The TBS will be identified during the dissection (soft tissue or parenchymal organ) related to the primary operative procedure. This will be the site assessed for haemostatic effectiveness.

	Once the TBS is identified, the surgeon will immediately randomize the subject into the study. The randomly assigned treatment (EVICEL® or SURGICEL®) will be applied immediately at the actively bleeding TBS. **Randomized Subjects** After placement of the assigned study treatment (EVICEL® or SURGICEL®), there will be an observation period during which the TBS will be assessed at 4, 7 and 10 minutes from randomization. *SURGICEL® must not be lifted or disturbed when assessing for haemostasis.* • Time to Hemostasis (TTH), from the time of randomization, is recorded once Haemostasis is achieved. Haemostasis will be defined as no detectable bleeding from the TBS at any time point. • If haemostasis is achieved before four minutes (<4 mins), between four and seven minutes (>4 and <7 mins), seven and ten minutes (>7 and 10< mins) or after 10 minutes, the absolute time to haemostasis must be recorded. • In the event of bleeding at the TBS during the ten-minute observational period (in either treatment or control group) that requires further haemostatic measures other than re-application of the assigned haemostatic adjunct (EVICEL® or SURGICEL®), the surgeon should perform these measures, and record the subject as a treatment failure for the endpoint "Incidence of treatment failures". • If re-bleeding occurs at the TBS after haemostasis has been achieved, any re-bleeding should be treated by the randomised study product, if clinically appropriate or per the surgeon's standard of care. This should be recorded as an adverse event. If additional soft tissue or parenchymal organ bleeding sites are identified, the surgeon may treat with the same treatment product according to the subject's randomization assignment, if clinically appropriate or their preferred standard of care. Haemostatic assessment of these additional bleeding sites will not be recorded.
TEST PRODUCT:	EVICEL® Fibrin Sealant (Human)
STUDY POPULATION:	Paediatric subjects, undergoing non-emergent abdominal, retroperitoneal, pelvic or thoracic (non-cardiac) surgery procedures, wherein an appropriate TBS is identified. Paediatric subjects for this study are defined as: • Neonates (birth to 30 days) with pre-term neonates born ≤37 weeks gestation included within this group; • Infants and toddlers (31 days to <24 months); • Children (2 to 11 years); and • Adolescent (12 to 18 years).

PRIMARY ENDPOINT:	Absolute time to haemostasis, defined as absolute time when there is no detectable bleeding at the Target Bleeding Site (TBS).
SECONDARY ENDPOINTS:	• Haemostasis at 4, 7 and 10 minutes following randomization; • Incidence of treatment failures (defined as haemostasis not achieved within 10 minutes or bleeding at the TBS during the ten-minute observational period that requires further haemostatic measures other than re-application of the assigned haemostatic adjunct); • Incidence of adverse events (including thrombotic events and events associated with TBS re-bleeding); • Proportion of subjects with no- rebleeding; and • Haemoglobin, Haematocrit, Platelets, Volume of blood loss, Volume of blood and blood products transfusions.
SAFETY:	Adverse events will be collected from time of randomization, throughout the follow-up period of 30 (± 14) days. Intra-operative bleeding at the TBS after 10 minutes will be an adverse event.
STATISTICAL ANALYSIS:	No formal sample size determination was performed for this study; however, a total of at least 40 randomized subjects, is considered adequate to provide sufficient information to evaluate data descriptively. For each treatment group, the continuous data will be summarised by number of subjects, mean, median and standard deviation (SD). The categorical data for each treatment group will be summarised by frequency along with associated percentages. Two-sided 95% confidence intervals (CIs) for median absolute time to hemostasis will be reported separately for EVICEL® and SURGICEL® groups. The two-sided 95% confidence interval for the proportion of subjects achieving hemostasis will be reported for each treatment group for binary hemostsis secondary endpoints (4, 7 and 10 minute endpoints).
SAMPLE SIZE:	At least 40 randomized subjects, recruited from sites within the European Union and Canada.
SURGICAL PROCEDURES:	Laparoscopic or open surgical procedures with challenging mild or moderate **soft tissue or parenchymal organ** target bleeding sites appropriate for evaluation in this study include, but are not limited to: • Abdominoperineal resections; • Retroperitoneal tumour resections • Hepatic or renal procedures
INCLUSION CRITERIA	***Pre-operative**:* 1. Paediatric subjects birth to <18 years of age, requiring non-emergent laparoscopic or open abdominal, retroperitoneal, pelvic or thoracic (non-cardiac) surgical procedures. 2. The subject and/or subject's parent or legal guardian must be willing to give permission for the subject to participate in the trial, and provide written

	informed consent for the subject. If possible, assent must be obtained from paediatric subjects who possess the intellectual and emotional ability to comprehend the concepts involved in the trial. If the paediatric subject is not able to provide assent (due to age, maturity and/or inability to intellectually and/or emotionally comprehend the trial), the parent/legal guardian's written informed consent for the subject will be acceptable for the subject to be included in the study. ***Intra-operative*** 3. Presence of an appropriate mild or moderate bleeding soft tissue or parenchymal organ TBS identified intra-operatively by the surgeon.
EXCLUSION CRITERIA	***Pre-operative*** 1. Subjects with known intolerance to blood products or to one of the components of the study product or is unwilling to receive blood products; 2. Female subjects, who are of childbearing age (i.e. adolescent), who are pregnant or nursing; 3. Subject is currently participating or, during the study is planned to participate in any other investigational device or drug trial without prior approval from the Sponsor; 4. Subjects who are known, current alcohol and/or drug abusers; 5. Subjects admitted for trauma surgery; 6. Subjects with any pre or intra-operative findings identified by the surgeon that may preclude conduct of the study procedure; ***Intra-operative*** 7. Subject with TBS in an actively infected field (Class III Contaminated or Class IV Dirty or Infected)[1]; or 8. Anastomotic bleeding sites will not be considered for randomization.

[1] See Appendix 1

SCHEDULE OF EVENTS

Procedures	**Screening** (within 21 days prior to procedure)	**Baseline** (within 24 hours prior to procedure)	**Surgical Procedure**	**Post-Surgery to Hospital Discharge** (within 72 hours prior to discharge)	**30-Day Follow Up** (±14 days)[4]
Inclusion / Exclusion	**X**	**X**	**X**		
Informed Consent / Assent (as applicable)	**X**				
Demographics	**X**				
Medical and Surgical History	**X**	**X**[2]			
Concomitant Medications		**X**	**X**	**X**	**X**
Physical Exam	**X**			**X**	
Full Blood Count (FBC) with Differential	**X**[3]	**X**[3]		**X**	
Coagulation (PT, aPTT, INR)	**X**[3]	**X**[3]		**X**	
Pregnancy Tests (if applicable)		**X**			
Randomization			**X**		
Treatment Application and Haemostasis assessment			**X**		
Determination of Haemostasis at TBS			**X**		
Use of other haemostatic measures at the TBS			**X**		
Bleeding or thrombotic events			**X**	**X**	**X**
Adverse Events			**X**	**X**	**X**
Operative/Surgical information[4]			**X**	**X**	

[2] Review for changes in medical history from screening visit.
[3] At least one FBC with differential, coagulation parameter, and pregnancy test are needed pre-procedure. If pre-operative blood tests are repeated, the blood test closest to the date prior to surgery will be used.
[3] Including length of stay and transfusion information.
[4] Visit can be conducted via telephone.

1. INTRODUCTION

Bleeding during surgical procedures may manifest in many forms. It can be discrete or diffuse from a large surface area. It can be from large or small vessels; arterial (high pressure) or venous (low pressure) of high or low volume. It may be easily accessible or it may originate from difficult to access sites. The bleeding tissues may be firm or friable.

Conventional methods to achieve haemostasis include use of surgical techniques, sutures, ligatures or clips, and energy-based coagulation or cauterisation. When these conventional measures are ineffective or impractical, adjunctive haemostasis techniques and products are typically utilised, including topical absorbable haemostats such as oxidised regenerated cellulose, gelatin, or collagen and active haemostats such as topical thrombin or fibrin sealants.

Fibrin sealants are typically dual component systems consisting of virus-inactivated, human plasma-derived thrombin and fibrinogen. The two components are mixed during application to a target site and upon combination mimic the final step in the coagulation pathway to form a stable, physiological fibrin clot that assists in healing[i]. The fibrinogen component may also contain anti-fibrinolytic agents. Fibrin sealants have proven to be valuable adjuncts for haemostasis in a variety of surgical and endoscopic procedures. They have been successfully used as biodegradable topical agents for haemostasis, wound healing, or tissue sealing purposes in cardiovascular, thoracic, neurologic, gastrointestinal, urologic, gynaecologic, hepatic and plastic and reconstructive surgical procedures[ii,iii,iv,v,vi]. They have also been evaluated in bleeding from soft tissue tumour beds or parenchymal organs following surgical resection[vii]. Fibrin sealants have been shown to reduce post-operative complications, including blood loss and reduce the need for repeated procedures by promoting wound healing[viii].

EVICEL® is a topical haemostat and will be evaluated in this study to measure its safety and effectiveness in controlling mild/moderate bleeding from soft tissue as required by the Paediatric Investigational Plan.

The Product

CROSSEAL (US)/QUIXIL (EU), the predecessor of EVICEL®, was previously launched in the United States (US) and EU in 2003 and 1999, respectively. EVICEL® was approved in the US in June 2006 as a manufacturing supplement to the CROSSEAL BLA (BLA # 1603), at which time the antifibrinolytic agent tranexamic acid was removed and the proprietary name changed to EVICEL®.

EVICEL® is manufactured by Omrix biopharmaceuticals Ltd., Israel and is approved for marketing in the many countries worldwide. In the European Union (EU), EVICEL® is approved for use as an adjunctive treatment in surgery where standard surgical techniques are insufficient for improvement of haemostasis. EVICEL® is also indicated as suture support for haemostasis in vascular surgery and for suture line sealing in dura mater closure. In the US, the approved indication is as an adjunct to haemostasis for use in patients undergoing surgery, when control of bleeding by standard surgical techniques is ineffective or impractical.

EVICEL® is a human plasma derived fibrin sealant consisting of two components: (1) Biologically Active Component 2 (BAC2), a concentrate of human clottable protein (containing mainly human fibrinogen), and (2) Human Thrombin. Please refer to the Investigator Brochure for the application of EVICEL®.

The safety and efficacy of EVICEL® (and its predecessor - Crosseal/Quixil) has been investigated in several clinical trials in different clinical settings (retroperitoneal or intra-abdominal, liver, orthopaedic and vascular surgery). Information from these clinical studies indicated no particular safety concerns.

2. STUDY OBJECTIVES

To evaluate the safety and haemostatic effectiveness of the EVICEL® versus SURGICEL® in controlling mild or moderate soft tissue or parenchymal organ bleeding during abdominal, pelvic, retroperitoneal or thoracic (non-cardiac) surgery.

The primary endpoint will be the absolute time to haemostasis, defined as the absolute time when there is no detectable bleeding at the Target Bleeding Site (TBS).

The secondary endpoints of this study include:

- Haemostasis at 4, 7 and 10 minutes following randomization;
- Incidence of treatment failure (defined as haemostasis not achieved within 10 minutes);
- Incidence of adverse events (including thrombotic events and events associated with TBS re-bleeding);
- Proportion of subjects with no- rebleeding; and
- Haemoglobin, Haematocrit, Platelets, Volume of blood loss, Volume of blood and blood products transfusions.

3. OVERVIEW OF STUDY DESIGN

This is a multicentre, prospective, randomized, controlled, study in paediatric patients evaluating the safety and effectiveness of EVICEL® compared with SURGICEL® to control mild or moderate bleeding in soft tissue or parenchymal organ for which standard methods of achieving haemostasis are ineffective or impractical.

Eligible subjects will be randomized in a 1:1 allocation ratio to either EVICEL® or SURGICEL® treatment. The randomly assigned treatment (EVICEL® or SURGICEL®) will be applied at the actively bleeding TBS. Subjects will be followed post-operatively through discharge and at 30 days (±14 days) post-surgery.

Ongoing safety assessment will ensure adequate safety monitoring occur during enrolment..

3.1 Target Bleeding Site (TBS) Identification

For this study, the target bleeding site (TBS) will be identified during the soft tissue or parenchymal organ dissection, related to the primary operative procedure.

For instance, the TBS might be the retroperitoneal bed during or following nephrectomy or the pelvic wall during low anterior resection of the colon or within a parenchymal organ during dissection or resection).

Parenchymal organs which are eligible for inclusion are: *Kidney, Liver, Pancreas and Spleen*
Soft Tissue includes but may not be limited to the following tissue types: *Muscle*, *Lymph node beds*, *Lymphatic Tissue, Fatty tissue Loose Areolar Connective Tissue*

For this study, the TBS will be defined as the FIRST actively bleeding site identified during the soft tissue or parenchymal organ dissection related to the primary operative procedure with challenging mild to moderate bleeding, where conventional methods of control (i.e. suture, ligature, cautery) have been deemed ineffective or impractical, and require an alternative method to achieve haemostasis. The TBS

must be a site where occlusion of the injured tissue or parenchymal organ surface blood vessels is required to achieve haemostasis.

As a frame of reference, the following scale of bleeding intensity will be utilised. Only target bleeding sites with mild or moderate bleeding as defined by this scale will be randomized:

Mild Bleeding: A TBS with a small area of capillary, arteriole or venule oozing.

Moderate Bleeding:

1. A TBS with a **larger area** of capillary, arteriole, or venule oozing that presents a significant challenge because of the larger area involved, increasing the volume of blood loss.
   Or
2. A TBS with bleeding that is more pronounced than oozing, that could also come from a small artery or vein, but is not massive, pulsatile, and flowing.

Severe Bleeding (EXCLUDED BY THIS PROTOCOL):

Bleeding (arterial, venous, or mixed) that is rapidly flowing, pulsatile or spurting that in the surgeon's judgment requires rapid control to prevent haemodynamic consequences (e.g. hypovolemia, tachycardia, or hypotension) and could involve major volume loss which if not treated rapidly could be life threatening. EVICEL® should not be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial bleeding.

4 STUDY POPULATION

4.1 General Considerations

The Investigator is expected to invite all subjects expected to meet the study entry criteria to participate in the study.

4.1.1 Inclusion Criteria

Pre-operative:

1. Paediatric subjects birth to <18 years of age, requiring non-emergent laparoscopic or open abdominal, retroperitoneal, pelvic or thoracic (non-cardiac) surgical procedures.
2. The subject and/or subject's parent or legal guardian must be willing to give permission for the subject to participate in the trial, and provide written informed consent for the subject. If possible, assent must be obtained from paediatric subjects who possess the intellectual and emotional ability to comprehend the concepts involved in the trial If the paediatric subject is not able to provide assent (due to age, maturity and/or inability to intellectually and/or emotionally comprehend the trial), the parent/legal guardian's written informed consent for the subject will be acceptable for the subject to be included in the study.

Intra-operative

3. Presence of an appropriate mild or moderate bleeding soft tissue or parenchymal organ Target Bleeding Site identified intra-operatively by the surgeon;

4.1.2 Exclusion Criteria

Pre-operative

1. Subjects with known intolerance to blood products or to one of the components of the study product or is unwilling to receive blood products;

2. Female subjects, who are of childbearing age (i.e. adolescent), who are pregnant or nursing;

3. Subject is currently participating or, during the study is planned to participate in any other investigational device or drug trial without prior approval from the Sponsor;

4. Subjects who are known, current alcohol and/or drug abusers;

5. Subjects admitted for trauma surgery;

6. Subjects with any pre or intra-operative findings identified by the surgeon that may preclude conduct of the study procedure;

Intra-operative

7. Subjects with TBS in an actively infected field (Class III Contaminated or Class IV Dirty or Infected)[5]; or

8. Anastomotic bleeding sites will not be considered for randomization.

5 RANDOMIZATION

Randomization will be used to avoid bias in the assignment of treatment to each subject, to increase the likelihood that attributes of the subject are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

ETHICON will provide each site with computer-generated randomization envelopes, each bearing the subject randomization number, and containing the treatment allocation.

Treatment will be assigned randomly to each subject on a 1:1 basis to either EVICEL® or SURGICEL® treatment.

In the event that a potential subject fails intra-operative criteria (i.e. no TBS identified, or an intra-operative exclusion), and is not randomized to the study, the unused randomization envelope should be returned to the series, and used for the next subject.

Given the difference between the EVICEL® and SURGICEL® treatment groups, it will not be possible for the surgeon to be blinded to the treatment. However, to avoid any bias in the conduct of the surgical procedure, randomization should only take place after completion of the following steps:

1. EVICEL® and SURGICEL® will be prepared and available in the sterile field in the operating room, ready for administration for each patient.
2. The investigator must perform the surgical procedure according to his/her standard of care.
3. Once the investigator encounters an appropriate soft tissue or parenchymal organ TBS related to the primary operative procedure, randomization should immediately take place.

[5] See Appendix 1

6 INVESTIGATIONAL PRODUCT AND CONTROL GROUP

6.1 EVICEL® (Treatment Group)

6.1.1 Formulation

EVICEL® is a human plasma-derived fibrin sealant. EVICEL® consists of two components: a concentrate of Human Clottable Protein (referred to as Biological Component 2; BAC2) and a solution of Human Thrombin. No material of animal origin is present in the product. A purpose-designed application device is used to apply EVICEL® to the surgical site by spraying or dripping. Said device has been designed to ensure even mixing of the two components.

Composition of EVICEL®

	Component 1(Clottable protein)	Component 2 (Thrombin)
Active Ingredient	Concentrate of human clottable protein (containing mainly human fibrinogen)	Human Thrombin
Other Ingredients	Arginine hydrochloride, Glycine, Sodium chloride, Sodium citrate, Calcium chloride, Water for injection (WFI)	Calcium chloride, Human albumin, Mannitol, Sodium acetate, Water for Injection (WFI)

6.1.2 Labelling and Packaging

The investigational product will have two vials contained within a single box. The product will be labelled according to local regulatory requirements and may contain the following information:

- Name and address of manufacturer;
- Protocol number;
- Lot/Batch number;
- Expiry date;
- EudraCT number;
- Storage conditions; and
- Statement that the product is limited for clinical trial use only.

6.1.3 Shipping, Handling and Storage Conditions

Distribution of EVICEL® to the clinical sites will be performed by a qualified distribution center with proper inventory and quality control capabilities once all the necessary documentation and approvals are obtained. For distribution in the EU, a qualified person (QP) release will be done prior to distribution.

The two components of the EVICEL® Kit are frozen, and must be stored at –18°C or colder. EVICEL® will be shipped to each site on dry ice (or other applicable method) during which the temperature will be monitored continuously. Once at the site, the product will be stored in a freezer at –18°C or colder, or in a refrigerator (2-8°C) where it will have a 30-day shelf life.

The application devices and tips will be shipped and stored at ambient temperature.

6.1.4 Application Device

The application device is commercially available in the US, Canada and several European countries. It is not considered as an investigational product. Depending on its regulatory status, the product will be labelled according to local regulatory requirements, and may contain the following information:

- Name and address of manufacturer;
- Protocol number; and
- Statement that the product is limited for clinical trial use only.

6.1.5 Accessory Tips

The accessory tips are commercially available in the US, Canada and several European countries. They are not considered as an investigational product. There will be the following accessory tips provided for use with the application device:

- 35 cm rigid tips;
- 45 cm flexible tips;
- Airless Spray Accessory
- 4 cm tip (control tip)

Any of the above mentioned accessory tips may be used, according to surgeon preference. Tips should be used in accordance with their Product Assembly Guide.

6.1.6 Pressure Regulators

Only ETHICON/Omrix pressure regulators may be used. The pressure regulators may be provided when commercially available. They will be used according to their intended Instructions for Use/Investigator Brochure and are not considered as an investigational product.

6.1.7 Preparation

The two frozen components of EVICEL® (BAC2 and Thrombin) must be thawed before use, using one of the following methods:

- 2-8°C (refrigerator): vials thaw within one day; or
- 20-25°C (room temperature): vials thaw within one hour; or
- 37°C; vials thaw within ten minutes and should not be left at 37°C for more than 10 minutes. The temperature must not exceed 37°C.

Thawed, unopened vials must be stored, at the temperature range stated within the Package Leaflet. Thawed vials must not be re-frozen.
Before use, the product must reach 20-30°C.

After thawing, preparation of the product must occur in a sterile surgical field. The two components should be drawn into the application device, following directions enclosed in the application device package. Both syringes must be filled with equal volumes, and should not contain air bubbles. Selection of the appropriate application tip will be left to the discretion of the surgeon.

6.1.8 Dose, Route and Duration of Administration

For each subject, at least one kit of EVICEL® (BAC2 and Thrombin) will be thawed and available for administration prior to randomization. EVICEL® will be sprayed or dripped onto the tissue to produce a thin, even layer. A cure time of 1-2 minutes should be allotted between applications to allow for polymerisation. The amount of EVICEL® required depends upon the area of tissue to be treated and the method of application.

Application can be made by dripping or spraying in accordance with the EVICEL® Investigator Brochure, Accessory Tip Directions and Device and Pressure Regulator Instructions for Use.

6.2 Investigational Product Dispensation and Accountability

A dispensing log will be kept by the designated study personnel. This log will contain information on the date of administration, subject ID and quantity of EVICEL® dispensed, details of any remaining product, and subsequent destruction. The study monitor will verify these logs during the course of the study.

6.3 SURGICEL® (Control Group)

For this study, SURGICEL® will be provided by the Sponsor and must be used according to the Instructions for Use.

6.4 Concomitant Medications

6.4.1 Topical Haemostats

The use of any other Topical Absorbable Haemostat (TAH) will be permitted as outlined in section 7.1.3.4 below.

Other haemostasis products, including Topical Absorbable Haemostat (TAH) and fibrin sealants, may be used at additional bleeding sites other than the TBS as necessary during the 10 minute haemostasis assessment period.

Details of all Topical Absorable Haemostats used for the subject throughout the procedure will be recorded on the Concomitant Medication eCRF.

6.4.2 Documentation of Concomitant Medications

Indication and start-stop dates of concomitant medications administered from 24 hours prior to surgery up to the follow up contact or evaluation will be recorded. This will include medications that patients are using chronically.

Anaesthetics used for surgery and over the counter (OTC) drugs will not be recorded as concomitant medication (with the exception of prophylactic aspirin, which should be documented). Concomitant medications used to treat Adverse Events must also be documented.

7 STUDY EVALUATIONS

7.1 Study Procedures

The schedule of events included in the synopsis summarises the frequency and timing of the study procedures. Data collected for the subject during the study will be recorded in the subject's medical records, and study worksheets/source documents, as appropriate, and transcribed into the eCRF.

7.1.1 Screening (Within 21 Days Prior to Surgical Procedure)

Prospective subjects will be screened within 21 days prior to surgery. Screening and baseline visits may occur at the same time. Prior to any study related procedures, subjects and/or parent or legal

representative will be fully informed of all aspects of the study. Subjects and/or their parent or legal representative will be asked to sign a Consent Form or assent as applicable.

The following tests and activities will be performed at the screening visit unless existing data from within 21 days prior to surgery is available, in which case the test/activity will not be repeated. The timing of these activities may occur based on routine hospital practice but may be done up to the day of, but prior to, surgical procedure. If blood tests required at screening are performed, only the result closest to the date of surgery will be collected.

- Informed consent/assent process, as applicable;
- Allocation of screening number;
- Review of Inclusion / Exclusion criteria to confirm subject pre-operative eligibility;
- Documentation of demography information;
- Physical examination as per institutions normal procedure;
- Documentation of relevant medical and surgical history;
- Full blood count (FBC) with differential (samples taken closest to surgery date will be recorded);
- Coagulation parameters to include prothrombin (PT), activated partial thromboplastin time (aPTT), International Normalised Ratio (INR) (samples taken closest to surgery date will be recorded);
- In the event that a subject is not eligible, the reason will be documented on the screening log.

7.1.2 Baseline Assessments (Within 24 Hours Prior to Procedure)

The following activities will be performed within 24 hours prior to the procedure. The timing of these activities may occur based on routine hospital practice.

- Review of inclusion / exclusion criteria to confirm subject pre-operative eligibility. In the event that a subject is not eligible, the reason will be documented on the source documentation and screening log.
- Documentation of all concomitant medications starting 24 hours prior to surgery. (See Section 6.4)
- Documentation of any changes in medical history from the screening visit.
- Serum or urine pregnancy test (if applicable)

Note: At least one Full Blood Count (FBC) with differential, coagulation parameter testing and pregnancy test (if applicable) are needed pre-procedure. If pre-operative blood tests are repeated, only the test closest to the date prior to surgery will be collected.

7.1.3 Surgical Procedure

The surgeon will use his/her standard surgical techniques for the surgical procedure. The TBS will be identified, and will be the only specific site or region to be evaluated for time to haemostasis in this clinical study. The following activities will be performed, and information will be collected, during the surgical procedure:

- Details of procedure including operating room/theatre time, procedure time, estimated blood loss and transfusion information (blood and blood products) (if applicable);
- Documentation of concomitant medications; and
- Adverse events from start of randomization, including any complications potentially related to bleeding and/or thrombotic events.

7.1.3.1 Pre-Randomization Procedures

EVICEL® and SURGICEL® will be prepared and available in the sterile field of the operating room, ready for administration for each patient. The investigator will perform the surgical procedure according to their standard practice.

When the surgeon encounters the first appropriate TBS with mild/moderate bleeding in the soft tissue or a parenchymal organ related to the primary operative procedure where conventional methods of control (i.e. suture, ligature, cautery) are ineffective or impractical, the subject can be considered for randomization. The following information will be recorded:

- Intra-operative confirmation of eligibility and classification of the target bleeding site (TBS);
- TBS location information, e.g. abdominal, pelvic, retroperitoneal, or thoracic (non-cardiac);
- TBS tissue type, e.g. loose areolar connective tissue, fat, lymphatic tissue/lymph node beds, muscle or other (specify); and
- TBS organ type, e.g. kidney, liver, spleen or pancreas;
- Type of bleeding, e.g. mild or moderate.

7.1.3.2 Randomization

Once intra-operative eligibility is confirmed and the TBS identified, the appropriate randomization envelope will be opened, randomization treatment called out and the stopwatch will be started. The time of randomization will be recorded (by the wall clock using 24-hour clock), this will be considered T_0.

If the subject is randomized to SURGICEL®, the unused EVICEL® treatment product **MUST** immediately be removed from the sterile field. After the procedure, accountability of the product should be documented.

If the subject is randomized to EVICEL®, the unused SURGICEL® control treatment product **MUST** immediately be removed from the sterile field. After the procedure, accountability of the product should be documented.

7.1.3.3 Treatment Application

The following procedures must be followed following randomization:

- Subjects assigned to EVICEL® should have a thin, even layer of EVICEL® applied by either dripping or spraying the product in accordance with the Investigator Brochure; or
- Subjects assigned to SURGICEL® should have SURGICEL® applied on the TBS, according to the product Instructions for Use.

7.1.3.4 Haemostasis Assessment

After placement of the assigned study treatment (EVICEL® or SURGICEL®), there will be an observation period during which the TBS will be assessed at 4, 7 and 10 minutes from randomization and for absolute time for haemostasis. **SURGICEL® must not be lifted or disturbed when assessing for haemostasis.** Once haemostasis has been achieved, excess SURGICEL may be removed according to the IFU assuring that the clot is not disturbed to avoid potential rebleeding. For additional details consult the IFU Contraindications, Warnings and Precautions sections.

- Absolute time to haemostasis (TTH from the time of randomization) is recorded once haemostasis is achieved. Haemostasis will be defined as no detectable bleeding from the TBS.
- Haemostasis is also assessed at the specified time-points (4, 7 and 10 minutes following randomization), which is outlined in the following timetable:

T_0	Start time when randomization envelope is opened
T_{APP}	Time when randomised haemostatic product (EVICEL® or SURGICEL®) is initially applied
T_4	TBS Bleeding assessment 4 minutes following randomization.
T_7	Bleeding is assessed 7 minutes after randomization
T_{10}	Bleeding is assessed 10 minutes after randomization
T_{ABS}	Exact time when absolute haemostasis has been achieved

If haemostasis is achieved before four minutes (<4 min.) after randomization, the absolute time to haemostasis must be recorded.

- If haemostasis is achieved between four and seven minutes (>4 and <7 min.) after randomization, the absolute time to haemostasis must be recorded.
- If haemostasis is achieved between 7 and ten minutes (>7 and <10 min.) after randomization, the absolute time to haemostasis must be recorded.
- If haemostasis is achieved after 10 minutes, this absolute time to haemostasis must be recorded.

Haemostasis Scenarios

- If breakthrough bleeding occurs at the TBS during the 10-minute treatment period, the surgeon may re-treat with the randomised study product, if clinically appropriate. **If the subject is randomised to EVICEL®, re-treatment must be performed according to the Investigator Brochure.**

- In the event of bleeding at the TBS during the 10 minute observational period (in either EVICEL® or SURGICEL treatment group) that requires further and immediate haemostatic measures other than re-application of the assigned haemostatic adjunct (EVICEL® or SURGICEL®), the surgeon should perform these measures, and the subject will be **a failure for the secondary endpoint "incidence of treatment failures".**

- If haemostasis is not achieved by the end of the 10 minute observational period, the surgeon may then apply the use of further haemostatic measures according to his/her preference, and record the subject as a treatment failure.

- If additional soft tissue or parenchymal organ bleeding sites are identified, the surgeon may treat with the same treatment product according to the subject's randomization assignment, if clinically appropriate. Time to haemostasis does not need to be recorded for these additional bleeding sites. **However if a subject is randomised to SURGICEL® treatment group, EVICEL® should not be used to treat any other soft tissue bleeding sites. There is no restriction on the use of SURGICEL® in the EVICEL® treatment group to treat other bleeding sites. SURGICEL® must be used per its instructions for use.**

- If re-bleeding at the TBS occurs after the 10-minute haemostatic assessment period, this can be treated with the randomised study product or the surgeon's standard of care and **must be recorded as an adverse event.**

- Any additional treatments at the TBS at any time during the procedure whether it be the randomized treatment or other clinically appropriate treatments will be recorded, including time and method of retreatment.

- Number of EVICEL® kits used; or Number of SURGICEL® product kits used and standard of care treatments (if applicable) will be recorded.

7.1.4 Post-Surgery until Hospital Discharge

Prior to discharge, the following blood samples must be drawn and data will be recorded:

- Post-operative blood samples will be taken for Full Blood Count (FBC) with Differential and Coagulation parameters (PT, aPTT, INR). The last set of blood samples taken prior to discharge will be recorded;

- Physical examination as per institutions normal procedure;

- Concomitant medications;

- Details of hospital stay including: date of hospital discharge; overall stay in days (admission to discharge); ventilator time (if applicable);

- Incidence of adverse events; and

- Incidence of potential bleeding-related complications, including thrombotic events.

7.1.5 30-day Follow-Up Visit (±14 days)

The following information will be recorded during and in person visit or phone call, approximately 30 days following surgery:

- Changes in concomitant medications, including use of any blood products following hospital discharge;
- Incidence of adverse events; and
- Incidence of potential bleeding-related complications, including thrombotic events.

7.2 Procedures for Handling Biological Samples

7.2.1 Laboratory Tests

All laboratory investigations for FBC and Coagulation parameters will be performed at the local hospital laboratory. The volume of blood to be taken will be determined according to the standard practices of each hospital. The normal reference ranges and laboratory accreditation certificates must be provided to ETHICON. Local labs will be performing the tests in a blinded fashion as the local labs will not be aware of the randomized treatment.

7.3 Premature Withdrawal of Subjects for the Study

All randomized subjects should be encouraged to remain in the study until they have completed the 30-day follow-up visit. Subjects and/or their parent or legal guardian may discontinue participation in the study at any time and for any reason. However, if the subject decides to discontinue participation in the study, the reason must be documented when possible. Reasons for early withdrawal include, but are not limited to:

- Consent withdrawn by the subject and/or parent or legal guardian;
- Subject refusal to complete study visits and/or procedures;
- Lost to follow-up: a recorded delivery letter will be sent to the subject at their last known address, after a minimum of three attempts to reach the subject by telephone have failed. If communication via certified letter is unsuccessful, the subject will be considered lost to follow-up.

Subjects who are randomized and discontinue from the study prematurely will not be replaced.

8 STATISTICAL METHODS

The Data Management and Biostatistics groups of Clinical Development, at Johnson & Johnson Global Surgery Group will be responsible for the overall analysis of data from this protocol. The detailed Statistical Analysis Plan (SAP) will be based on and will supplement the statistical design and analysis described in this section.

8.1 Sample Size Determination

No formal sample size determination is required for this study, however a total of at least 40 subjects, 20 in each group, is a sufficient sample size to achieve the study objectives.

8.2 Data Analysis

The categorical data will be summarised descriptively by frequencies along with associated percentages for each group. The continuous variables will be summarised descriptively by number of subjects, mean, standard deviation, minimum, and maximum for each group. If applicable, a 5% significance level will be used for any statistical tests. Two-sided 95% confidence intervals will be quoted. Two-sided 95% confidence intervals (CIs) for median absolute time to hemostasis will be reported separately for EVICEL® and SURGICEL® groups. For the success/failure data (4, 7 and 10 minute hemostasis endpoints), the 95% CI will be quoted for P_F , P_C and for ratio P_F /P_C, where P_F is the proportion of success in EVICEL® subjects and P_C is the proportion of success in SURGICEL® control subjects. The lower limits of these 95% CI will be utilised for statistical inferences.

8.2.1 Analysis Sets

There will be three analysis sets defined:

- Full analysis set (FAS or intent-to treat) consists of all randomized subjects.
- Per-protocol analysis set (or evaluable) consists of all FAS subjects who have no major protocol violations.
- Safety analysis set will consist of all subjects who received treatment.

If any patients are mis-randomized (randomized to one treatment, but received the other) the FAS will summarise data ‘as randomized’, and the safety set will summarise ‘as treated’.

If more than 2 patients are mis-randomized then the data will be summarised 'as treated', within a separate analysis set. Patients who are mis-randomized will be considered major protocol violations.

The primary endpoint analysis will be based on the Full Analysis Set (FAS).

Major protocol violations are violations that have an impact on the primary endpoint. These will be determined prior to database lock.

8.3 Effectiveness

8.3.1 Effectiveness Variables

The following primary endpoint will be analysed using the FAS and Per-protocol Sets:

- Absolute time to haemostasis (elapsed from randomization);

The following secondary endpoints will be analysed using the FAS only:

- Haemostasis at the TBS at 4, 7 and 10 minutes following randomization; and
- Incidence of treatment failures (defined as haemostasis not achieved within 10 minutes or bleeding requiring treatment other than re-application of the assigned haemostatic adjunct within 10 minutes).

8.3.2 Methods of Analysis

Descriptive statistical analysis will be conducted overall and by treatment. Primary endpoint data will also be descriptively summarised into Neonates (birth to 30 days), Infants and toddlers (31 days to <24 months), Children (2 to 11 years) and Adolescent (12 to <18 years). Two-sided 95% confidence intervals (CIs) for median absolute time to hemostasis will be reported separately for EVICEL® and control groups. For the success/failure data (4, 7 and 10 minute hemostasis endpoints), the two-sided 95% CI will be quoted for P_F , P_C and for ratio P_F /P_C, where P_F is the proportion of success in EVICEL® subjects and P_C is the proportion of success in SURGICEL® control subjects. The lower limits of these 95% CI will be utilised for statistical inferences.

8.4 Safety

8.4.1 Safety Variables / Criteria

The following will be summarised using the Safety Set:

- Incidence of treatment failures (defined as haemostasis not achieved within 10 minutes or bleeding at the TBS during the ten-minute observational period that requires further haemostatic measures other than re-application of the assigned haemostatic adjunct);
- Incidence of adverse events (including thrombotic events and events associated with TBS re-bleeding).
- Proportion of subjects with no rebleeding;
- Laboratory and Blood Loss/Transfusion data will be summarised; and
- Clinically significant events will be recorded as AEs (Haemoglobin, Haematocrit, Platelets, Volume of blood loss; Volume of blood and blood products transfusion).

8.4.2 Methods of Analysis

Adverse events will be summarised descriptively by the treatment received, using Medical Dictionary for Regulatory Activities (MedDRA) terminology. Coagulation parameters (baseline and post-surgery samples) will use SI units.

Laboratory values (including coagulation parameters) will be reported in International System (SI) units. Values and changes from baseline will be listed and summarised. Clinically significant changes will be reported as part of the AE summary.

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8.5 Interim Analyses

None.

8.6 Handling of Missing Data

It is not anticipated that there will be any data missing for treated subjects for the primary endpoint, but if there is, missing data will not be imputed for the primary analysis.

Analyses of secondary endpoints will consider missing data as failures.

9 SAFETY DEFINITIONS

9.1 Adverse event

An adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a drug, without any judgment about causality. **Since post operative pain is an expected outcome of this type of surgery, for purposes of this study, only exacerbations of expected post operative pain based on the Investigator's judgment should be reported as an AE.**

The Investigator may also need to consider whether an adverse event is attributable to the application device, based on any of the following:

- Resulting from insufficiencies or inadequacies in the IFU;
- In the actual use of the application device or tips or regulator; or
- The result of user error.

9.2.1 Suspected adverse reaction

A suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction.

9.2.2 Adverse reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

9.2.3 Serious Adverse Event

A "serious" adverse event (SAE) is any untoward medical occurrence that, in the view of either the investigator or sponsor, it:

- Results in death;
- Is considered to be life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability, incapacity or substantial disruption of the ability to conduct normal life functions;
- Results in a congenital anomaly or birth defect;
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2.3.1 Life threatening

Life threatening refers to an adverse event or suspected adverse reaction in which, in the view of the investigator or sponsor, the subject was at immediate risk of death at the time of the event; it does not include an event that might have caused death if it were more severe.

9.2.3.2 Hospitalizations

Any event requiring inpatient hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

- Social reasons in absence of an adverse event;
- Surgery or procedure planned before entry into the study (must be documented in the eCRF).

9.2.4 Unexpected

An adverse event or suspected adverse reaction is considered ''unexpected'' if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed in human studies; or, though they are mentioned as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, they are not specifically mentioned as occurring with the particular drug under this investigation.

9.2.5 Suspected unexpected serious adverse reaction (SUSAR)

A suspected unexpected serious adverse reaction (SUSAR) is a suspected adverse reaction, i.e. SAE related to the investigational product, that is both serious and unexpected.

9.2.6 Relationship

The relationship of the investigational product to an adverse event must be determined using the following classification based on the information on the Investigator Brochure:

None: No relationship with investigational product.

Possible: Reasonable possibility that the event was caused by the investigational product.

Related: The event was certainly or probably caused by the investigational product.

9.2.7 Severity

The following definitions should be used to determine the severity rating of all AEs:

Mild: Awareness of signs or symptoms, but these are easily tolerated and are transient and mildly irritating only. There is no loss of time from normal activities and symptoms do not require medication or a medical evaluation.

Moderate: Discomfort enough to cause interference with usual activities or require therapeutic intervention, such as concomitant medication.

Severe: Incapacity with inability to work or do usual activities.

9.2.8 Collection of Adverse Events

AEs will be recorded as they are reported, whether spontaneously volunteered or in response to questioning about well-being. AEs will be collected from the point of randomization during the surgical procedure, throughout the hospital admission, and until completion of the 30-day follow-up visit.

All AEs will be documented in the subject's source documents (e.g. medical records) and eCRF. All AEs will be followed until completion of the 30-day follow-up visit or until a stable resolution, whichever is sooner.

Details of all AEs occurring during the study must be recorded on the AE form with the following information:

- Description of the event;
- Dates of onset and resolution;
- Severity;
- Action taken;
- Outcome;
- Relationship to investigational product; and
- Whether the AE is serious or not.

Expectedness of an SAE will be defined based on whether the specificity or severity of which is not consistent with the current investigator brochure.

Other: The investigator may also need to consider whether an event is attributable to the investigational product, based on insufficiencies or inadequacies in the instructions for use or as a result of user error. The investigator must contact the Sponsor should this occur.

9.2.9 Adverse Event Reporting

It is a requirement that the Investigator promptly reports all SAEs (irrespective of relationship) to [redacted] as soon as possible, but no later than 24 hours after becoming aware of the event occurring.

SAE reports must be communicated as follows:

[redacted]

Suspected, unexpected serious adverse drug reactions (SUSARs) will be reported to all relevant competent authorities and IRBs/Ethics Committees within the required timeframes of seven calendar days for SUSARs that are fatal or life-threatening, and fifteen calendar days for all other SUSARs by the Sponsor.

For Health Canada, reporting will also include any unusual failure in efficacy within fifteen calendar days.

All other Adverse Events (AEs) must be reported (entered) into the RAVE EDC clinical trial database (electronic case report form (eCRF) within two weeks from the date the site becomes aware of the AE.

10 DEVICE COMPLAINT HANDLING

If a device failure occurs with the applicator device, tips or regulators, a Device Complaint Form must be completed and faxed immediately (within 24 hours to [redacted]
Included are those complaints related to the applicator devices, tips or regulators that have been open but unused (e.g. sterile container was opened inadvertently). Upon receipt of the Complaint Form, instructions will be given on handling/returning of the defective device.

11 REGULATORY OBLIGATIONS

11.1 Informed Consent

Prior to participation, the study procedures and any known or likely risks will be explained to the subjects and/or their parent or legal guardian by the investigator or other qualified study personnel. An Informed Consent Form and patient information leaflet, when applicable, will also be provided containing all the required information. Any questions will be answered and the patient and/or their parent or legal guardian will then be given sufficient time to consider their participation in the study before signing a consent form. For paediatric subjects who possess the intellectual and emotional ability to comprehend the concepts involved in the trial, must also give their assent to participate in the study. If the paediatric subject is not able to provide assent (due to age, maturity and/or inability to intellectually and/or emotionally comprehend the trial), the parent/legal guardian's written informed consent for the subject will be acceptable for the subject to be included in the study. An age appropriate patient leaflet and assent document will be provided when applicable. Subjects and/or their parent or legal guardian should receive a copy of the Informed Consent Form.

The Investigator (or designee) will explain that the subjects and/or parent or legal guardian are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify.

Each subject and/or their parent or legal guardian will be informed that the subject's source medical records may be checked by representatives from the Sponsor or from a regulatory agency, in accordance with applicable regulations. However, they should be made aware that all information will be treated with confidentiality, and a study ID code or number will identify them.

11.2 Institution Approval / Ethics Committees

The investigator must submit the Protocol and the Consent Form to the appropriate Institution department/EC according to local requirements. Approval from the Institution/EC must be obtained prior to starting any study-related procedure.

12 DATA MANAGEMENT

12.1 Electronic Data Capture (EDC)

An EDC system will be utilized by trial site personnel to transfer trial data from source records (medical records and/or source document worksheets) onto common eCRFs (electronic Case Report Forms). This system is a web-based, secure electronic software application. This system was designed and is developed and maintained by [redacted] 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 trial 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 [redacted] website to assist in the collection and entry of source data into the electronic casebook. A 24/7/365 Help Desk Support line staffed by the outsourced vendor will be available to respond to site and monitor questions.

12.2 Data Collection

The Investigator must maintain required records on all study subjects. Data for this study will be recorded in the subject's medical records, study-specific worksheets, and on eCRFs provided by the Sponsor in accordance with the parameters set forth in ICH Topic E6 for GCP (1.5.96) Guidelines – Responsibilities of Sponsor, Monitor, and Investigator with 21 CFR Part 312. All data on the CRFs should be recorded from appropriate source documentation.

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. A unique ID number will be visible on each eCRF. At no time should the subject name appear on the eCRFs. Complete data is needed in order to provide statistical analysis for each subject. 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.

12.3 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 [redacted]

12.4 Source Documentation

Investigators must keep accurate separate records (other than the eCRFs) of all subjects' visits, being sure to include all pertinent study related information. A statement should be made indicating that the subjects have been enrolled in Protocol and have provided written Informed Consent. Any and all side effects and adverse events must be thoroughly documented. Results of any diagnostic tests conducted during the study should also be included in the source documentation. Telephone conversations with the subjects concerning the study must also be recorded.

The Investigator is responsible for maintaining a Subject Identification Log, which will include all subjects who provided informed consent (i.e. to include randomized subjects and screening failures). This confidential subject identification code provides the link between named subject source records in the subject file and anonymous eCRF data provided to ETHICON.

The Investigator must retain all study related documentation until at least two years after the final marketing application is approved, or at least two years have elapsed since the formal discontinuation of the clinical study. Study documents should not be destroyed without prior written agreement between the Investigator and ETHICON. The sponsor must be notified if the Investigator wishes to assign the study records to another party, or move them to another location.

13 SPONSOR OBLIGATIONS

13.1 Monitoring

The Sponsor monitor will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the trial. The monitor will visit as soon as possible following enrollment of the first subject and at regular intervals during the study, as deemed necessary. It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries. The study monitor will have access to laboratory test reports and any other source records and data needed to verify the entries on the eCRFs, unless restricted by local laws. The Investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.2 Regulatory Requirements

This study will be conducted in accordance with applicable regulations including but not limited to FDA Regulations (21 Code of Federal Regulations Part 312), ICH Harmonized Tripartite Guideline for Good Clinical Practice (1996), the Declaration of Helsinki (1996), the European Union Clinical Trial Directive (2001/20/EC, May 2001), EU GCP Directive 2005/28/EC, Health Canada's Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications and the Canadian Good Pharmacovigilance Practices (GVP) Guidelines (GUI-0102).

13.3 Liability and Insurance Conditions

In case of any damage or injury occurring to a subject in association with the trial medication or participation in the study, ETHICON has provided insurance cover. A copy of this policy is on file at ETHICON.

14 INVESTIGATOR OBLIGATIONS

14.1 Audit and Inspection

The Investigator will make source data and documents for this study available to an appropriately qualified quality assurance auditor mandated by ETHICON, or to regulatory authority inspectors, after appropriate notification.

14.2 Confidentiality of Subject Records

The Investigator will ensure that the subjects' anonymity will be maintained. On eCRFs or other study documents submitted to ETHICON, subjects will not be identified by their names, but by an identification code *that may consist of a combination of the site, randomization or enrollment number*. Documents not for submission to ETHICON i.e. the Subject Identification Log and original subjects' consent forms will be maintained in the Investigator Site File.

14.3 Record Retention

The Investigator will maintain all eCRFs and all source documents that support the data collected from each subject, and all trial documents as specified by applicable regulatory requirement(s). The Investigator will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least 2 years after the last approval of a marketing application worldwide, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with ETHICON. It is the responsibility of ETHICON to inform the Investigator as to when these documents no longer need to be retained. If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. ETHICON must be notified in writing of the name and address of the new custodian.

15 CHANGES TO THE PROTOCOL

15.1 Protocol Amendments

All protocol amendments are required to be submitted for information / consideration to the regulatory authorities, IRBs and ECs.

15.2 Clinical Trial Termination

Both the Investigator and ETHICON reserve the right to terminate the study at any time. Should this be necessary, the procedures will be arranged on an individual study basis after review and consultation with both parties. In terminating the study, ETHICON and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests and safety.

15.3 Use of Information and Publication

All information concerning study data, ETHICON's operations, patent application, formulas, manufacturing processes, basic scientific data, and formulation information, supplied by the Sponsor or Sponsor designee to the investigator and not previously published, is considered confidential and remains the sole property of ETHICON. The Investigator agrees to use this information only to accomplish this study and will not use it for other purposes without the sponsor's written consent.

The Investigator understands that the information developed in the clinical study will be used by ETHICON in connection with the continued development of the EVICEL® product, and thus may be disclosed as required to other clinical investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the sponsor with all data obtained in the study.

Any publication or other public presentation of results from this study requires prior review by ETHICON. Draft abstracts, manuscripts, and materials for presentation at scientific meetings must be sent to the sponsor at least 30 working days prior to abstract or other relevant submission deadlines. Authorship of publications resulting from this study will be based on generally accepted criteria for major medical journals.

The investigator understands not to use the name of ETHICON, EVICEL®, or any its employees, in any publicity, news release or other public announcement, written or oral, whether to the public, press or otherwise, relating to this protocol, to any amendment hereto, or to the performance hereunder, without the prior consent of ETHICON.

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Appendix 1: U.S. Center for Disease Control (CDC) Guideline for Prevention of SSI Surgical Wound Classification

CLASS I/CLEAN:

An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital and urinary tracts are not entered. Clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow non-penetrating (blunt) trauma should be included in this category if they meet these criteria.

CLASS II/CLEAN-CONTAMINATED:

An operative wound in which the respiratory, alimentary, genital and urinary tract is entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.

CLASS III/CONTAMINATED:

Open, fresh, accidental wounds, operations with major breaks in sterile technique or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent inflammation is encountered.

CLASS IV/DIRTY OR INFECTED:

Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.