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A Prospective, Clinical Study Evaluating the Safety and Haemostatic Effectiveness of SURGICEL®/TABOTAMP® Powder, Absorbable Haemostatic Powder (oxidized regenerated cellulose) in Controlling Mild or Moderate Parenchymal or Soft Tissue Intraoperative Bleeding during General, Gynaecological, Urological, and Cardiothoracic Surgery in Adult Subjects

SURGICEL®/TABOTAMP® Powder in Controlling Mild or Moderate Parenchymal or Soft Tissue Intraoperative Bleeding in Adult Subjects (Europe-PMCF Study)

Protocol Number: BIOS-2017-01

Original Protocol:	04 May 2018
Amendment I:	28 August 2018
Administrative II:	16 April 2019

Sponsor:

ETHICON Inc.
P.O. Box 151
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Somerville, NJ 08876-0151

A Prospective, Clinical Study Evaluating the Safety and Haemostatic Effectiveness of SURGICEL®/TABOTAMP® Powder, Absorbable Haemostatic Powder (oxidized regenerated cellulose) in Controlling Mild or Moderate Parenchymal or Soft Tissue Intraoperative Bleeding during General, Gynaecological, Urological, and Cardiothoracic Surgery in Adult Subjects

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Document	**Effective Date**
Original (version 1.0)	04 May 2018
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Compliance Statement

This study will be performed in compliance with Good Clinical Practice (GCP) and in accordance with the Declaration of Helsinki, as well as all applicable local regulations.

A Prospective, Clinical Study Evaluating the Safety and Haemostatic Effectiveness of SURGICEL®/TABOTAMP® Powder, Absorbable Haemostatic Powder (oxidized regenerated cellulose) in Controlling Mild or Moderate Parenchymal or Soft Tissue Intraoperative Bleeding during General, Gynaecological, Urological, and Cardiothoracic Surgery in Adult Subjects

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Investigator Agreement:

I have read this protocol and agree to conduct this clinical investigation in accordance with the design and specific provisions outlined herein. I understand the protocol, and I understand I am solely responsible to ensure the investigation is conducted in accordance with Good Clinical Practices (GCP), applicable country regulations, the Declaration of Helsinki, the signed clinical study contract with Sponsor, and with the protocol outlined herein. I will conduct this study as outlined therein and will make reasonable effort to complete the study within the time period designated by the Sponsor.

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

I will fulfil the requirements of my Institutional Review Board (IRB)/Ethics Committee (EC), or other oversight committee, to ensure complete and continual oversight of this clinical investigation. I will use an Informed Consent Document approved by the Sponsor and my reviewing IRB/EC (where required).

I agree to report all information or data in accordance with the protocol including any serious adverse events, device related adverse events, or procedure related adverse events as defined in this protocol to the Sponsor, and comply with all adverse event reporting requirements of my reviewing IRB/EC. I agree to permit the Sponsor, its authorised representatives, my reviewing IRB/EC, and any regulatory authority/body access to all records relating to the clinical investigation.

The below signature confirms I have read and understood this protocol and its associated amendments or attachments, and will accept respective revisions or amendments provided by the Sponsor.

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

_____ _____

Investigator Signature Date

_____

Investigator Name (printed)

TABLE OF CONTENTS

1. PROTOCOL SUMMARY

FULL TITLE: A Prospective, Clinical Study Evaluating the Safety and Haemostatic Effectiveness of SURGICEL®/TABOTAMP® Powder, Absorbable Haemostatic Powder (oxidized regenerated cellulose) in Controlling Mild or Moderate Parenchymal or Soft Tissue Intraoperative Bleeding during General, Gynaecological, Urological, and Cardiothoracic Surgery in Adult Subjects.

PROTOCOL NUMBER: BIOS-2017-01

SHORT TITLE: SURGICEL®/TABOTAMP® Powder in Controlling Mild or Moderate Parenchymal or Soft Tissue Intraoperative Bleeding in Adult Subjects

SPONSOR: Ethicon, Inc.

INDICATION: SURGICEL®/TABOTAMP® Powder, Absorbable Haemostatic Powder (oxidized regenerated cellulose) – **[herein – SURGICEL Powder]** is used adjunctively in surgical procedures to assist in the control of capillary, venous, and small arterial haemorrhage when ligation or other conventional methods of control are impractical or ineffective.

STUDY DEVICES: SURGICEL Powder is oxidised regenerated cellulose (ORC) prefilled in an applicator to dispense on the site of bleeding.

The SURGICEL Powder endoscopic applicator is an accessory device intended for the use in delivering SURGICEL Powder through a 5mm or larger trocar in minimally invasive procedures.

PRIMARY OBJECTIVE: The objective of this single-arm, post market clinical study is to evaluate the safety and haemostatic effectiveness of SURGICEL Powder in controlling mild or moderate parenchymal or soft tissue intraoperative bleeding during general, gynaecological, urological, and cardiothoracic surgery.

STUDY DESIGN: This is an open label, prospective, single arm, multicentre, multispecialty, post market, clinical study evaluating SURGICEL Powder as an adjunct to achieve haemostasis in the control of capillary, venous, and small arterial haemorrhage when ligation or other conventional methods of control are impractical or ineffective during surgery (open, laparoscopic or thoracoscopic) in adult subjects (18 years or older).

After application of SURGICEL Powder, the Target Bleeding Site (TBS) will be assessed for haemostasis (no detectable bleeding) at 3, 5, and 10 minutes from application and prior to initiation of final fascial closure in open surgery or port site closure in laparoscopic or thoracoscopic procedures.

All treated subjects will be followed post-operatively through discharge and again at 30 days (+14 days) and 6 months (+/-30 days) post-surgery via phone call or office visit.

SAMPLE SIZE: At least 100 evaluable subjects. There will be approximately 8 investigative sites and each site will enroll no more than 20 evaluable subjects.

RANDOMISATION: This study will be a single-arm study and, therefore, randomisation will not be performed.

STUDY POPULATION: Adult subjects, 18 years or older, undergoing elective/non-emergent general, gynaecological, urological, or cardiothoracic surgical procedures, wherein an appropriate mild or moderate TBS is identified.

TBS DEFINITION:

The TBS will be defined as the first accessible bleeding site requiring an adjunctive haemostat to assist in the control of mild or moderate capillary, venous, and small arterial haemorrhage when ligation or other conventional methods of control are impractical or ineffective.

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, which could also come from a small artery or vein, but is not massive.

Severe Bleeding (excluded from this protocol): TBS (arterial, venous, or mixed) that is rapidly flowing, pulsatile, or spurting, which, in the surgeon's judgment, requires rapid control to prevent hemodynamic consequences (e.g., hypovolemia, tachycardia, or hypotension) and could involve major volume loss which if not treated rapidly could be life threatening.

Note: SURGICEL Powder should NOT be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial or venous bleeding or major defects in arteries and veins.

PROCEDURE:

The TBS will be defined as the first active bleeding site identified during dissection, related to the primary operative procedure requiring an adjunctive haemostat. The TBS will be the only site assessed for haemostatic effectiveness.

Once the TBS is identified and conventional techniques were considered impractical or ineffective, the surgeon will apply SURGICEL Powder at the TBS to cover the entire bleeding area. The bleeding severity will describe the intensity of the bleeding that is present at the time the surgeon determines that an adjunctive haemostatic product is required.

Refer to the Instructions for Use (IFU) for detailed instructions on the application of SURGICEL Powder.

In the event of continued bleeding or re-bleeding at the TBS at any time prior to closure, the surgeon may add additional SURGICEL Powder, if clinically appropriate, or revert to their institutional standard of care.

If additional soft tissue bleeding sites are identified intra-operatively, the surgeon should treat according to their institution's standard of care.

SURGICAL PROCEDURES:

Open, laparoscopic, or thoracoscopic surgical procedures with a mild or moderate parenchyma or soft tissue identifiable TBS.

Surgical procedures may include the following:

- General
- Gynaecological
- Cardiothoracic
- Urological

Examples of types of surgical procedures considered for this study include but are not limited to: colectomy, low anterior resections, retroperitoneal tumour resection, liver resection, soft tissue bleeding after adhesiolysis, hernia repair, radical hysterectomy, lymphadenectomy, tumour removal surgery, simple or radical nephrectomy, kidney tumour resection, adrenalectomy, radical cystectomy, radical prostatectomy, pyeloplasty, diffuse bleeding on visceral or parietal pleura and soft tissue in cardiothoracic procedures.

STUDY LOCATION:

Europe

STUDY DURATION:

All treated subjects will be followed post-operatively through discharge and by telephone at 30 days (+14 days) and 6 months (+/-30 days) post-surgery.

INCLUSION CRITERIA:

Pre-operative:

1. Adult subjects ≥ 18 years requiring elective/non-emergent open or laparoscopic general, gynaecological, cardiothoracic, or urological surgical procedures;
2. Subject or authorised representative has signed the approved Informed Consent;
3. Subject(s) whose International Normalised Ratio is <1.5 within 24 hours of surgery.

Intra-operative:

4. Presence of an appropriate TBS identified intra-operatively by the surgeon;
5. Subject(s) undergoing cardiothoracic surgery with anticoagulation must have anticoagulation reversed prior to TBS identification and treatment.

EXCLUSION CRITERIA:

Pre-operative:

1. Female subjects who are pregnant or nursing;
2. Subjects on anticoagulant medication (with the exception of aspirin) prior to surgery. Washout periods for respective medications must be observed. If information is not readily available within the Instructions for Use (IFU), a conservative approach should be taken and intravenous heparin stopped 12 hours prior to surgery and 2 days prior for oral medication;
3. Subjects on antiplatelet/P2Y12 inhibitor medication prior to surgery. Platelet recovery times for respective medication must be observed. If information is not readily available within the IFU, a conservative approach should be taken and medication stopped 5 days prior to surgery.
4. Subject is currently participating or plans to participate in any other investigational device or drug without prior approval from the Sponsor;
5. Subjects who are known, current alcohol and/or drug abusers;
6. Subjects with any pre-operative findings identified by the surgeon that may preclude conduct of the study procedure.

Intra-operative:

7. Subjects with any intra-operative findings identified by the surgeon that may preclude the use of study product;
8. Subject with TBS in an actively infected field [Class III Contaminated or Class IV Dirty or Infected (see Section 15.2, Appendix 2);
9. TBS is on arteries or veins where application of SURGICEL Powder would present a risk of introducing the study product into an open blood vessel;
10. Major arterial or venous bleeding or major defects in arteries and veins;
11. TBS where silver nitrate or any other escharotic chemicals have been applied;
12. TBS is in, around, or in proximity to foramina in bone, or areas of bony confine, the spinal cord, or optic nerve and chiasm;
13. TBS in urological procedures where plugging (blocking) of the urethra, ureter or a catheter is possible by the study product.

PRIMARY EFFECTIVENESS ENDPOINT:

Proportion of subjects achieving haemostatic success at **5** minutes following the application of SURGICEL Powder with no re-bleeding requiring additional treatment at the TBS any time prior to initiation of final fascial closure.

SECONDARY EFFECTIVENESS ENDPOINTS:

- Proportion of subjects achieving haemostatic success at **3** minutes following the application of SURGICEL Powder with no re-bleeding that requires additional treatment at the TBS any time prior to initiation of final fascial closure;
- Proportion of subjects achieving haemostatic success at **10** minutes following the application of SURGICEL Powder with no re-bleeding that requires additional treatment at the TBS any time prior to initiation of final fascial closure.

SAFETY ENDPOINTS:

- Incidence of thromboembolic events that were assessed as having either a possible, probable or causal relationship to the study treatment (from time of SURGICEL Powder application at TBS through 30-day follow-up phone call or office visit);

- Incidence of post-operative re-bleeding that was assessed as having either a possible, probable or causal relationship to the TBS and requiring medical/surgical intervention (from initiation of final fascial closure through 30-day follow-up phone call or office visit);
- Incidence of serious adverse events requiring surgical intervention and assessed as having either a possible, probable or causal relationship to the study treatment (from time of SURGICEL Powder application at TBS through 6-month follow-up phone call or office visit).

SAFETY ASSESSMENTS:

The Sponsor's Medical Director (Study Medical Monitor/Safety Lead) will assess all serious adverse events for causality and expectedness and will utilise Ethicon's Product Safety Committee (PSC) to review and adjudicate the following safety signals:

- Thromboembolic events
- Postoperative re-bleeding
- Reoperations for complications assessed as having either a possible, probable or causal relationship to the study treatment

The PSC will also review cumulative safety data from the study. The PSC will advise on the continuing safety of study subjects and those yet to be recruited to the study. Based on cumulative data from the study, the PSC may recommend whether to continue, suspend, modify, or stop the study. At the conclusion of the study, the PSC will also give a final assessment of the safety of the product from this study. The composition, responsibilities, frequency of PSC meetings, handling of emergency situations, and documentation of PSC meetings will be specified in the Safety Management Plan (SMP).

Stopping Rules:

The rules outlined below will be used to determine if the clinical trial should be put on hold contingent on PSC recommendations:

- If three confirmed thromboembolic serious adverse events (PE/DVT SAEs) are reported and assessed as being related to the study treatment.
- If one or more subject(s) develops post-operative bleeding and the TBS is confirmed as the cause of the re-bleeding. The relatedness of the SAE to the study treatment is to be determined by the following:
    - Findings at re-operation
    - Findings of TBS re-bleeding at autopsy (if applicable)

EXPLORATORY DATA:

Demographic information and data collected in this study may be used in Health Economics and Outcomes Research (HEOR). In addition, data using the surgeon EUQ (Ease of Use Questionnaire), a tool validated in prior clinical trials, will also be collected and analysed descriptively.

STATISTICAL ANALYSIS:

No formal sample size determination was performed for this study; however, a sample size of 100 evaluable subjects is considered adequate to provide sufficient information to evaluate safety and effectiveness outcomes using descriptive summaries. The continuous data will be summarised by number of subjects, mean, standard deviation (SD), median, minimum and maximum. The categorical data will be summarised by frequency counts along with associated percentages. For binary (success/failure) primary and secondary effectiveness endpoints (3, 5, and 10 minutes haemostasis endpoints), two-sided 95% confidence interval (CI) will be constructed for the proportion of successes, using the Clopper-Pearson method. For the primary effectiveness endpoint, assuming a success rate of 85%, the estimation precision of the Clopper-Pearson two-sided 95% CI for the success rate (as measured by the half-width of the confidence interval) when the most likely number of successes (85) is observed, is 7.4%. Additionally, for evaluation of safety and observation of adverse events that occur at a rate as low as 2.5% in the population, a sample size of 100 subjects provides greater than 90% probability for observing at least 1 such adverse event. Thus, a sample size of at least 100 evaluable subjects should give reasonable assurance that the absence of such events in the study is not a result of too few patients being studied, should none be observed.

INTERIM ANALYSIS:

No interim analysis is planned for this study. Two analyses will be performed. The first analysis will occur after all subjects complete phone call or office visit 1 [30 days (+ 14 days) post-surgery]. All data collected through 30-day (+14 days) follow-up will be analysed. The second analysis will occur after all subjects complete phone call or office visit 2 [6-month (+/-30 days) post-surgery] and the data collected at this follow-up is available. The second analysis will be performed on the data from the 6-month follow-up assessing any occurrences of SAEs requiring surgical intervention and assessed as having either a possible, probable or causal relationship to the study treatment.

SCHEDULE OF ACTIVITIES

Procedures	**Screening** within 21 days prior to procedure[1]	**Baseline** within 24 hours prior to procedure	**Surgical Procedure**	**Post-Surgery to Hospital Discharge**	**30-Day Post-Surgery** Phone Call (or visit) (+14 days)	**6-Month Follow-Up** Phone Call (or visit) (± 30 days)
Inclusion/exclusion	X	X	X			
Informed consent	X					
Demographics	X					
Medical/surgical history	X	X[2]				
Concomitant medications		X	X	X	X	
Physical exam	X			X		
Coagulation blood tests (PT, APTT, INR)		X[3]				
Pregnancy test (if applicable)		X[3]				
Treatment application			X			
Assessment and determination of haemostasis at TBS			X			
Operative/Surgical information			X[4]			
Assessment of bleeding			X			
Surgeon Ease of Use Survey			X[5]			
Adverse events			X	X	X	
Thromboembolic events possibly related or related to the TBS			X	X	X	
Postoperative re-bleeding possibly related or related to the TBS				X	X	
Serious adverse events assessed as having either a possible, probable or causal relationship to the study treatment and requiring surgical intervention			X	X	X	X[6]

Note: See Section 15.4 for List of Abbreviations and Acronyms.

[1] Screening visit may be combined with baseline visit.
[2] At the baseline visit, review for changes in medical history since screening visit.
[3] Blood tests to determine coagulation status and pregnancy test (if applicable) needed within 24 hours of surgery.
[4] Operative and surgical information includes length of hospital stay, blood loss, and transfusion information.
[5] Survey to be completed for the first 2 cases using SURGICEL Powder for open procedures for each Investigator. Survey to be completed for the first 2 cases using the Endoscopic Applicator for each Investigator.
[6] New SAEs requiring surgical intervention and assessed as having either a possible, probable or causal relationship to the study treatment. Follow-up on all SAEs assessed as having either a possible, probable or causal relationship to study treatment, which were ongoing at the 30-day post-surgery follow-up.

2. BACKGROUND AND SCIENTIFIC RATIONALE

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[i]. When these conventional measures are ineffective or impractical, adjunctive haemostatic techniques and products are routinely utilised to control the bleeding. Adjunctive haemostats can be categorised into two major groups based on their mode of action: those that provide a matrix to accelerate the subject's natural coagulation cascade, and those that contain active biologic components such as thrombin and/or fibrinogen that will allow them to achieve haemostasis regardless of the subjects' coagulation status. The group of haemostats that assist in the coagulation cascade are also referred to as the adjunctive topical absorbable haemostats, which includes products based on oxidised cellulose (OC), oxidised regenerated cellulose (ORC), gelatin, collagen, chitin, chitosan, and polysaccharides[ii].

With a clinical history spanning more than 50 years, SURGICEL® Original and its family of products has predominately been used to assist in achieving and accelerating haemostasis when various types of bleeding have been observed intra-operatively. These types of products are optimal when bleeding is confined, because the product can be placed on the source of bleeding with manual compression to facilitate haemostasis. When bleeding is not confined, continuous oozing from large friable and raw surfaces can cause delays and surgeon frustration during surgery[iii]. These situations require ready to use haemostatic products with minimal or no preparation time and in addition must be able to achieve quick coverage on the bleeding surface and the ability to achieve haemostasis.

SURGICEL Powder, an optimised powdered form of ORC is a topical absorbable haemostat being evaluated in this study to further measure its safety and haemostatic effectiveness in controlling mild/moderate parenchymal or soft tissue intra-operative bleeding. Although there is sufficient information supporting the safety and performance of SURGICEL Powder supported by data from acute and survival preclinical studies, this post-market clinical follow-up (PMCF) study will be implemented to further enhance our understanding of safety and performance of SURGICEL Powder in a real world clinical setting. The results of this European PMCF study may be combined with the results of an additional clinical study to support the PMCF and other registration requirements, as applicable.

The Product

SURGICEL (TABOTAMP) Absorbable Haemostatic Powder and accessory, the SURGICEL (TABOTAMP) Endoscopic Applicator are intended for use adjunctively in surgical procedures to assist in the control of capillary, venous, and small arterial haemorrhage when ligation or other conventional methods of control are impractical or ineffective.

NOTE: In some European countries, SURGICEL products are branded as TABOTAMP however the products are otherwise identical to SURGICEL Powder, SURGICEL Endoscopic Applicator, and SURGICEL Original, respectively.

The mechanism of action whereby ORC haemostats accelerates clotting is believed to be a physical effect rather than any alteration of the normal physiologic clotting mechanism. After SURGICEL Powder has been saturated with blood, it swells into a brownish or black gelatinous mass which aids in the formation of a clot, thereby serving as a haemostatic adjunct. SURGICEL Powder like its SURGICEL family counterparts, is bactericidal in vitro due to low pH characteristics against a wide range of pathogenic microorganisms.

3. STUDY OBJECTIVES

The objective of this single arm, post market, clinical study is to evaluate the safety and haemostatic effectiveness of SURGICEL Powder in controlling mild or moderate parenchymal or soft tissue bleeding during general, gynaecological, urological, and cardiothoracic surgery in adults.

The primary effectiveness endpoint of this study is:

- The proportion of subjects achieving haemostatic success at **5** minutes following the application of SURGICEL Powder with no re-bleeding requiring additional treatment at the TBS any time prior to initiation of final fascial closure.

The secondary effectiveness endpoints of this study include:

- Proportion of subjects achieving haemostatic success at **3** minutes following the application of SURGICEL Powder with no re-bleeding requiring additional treatment at the TBS any time prior to initiation of final fascial closure;
- Proportion of subjects achieving haemostatic success at **10** minutes following the application of SURGICEL Powder with no re-bleeding requiring additional treatment at the TBS any time prior to initiation of final fascial closure.

The safety endpoints of this study include:

- Incidence of thromboembolic events that were assessed as having either a possible, probable or causal relationship to the study treatment (from time of SURGICEL Powder application at TBS through 30-day follow-up via phone call or office visit);
- Incidence of post-operative re-bleeding that was assessed as having either a possible, probable or causal relationship to the TBS and requiring medical/surgical intervention (from initiation of final fascial closure through 30-day follow-up via phone call or office visit);
- Incidence of serious adverse events requiring surgical intervention and assessed as having either a possible, probable or causal relationship to the study treatment (from time of SURGICEL Powder application at TBS through 6-month follow-up done via phone call or office visit)

4. OVERVIEW OF STUDY DESIGN

This is an open label, prospective, single arm, multicentre, multispecialty, post-marketing clinical study evaluating SURGICEL Powder as an adjunct to achieve haemostasis in the control of capillary, venous, and small arterial haemorrhage when ligation or other conventional methods of control are impractical or ineffective during surgery (open, laparoscopic or thoracoscopic) in adult subjects (18 years or older). Prospective subjects will be informed about the nature of the research, given the informed consent form (ICF) to read, and, if he/she understands the content, will be asked to provide consent by signing the ICF.

Screening will continue until at least 100 evaluable subjects from approximately eight (8) investigational sites (up to 20 subjects for each site) with an appropriate mild or moderate Target Bleeding Site (TBS) are included into the study. The TBS will be the only region evaluated for the primary endpoint and all secondary effectiveness endpoints. Refer to section 7.1.3 for the definition of the TBS.

All treated subjects will be followed post-operatively through discharge, and via phone call or office visit at 30 days (+14 days) post-surgery. In addition, all treated subjects will receive a 6-month (+/-30 days) follow-up phone call or office visit to assess the occurrence of any serious adverse event (SAE) requiring surgical intervention and assessed as having either a possible, probable or causal relationship to the study treatment.

5. STUDY POPULATION

5.1 General Considerations

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

5.2 Inclusion Criteria

Pre-operative:

1. Adult subjects ≥ 18 years requiring elective/non-emergent open or laparoscopic general, gynaecological, cardiothoracic, or urological surgical procedures;
2. Subject or authorised representative has signed the approved Informed Consent;
3. Subject(s) whose International Normalised Ratio is <1.5 within 24 hours of surgery.

Intra-operative:

4. Presence of an appropriate Target Bleeding Site (TBS) identified intra-operatively by the surgeon;
5. Subject(s) undergoing cardiothoracic surgery with anticoagulation must have anticoagulation reversed prior to TBS identification and treatment.

5.3 Exclusion Criteria

Pre-operative:

1. Female subjects who are pregnant or nursing;
2. Subject on anticoagulant medication (with the exception of aspirin) prior to surgery. Washout periods for respective medications must be observed. If information is not readily available within the Instructions for Use (IFU), a conservative approach should be taken and intravenous heparin stopped 12 hours prior to surgery and 2 days prior for oral medication;
3. Subject on antiplatelet/P2Y12 inhibitor medication prior to surgery. Platelet recovery times for respective medication must be observed. If information is not readily available within the IFU, a conservative approach should be taken and medication stopped 5 days prior to surgery
4. Subject is currently participating or plans to participate in any other investigational device or drug without prior approval from the Sponsor;
5. Subjects who are known, current alcohol and/or drug abusers;
6. Subjects with any pre-operative findings identified by the surgeon that may preclude conduct of the study procedure.

Intra-operative:

7. Subjects with any intra-operative findings identified by the surgeon that may preclude the use of study product;
8. Subject with TBS in an actively infected field [Class III Contaminated or Class IV Dirty or Infected (see Section 15.2, Appendix 2);
9. TBS is on arteries or veins where application of SURGICEL Powder would present a risk of introducing the study product into an open blood vessel;
10. Major arterial or venous bleeding or major defects in arteries and veins;
11. TBS where silver nitrate or any other escharotic chemicals have been applied;
12. TBS is in, around, or in proximity to foramina in bone, or areas of bony confine, the spinal cord, or optic nerve and chiasm;
13. TBS in urological procedures where plugging (blocking) of the urethra, ureter or a catheter is possible by the study product.

6. INVESTIGATIONAL PRODUCT

6.1 SURGICEL Powder "Open-Tip" Applicator and Endoscopic Applicator

SURGICEL Powder is an absorbable haemostatic powder made of oxidised regenerated cellulose (ORC), which is prefilled in a sterile, single-use, "open-tip" applicator that dispenses the powder on a target intraoperative bleeding site during open procedures (Figure 1).

The applicator is provided sterile with 3 grams of SURGICEL Powder. The "open" tip applicator enables surgeons to topically apply powder to a desired anatomical site by manually compressing the bellows. The tip is flexible such that the surgeon can angle the tip in the direction of bleeding. The applicator is provided in the "closed" or "off" position so powder cannot be expressed.

The ORC powder is developed by producing fibrillar structured aggregates of ORC fine fibres using a proprietary process. The powder has a unique physical morphology; however, it maintains the chemical and bactericidal properties of the original ORC fabric. The ORC aggregates in SURGICEL Powder penetrate the surface layer of blood, initiating clotting and adhering to tissue for durable and sustained haemostasis. Because the ORC aggregates are chemically identical to ORC fabric products, they share key attributes and perform in ways that will be familiar to surgeons. Both induce haemostasis rapidly; both turn a dark reddish-black on exposure to blood; both are absorbed within approximately 2 weeks; and, both are bactericidal in vitro for a wide range of organisms[iv].

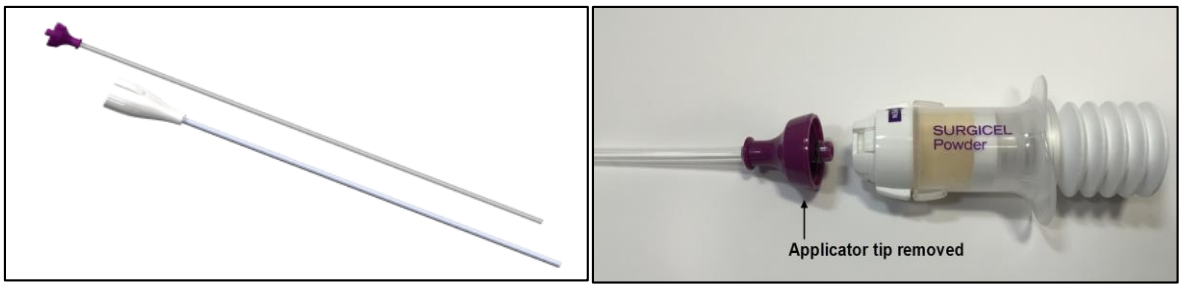
SURGICEL Powder ("Open Tip" Attached)

Figure 1: SURGICEL Powder Device

The image provided above is for illustration purposes only and may not represent the actual device.

The SURGICEL Endoscopic Applicator is a Class IIa accessory device that will be packaged and sold separately for use with the SURGICEL Powder device in endoscopic/laparoscopic procedures. As shown in Figure 2, the open tip is removable and can be replaced with the SURGICEL Endoscopic Applicator (also referred to as "lap tip").

The SURGICEL Endoscopic Applicator is supplied with a flexible inner tip and a rigid cannula and is designed to mate with the SURGICEL Powder Device, allowing for the delivery of SURGICEL Powder to a bleeding surgical site through a 5-mm or larger trocar (Figure 2).



SURGICEL Powder Endoscopic Applicator **Removal of Open Tip Applicator**

Figure 2: SURGICEL Endoscopic Applicator - Interchangeable with Open Tip

The images provided above are for illustration purposes only and may not represent the actual device.

6.1.1 Labelling and Packaging

SURGICEL Powder is packaged on an inner card which is further packaged inside an outer pouch composed of polyester laminated foil with an inner heat seal coating serving as a barrier to moisture and contamination.

The foil pouches are packed into a cardboard box as secondary packaging.

Labelling may include the following:

- Do not reuse
- Do not resterilise
- Do not use if package is damaged
- Caution
- Use-by date
- Temperature limit
- Manufacturer Catalogue number
- Batch code
- Sterilised using Irradiation
- CE Mark and Identification Number of Notified Body. The product meets the essential requirements of Medical Device Directive 93/42/EEC
- Authorised Representative in the European Community
- Quantity

6.1.2 Shipping, Handling and Storage Conditions

Shipping conditions should be 15º to 30 ºC.

Store unopened packages of SURGICEL Powder at controlled room temperature 15º to 30 ºC. SURGICEL Powder does not require refrigeration. Do not freeze. Do not use if package is opened or damaged. Sterility is guaranteed unless package is opened or damaged.

The applicator is provided sterile with 3 grams of SURGICEL Powder (ORC) and should not be re-sterilised/reused. Do not re-sterilise/reuse SURGICEL Powder or the SURGICEL endoscopic tip. Once opened, keep dry prior to use, so that it can remain in the sterile field throughout the surgery. Disposal of the device, the endoscopic tip (if used for appropriate surgery) and packaging will be in accordance with study facility policies and procedures regarding biohazardous materials and waste.

Distribution of SURGICEL Powder and the endoscopic accessory to the clinical sites will be performed by ETHICON Clinical Operations.

6.1.3 Preparation

SURGICEL Powder device with “open tip” applicator is prefilled with 3 grams of powder. The SURGICEL Powder “open tip” and the endoscopic tip are supplied sterile and ready to use out of the package. Only undamaged packages should be used. Once the foil pouch is opened, re-sterilisation is not possible. The following procedure for opening and applying the product should be followed to ensure that the sterility of SURGICEL Powder is maintained.

Non-sterile nurse / Study Personnel
Open outer foil pouch and transfer SURGICEL Powder delivery device and inner card to sterile field. If an endoscopic procedure, repeat the above for the endoscopic accessory.

Sterile nurse / field
Hold the body of the applicator, remove SURGICEL Powder delivery device from inner card and twist to open.

SURGICEL Powder delivery device is now ready for use. If an endoscopic procedure, repeat the above and replace the "open tip" attachment with the endoscopic accessory as per the IFU.

6.1.4 Dose, Route and Duration of Administration

For each subject, 2 applicators of SURGICEL Powder will be available in the theatre and ready for administration prior to TBS identification. Apply an adequate amount of SURGICEL Powder to cover the entire TBS. Use of a non-adhering substrate to apply pressure may prevent adhesion of the formed clot to the surgical glove or other instrumentation.

See application procedures in Section 7.1.3. Additional information can also be found in the IFU.

6.2 Investigational Product Dispensation and Accountability

The Principal Investigator or responsible person designated by the Principal Investigator must account for all study devices throughout and, at the end of, the clinical study. A dispensing log will be kept by the designated study personnel. This log will contain information on the date of administration, subject ID#, lot number, quantity of SURGICEL Powder dispensed, details of any remaining product, subsequent destruction (if applicable). The Principal Investigator must allow the study monitor access to the secured facility where the study devices and/or products are stored during the clinical trial to check inventory and verify the dispensing log. The study product will be stored according to the IFU and be kept in a secured area with access restricted. Study product is to be used for study subjects only.

6.2.1 Topical Haemostats

The use of any other topical haemostats will be permitted on non-target bleeding sites and must be used according to their respective labelling and the Investigator's usual practice. Haemostatic assessment of any additional bleeding sites treated with SURGICEL Powder will **not** be recorded. Details of all topical haemostats used for the subject throughout the procedure will be recorded on the Concomitant Medication CRF.

6.2.2 Documentation of Concomitant Medications

Indication and start-stop dates of concomitant medications administered from 24 hours prior to surgery up to the 30-day follow up will be recorded. This will include medications used chronically (even if temporarily halted for surgery) and those medications administered as a prophylactic before, during and after surgery.

Anaesthetics used for study surgery and over the counter (OTC) drugs will not be recorded as concomitant medication (except for aspirin, which should be documented). Concomitant

medications used to treat Adverse Events (even if the concomitant medication is an OTC drug or nutritional supplement) must also be documented.

7 STUDY EVALUATIONS

7.1 Study Procedures

The schedule of assessments included in the protocol summary, summarises the frequency and timing of the study procedures. All assessments will be performed by the Investigator or other study personnel with delegation of authority. 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 recorded into the eCRF.

7.1.1 Screening

Prospective subjects will be screened within 21 days prior to surgery. The following activities and tests will be performed at the screening visit. The timing of these activities may occur based on routine hospital practice but may be done up to the day of, but prior to, the surgical procedure.

- Informed consent
- Allocation of screening number
- Documentation of demography (age, gender, race/ethnic origin)
- Physical examination as per normal procedure
- Documentation of relevant medical and surgical history
- Review of Inclusion / Exclusion criteria to confirm subject pre-operative eligibility (section 5.2 and 5.3). If a subject is not eligible, the reason will be documented on the worksheet/screening log

7.1.2 Baseline Assessments

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 and may overlap with some of the screening visit activities (see section 7.1.1).

- Review of inclusion / exclusion criteria to confirm subject pre-operative eligibility (section 5.2 and 5.3). If a subject is no longer eligible, the reason for the screen failure will be documented on the source documentation and screening log
- Documentation of all concomitant medications as stated in Section 6.2.2
- Documentation of any changes in medical history since the screening visit (if done at a separate visit from Baseline)
- Serum or urine pregnancy test (if applicable)
- Coagulation blood tests (PT, aPTT, INR)
- International Normalised Ratio is <1.5 within 24 hours of surgery

7.1.3 Surgical Procedure

The surgeon will use his/her standard surgical techniques for the surgical procedure.

The TBS will be defined as the first active bleeding site identified during dissection, related to the primary operative procedure requiring an adjunctive haemostat. The TBS will be the only site assessed for haemostatic effectiveness.

Once the TBS is identified and conventional techniques were considered impractical or ineffective the surgeon will apply SURGICEL Powder at the TBS to cover the entire bleeding area. The bleeding severity will describe the intensity of the bleeding that is present at the time the surgeon determines that an adjunctive haemostatic product is required.

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 included:

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 hemodynamic consequences (e.g. hypovolemia, tachycardia, or hypotension) and could involve major volume loss which if not treated rapidly could be life threatening. SURGICEL Powder should not be used in place of sutures or other forms of mechanical ligation for the treatment of major arterial bleeding.

Refer to the IFU for detailed instructions on the application of SURGICEL Powder.

Types of Surgical Procedures

Open, laparoscopic or thoracoscopic surgical procedures may include the following surgical specialties:

- General
- Gynaecological
- Cardiothoracic
- Urological

Examples of types of surgical procedures considered for this study may include (but are not limited to):

- Colectomy
- Low anterior resections
- Retroperitoneal tumour resection

- Liver resection
- Soft tissue bleeding after adhesiolysis
- Hernia repair
- Radical hysterectomy
- Lymphadenectomy
- Tumour removal surgery
- Simple or radical nephrectomy
- Kidney tumour resection
- Adrenalectomy
- Radical cystectomy
- Radical prostatectomy
- Pyeloplasty
- Diffuse bleeding on visceral or parietal pleura
- Soft tissue in cardiothoracic procedures.

The following activities will be performed and information will be collected during the surgical procedure:

- Review of inclusion and exclusion criteria to confirm intra-operative eligibility. If a subject is no longer eligible, the reason for the screen failure will be documented in the source documentation and the screening log
- Medications as outlined in Section 6.2.2
  Hospital admission date (for overall Length of Stay)
- Theatre details:
  - Entry and exit time
  - Procedure time (first incision to final wound closure)
  - Transfusion information (if applicable)
- Primary Operative Procedure information: *Open, Laparoscopic, Thoracoscopic. Surgical specialty (General, Cardiothoracic, Gynaecological, Urological) and the type of procedure)*
- Haemostatic methods used at the TBS prior to SURGICEL Powder application *[none, (other methods are impractical), suture, ligation, cautery, other]*
- TBS information: *Parenchyma or soft tissue type and location*
- Type of bleeding *(mild or moderate)*
- Size of TBS *(length, width)*
- Heparin use and time of reversal (if applicable)
- Total number of applicators (units) used
- Adverse events, including any complications that may be related to bleeding and/or thrombotic events.
- Surgeon Ease of Use Questionnaire– one questionnaire needs to be completed per Investigator for their first 2 cases using SURGICEL Powder for open procedures. One questionnaire needs to be completed per Investigator for their first 2 cases using the Endoscopic Applicator (completed as soon as possible, but within approximately 72 hours).

Pre-Treatment Procedures:

- SURGICEL Powder will be available in the theatre, ready for administration to each subject.
- When the surgeon encounters the first appropriate TBS with mild or moderate bleeding in the parenchyma or soft tissue 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 treatment with SURGICEL Powder.

Treatment Application

Upon completion of application of SURGICEL Powder to the TBS, the stopwatch will be immediately started, (T_0) and the time on the wall clock will be recorded.

Haemostasis will be assessed at 3 minutes, 5 minutes and 10 minutes post SURGICEL Powder application and at initiation of final fascial closure for all subjects.

SURGICEL Powder should be applied dry so should **not** be moistened with water or saline prior to application. Apply an adequate amount of SURGICEL Powder by compressing the bellows, to cover the entire TBS. Depending on the bleeding intensity and anatomical location, more than one layer may be needed to achieve complete haemostasis. After SURGICEL Powder application to the TBS, the surgeon may apply pressure over the treatment site, as needed. Use of non-adhering substrate to apply pressure may prevent adhesion of the formed clot to the surgical glove or surgical instrumentation.

SURGICEL Powder is absorbable and may be left in situ, it is advisable to remove excess powder with irrigation and aspiration once haemostasis is achieved, without disturbing the clot.

In the event of continued bleeding or re-bleeding at the TBS at any time prior to initiation of final fascial closure, the surgeon may add additional SURGICEL Powder, if clinically appropriate, *or* revert to their institutional standard of care.

If the surgeon feels re-bleeding is due to insufficient coverage of the bleeding area, additional SURGICEL Powder may be applied.

HAEMOSTASIS ASSESSMENT (TIME TABLE):

T_0	Start time. When SURGICEL Powder application is complete (entire TBS covered)
T_3	TBS Bleeding assessment 3 minutes following **T_0**
T_5	TBS Bleeding assessment 5 minutes following **T_0**
T_{10}	TBS Bleeding assessment 10 minutes following **T_0**
T_F	TBS bleeding assessment post the 10-minute assessment, immediately prior to the initiation of final fascial closure

Time to Haemostasis Assessment:

- The Investigator is required to call out once he/she has completed application of the product (defined as adequate coverage including additional layer, if needed) - at the same time, the **stopwatch must be started and the wall clock recorded** by study personnel ($\mathbf{T_0}$).
- The TBS will be assessed at the time points 3 minutes ($\mathbf{T_3}$), 5 minutes ($\mathbf{T_5}$), and 10 minutes ($\mathbf{T_{10}}$) following application for assessment of haemostasis.
- The Investigator must evaluate for haemostasis at the TBS immediately prior to the initiation of final fascial closure (last time TBS is visible to confirm haemostasis, $\mathbf{T_F}$).
- Haemostasis will be defined as no detectable bleeding from the TBS.
- In the event of continued bleeding or re-bleeding at the TBS at any time prior to closure, the surgeon may add additional SURGICEL Powder, if clinically appropriate, *or* revert to their institutional standard of care. Information on the treatment methods of re-bleeding/continuous bleeding at the TBS must be recorded.

Success/Failure Assessment for the Binary Primary and Secondary Effectiveness Endpoints

- During the 10-minute assessment period and following the initial application of SURGICEL Powder, the surgeon may reapply SURGICEL Powder. The subject will be considered a failure for *preceding* binary primary and secondary effectiveness endpoints [e.g. if subjects achieve haemostasis at 3 minutes and re-bleeding occurs at 6 minutes, then the subject will be considered a failure for the *preceding* effectiveness endpoints (at 3 and 5 minutes)].
- Reapplication of SURGICEL Powder does not have an impact on the success/failure evaluation of *subsequent* binary effectiveness endpoints (e.g. if haemostasis is achieved by reapplication of SURGICEL Powder, the *subsequent* binary endpoints will not be impacted. If any additional SURGICEL Powder is applied to the TBS and the TBS is haemostatic at the 10-minute assessment period and maintained up until initiation of final fascial closure, the subject will be considered a success for the effectiveness 10-minute endpoint).
- If during the 10-minute assessment period the TBS requires further haemostatic measures (other than additional application of SURGICEL Powder), the surgeon should perform these measures, and the subject will be considered a failure for all binary primary and secondary effectiveness endpoints (at 3, 5, and 10 minutes).
- Any intra-operative bleeding or any haemostatic measures at the TBS after 10 minutes and prior to initiation of final fascial closure will be considered a failure for all binary primary and secondary effectiveness endpoints.

7.1.4 Post-Surgery until Hospital Discharge

Prior to discharge, the following data will be recorded:

- Physical examination as per the institution's normal procedure
- Changes in concomitant medications
- Adverse events, including reoperation, any complications possibly related to bleeding and/or thrombotic events
- Date of hospital discharge (for overall Length of Stay).

7.1.5 30-day Follow-Up Phone Call/Office Visit (+ 14 days)

The following information will be recorded at the clinical follow-up phone call or office visit approximately 30 days following the study surgery:

- Changes in concomitant medications, including use of any blood products following hospital discharge.
- Adverse events

7.1.6 6-Month Follow-Up Phone Call/Office Visit (+/- 30 days)

All treated subjects will receive a 6-month (+/-30 days) follow-up phone call or office visit to assess:

- Any SAEs requiring surgical intervention and assessed as having either a possible, probable or causal relationship to the study treatment. Detailed data on action taken for the SAE will not be reportable.

7.2 Procedures for Handling Biological Samples

7.2.1 Laboratory Tests

All laboratory investigations 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 will be provided to the Sponsor.

7.3 Premature Withdrawal of Subjects for the Study

All subjects should be encouraged to remain in the study until they have completed all study required follow-up phone calls or office visits. Subjects 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;
- Subject refusal to complete study follow-ups 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 documented 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;
- Adverse events; or
- Other reason, specify.

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

8 STATISTICAL METHODS

The Data Management and Biostatistics groups at Ethicon 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 was performed for this study; however, a sample size of 100 evaluable subjects is considered adequate to provide sufficient information to evaluate the safety and effectiveness outcomes using descriptive summaries. Although no inferential statistical analyses or hypothesis testing will be performed for the purpose of making claims in this study, a two-sided Clopper-Pearson 95% confidence interval for the proportion of successes will be reported for the primary effectiveness endpoint. Assuming a success rate of 85%, the estimation precision of the Clopper-Pearson two-sided 95% CI for the success rate (as measured by the half-width of the confidence interval) when the most likely number of successes (85) is observed, is 7.4%. Additionally, for evaluation of safety and observation of adverse events that occur at a rate as low as 2.5% in the population, a sample size of 100 subjects provides greater than 90% probability for observing at least 1 such adverse event. Thus, a sample size of at least 100 evaluable subjects should give reasonable assurance that the absence of such events in the study is not a result of too few patients being studied, should none be observed.

8.2 Data Analysis

The continuous data will be summarised descriptively by number of subjects, mean, standard deviation (SD), median, minimum and maximum. The categorical data will be summarised descriptively by frequency counts along with associated percentages.

8.2.1 Analysis Sets

The following three analysis sets are defined:

- Intent-to-Treat (ITT) analysis set consists of all subjects for whom TBS was identified. Subjects who do not complete the procedure after TBS identification will be included in the ITT.
- Per-Protocol (PP) (Evaluable) analysis set consists of all ITT subjects who have no major protocol deviations affecting the primary effectiveness endpoint and have data available for this endpoint.
- Safety analysis set consists of all subjects who received study product.

The primary effectiveness endpoint will be analysed using the ITT and the PP sets. However, the primary analysis will be based on the ITT set. The PP analysis will be considered supportive.

All secondary effectiveness endpoints (listed in section 8.3.1) will be analysed using the ITT set, while safety endpoints (listed in section 8.4.1) will be analysed using the Safety set.

It is not anticipated that there will be data missing for the primary or secondary effectiveness endpoints, but, if there is, the analyses based on the ITT set will consider missing data as failures for these endpoints. Missing data for safety endpoints will not be imputed.

Major protocol deviations will be determined prior to database lock.

8.3 Effectiveness

8.3.1 Effectiveness Variables

The following primary endpoint will be analysed using the ITT and per protocol sets:

- Proportion of subjects achieving haemostatic success at **5** minutes following the application of SURGICEL Powder with no re-bleeding requiring additional treatment at the TBS any time prior to initiation of final fascial closure.

The following secondary endpoints will be analysed using the ITT set only:

- Proportion of subjects achieving haemostatic success at **3** minutes following the application of SURGICEL Powder with no re-bleeding requiring additional treatment at the TBS any time prior to initiation of final fascial closure.
- Proportion of subjects achieving haemostatic success at **10** minutes following the application of SURGICEL Powder with no re-bleeding requiring additional treatment at the TBS any time prior to initiation of final fascial closure.

8.3.2 Methods of Analysis

For binary (success/failure) primary and secondary effectiveness endpoints (3, 5, and 10 minutes haemostasis endpoints), the number and percentage of subjects with treatment success as well as the two-sided Clopper-Pearson 95% CI around the proportion of successes will be reported. Missing outcomes in the ITT set will be treated as effectiveness failures. No inferential statistical analysis will be performed for the effectiveness endpoints.

8.4 Safety

8.4.1 Safety Variables / Criteria

The safety endpoints for the study include;

- Incidence of thromboembolic events that were assessed as having either a possible, probable or causal relationship to the study treatment (from time of SURGICEL Powder application at TBS through 30-day follow-up via phone call or office visit);
- Incidence of post-operative re-bleeding that was assessed as having either a possible, probable or causal relationship to the TBS and requiring medical/surgical intervention (from initiation of final fascial closure through 30-day follow-up via phone call or office visit);
- Incidence of serious adverse events requiring surgical intervention and assessed as having either a possible, probable or causal relationship to the study treatment (from time of

SURGICEL Powder application at TBS through 6-month follow-up done via phone call or office visit)

8.4.2 Methods of Analysis

Adverse events will be summarised descriptively, using Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Safety data will be summarised descriptively as described in section 8.2. No inferential statistical analysis will be performed for the safety endpoints.

8.5 HEOR (Health Economics & Outcomes Research)

Data collected in this study may be used in Health Economics and Outcomes Research (HEOR). In addition, data using the surgeon EUQ (Ease of Use Questionnaire), a tool validated in prior clinical trials, will also be collected.

HEOR data will be summarised descriptively as described in section 8.2. No inferential statistical analysis will be performed for the HEOR outcomes.

8.6 Schedule of Analyses

Two analyses will be performed. The first analysis will occur after all subjects complete phone call or office visit 1 [30 days (+ 14 days) post-surgery]. All data collected through 30-day (+14 days) follow-up will be analysed. The second analysis will occur after all subjects complete phone call or office visit 2 [6-month (+/-30 days) post-surgery] and the data collected at this follow-up is available. The second analysis will be performed on the data from the 6-month follow-up assessing any occurrences of SAEs requiring surgical intervention and assessed as having either a possible, probable or causal relationship to the study treatment

8.7 Handling of Missing Data

It is not anticipated that there will be data missing for the primary or secondary effectiveness endpoints, but, if there is, the analyses based on the ITT set will consider missing data as failures for these endpoints. Missing data for safety endpoints will not be imputed.

9 ASSESSMENT OF SAFETY

Sponsor's Medical Director (Study Medical Monitor/Safety Lead) will assess all serious adverse events for causality and expectedness and will utilise Ethicon's Product Safety Committee (PSC) to review and adjudicate the following safety signals:

- Thromboembolic events
- Postoperative re-bleeding
- Reoperations for complications assessed as having a possible, probable or causal relationship to the study treatment

The PSC will also review cumulative safety data from the study. The PSC will advise on the continuing safety of study subjects and those yet to be recruited to the study. Based on cumulative data from the study, the PSC may recommend whether to continue, suspend, modify, or stop the study. At the conclusion of the study, the PSC will also give a final assessment of the safety of the product from this study. The composition, responsibilities, frequency of PSC meetings, handling of emergency situations, and documentation of PSC meetings will be specified in the Safety Management Plan (SMP).

Stopping Rules:
The rules outlined below will be used to determine if the clinical trial should be put on hold contingent on PSC recommendations:

- If three confirmed thromboembolic serious adverse events (PE/DVT SAEs) are reported and assessed as being related to the study treatment.
- If one or more subject(s) develops post-operative bleeding and the TBS is confirmed as the cause of the re-bleeding. The relatedness of the SAE to the study treatment is to be determined by the following:
    - Findings at re-operation
    - Findings of TBS re-bleeding at autopsy (if applicable)

10 ADVERSE EVENTS

Adverse Events associated with the device, or the procedure, and incidents such as those specified in local laws and regulations will be captured and reported during this study. Monitoring of study sites by Sponsor personnel will ensure that adverse events and product complaints are documented.

The Sponsor will review reported AEs and SAEs according to the current Safety Management Plan.

10.1 Definitions

10.1.1 Pre-existing Condition

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

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

10.1.2 Enrolled Subject

A subject that has signed the informed consent form.

10.1.3 Treated Subject

A subject that has received SURGICEL Powder at TBS. Routine use of SURGICEL Powder is not included in this definition.

10.1.4 Evaluable Subject

A subject for whom the TBS was identified, who has no major protocol deviations that affect the primary effectiveness endpoint and has data for this endpoint.

10.1.5 Adverse Event

For this study, an AE is an untoward medical occurrence (sign, symptom or disease) in a subject or clinical trial subject and which does not necessarily have a causal relationship with the study medical device. An untoward medical occurrence includes any new, undesirable medical experience or worsening of a pre-existing condition.

SURGICEL Powder application at TBS through the 30-Day Follow-Up: All AEs, whether attributable to the device/procedure or not, are to be recorded in the eCRF and reported to the Sponsor.

10.1.6 Adverse Device Effect

An Adverse Device Effect (ADE) is an adverse event related to the use of a study medical device. This includes any adverse event resulting from insufficient or inadequate Instructions for Use, deployment, implantation, or operation, or any malfunction of the study medical device. An ADE may also include any event resulting from use error or from intentional misuse of the study medical device.

10.1.7 Unexpected Adverse Device Effect

An unexpected ADE is an adverse device effect, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure or product labelling).

10.2 Serious Adverse Event

It is the Investigator's responsibility to determine the "seriousness" of an AE using the protocol defined terms below. An SAE is any AE that results in any of the following:

- Death or a life-threatening event.
- Inpatient hospitalisation or prolongation of hospitalisation.
- Persistent or significant disability/ incapacity.
- Congenital anomaly/ birth defect.

Notes:

1. For this protocol, adverse events of special interest (AESI) include: thromboembolic events, post-operative re-bleeding from the TBS, and re-operations for conditions considered as having either a possible, probable or causal relationship to the study treatment. If the AESI does not meet any other seriousness criteria it will still be considered serious as defined by medically important event criterion.

2. "Death" should not be reported as an AE. The cause of death should be reported as an AE. The only exception is "Sudden Death", when the cause is unknown.
3. Planned hospitalisation for a pre-existing condition is not considered an SAE.
4. A procedure required by the protocol is not considered an SAE, unless the subject experiences a serious deterioration in health or hospitalisation is prolonged.

SURGICEL Powder application at TBS through 30-Day Follow-Up: All SAEs, whether attributable to the device/procedure, are to be recorded in the eCRF and reported to the Sponsor.

6-Month Follow-Up: SAEs requiring surgical intervention and assessed as having either a possible, probable or causal relationship to the study treatment are to be recorded in the eCRF and reported to the Sponsor.

Follow-up on all SAEs assessed as having either a possible, probable or causal relationship to the study treatment, which were ongoing at the 30-day post-surgery follow-up will be assessed.

10.2.1 Serious Adverse Device Effect (SADE)

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

10.2.2 Unexpected Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: Expected serious adverse device effect is an effect which by its nature, incidence, severity or outcome has been identified in the IFU and IB.

10.3 Severity of Adverse Events

It is the Investigator's responsibility to assess the severity of an AE. A change in severity may constitute a new reportable AE. The following guideline should be used to determine the severity of each AE:

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

10.4 Relationship/Attribution of Adverse Events

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

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

- **NOT RELATED**
- **UNLIKELY**
- **POSSIBLE**
- **PROBABLE**
- **CAUSAL RELATIONSHIP**

Refer to the Adverse Event Causality Assessment Guide in Appendix 3, Section 15.3 for detailed guidance on determining the relationship.

10.5 Reporting Adverse Events

SURGICEL Powder application at TBS through 30-Day Follow-Up: All adverse events (both serious and non-serious), whether attributable to the device/procedure or not, will be reported from time of SURGICEL Powder application at TBS until completion of the 30-day follow-up. The Investigator will evaluate the severity of the event, and its relatedness to the study device or procedure and the information will be entered in the AE eCRFs.

6-Month Follow-Up:

Follow-up on all SAEs that Investigator reported as having either a possible, probable or causal relationship to study treatment, which were ongoing at the 30-day post-surgery visit will be assessed.

SAEs requiring surgical intervention and assessed as having either a possible, probable or causal relationship to the study treatment will be reported at the 6-month follow-up. The Investigator will evaluate the severity of the event, and its relatedness to the study device or procedure and the information will be entered in the AE eCRFs.

Any necessary medical management of the event will be recorded in the subject's medical record/source document.

The Investigator will record all AEs (both serious and non-serious) in the source documents. CTC (Common Terminology Criteria) should be used when recording AEs. In addition, the following information should be recorded:

- Onset date
- Resolution date or date of death
- Severity of the event

- Action taken
- Event status (ongoing at study end or resolved)
- Relationship of AE to the study treatment
- Relationship of AE to the study procedure
- Indication of seriousness

Reporting Serious Adverse Events to the Sponsor

SURGICEL Powder application at TBS through 30-Day Follow-Up:
The study site must report all SAEs, whether they are related to the device or procedure, to the Sponsor as soon as possible, but no later 72 hours of becoming aware of the SAE.

6-Month Follow-Up:
The study site must report SAEs requiring surgical intervention and assessed as having either a possible, probable or causal relationship to the device or procedure to the Sponsor as soon as possible, but no later 72 hours of becoming aware of the SAE.

The study site will report SAEs by entering the event into the EDC system via the Adverse Event eCRF, which will trigger an automated email to the Sponsor. Additional information, including the Investigator's assessment, may be added to the eCRF later; however, the study site must complete the AE eCRF within 72 hours of becoming aware of the SAE. If the Sponsor requires supporting documentation or other information, the Sponsor will contact the study site.

In the event of death, the Investigator must report all available information to the Sponsor.

The report of an SAE by a site does not constitute an admission that study personnel or the user facility (hospital/clinic) caused or contributed to the event. The study site is responsible for submitting AEs to the reviewing IRB/EC, per their IRB/EC procedures.

Reporting Non-Serious Adverse Events to the Sponsor

SURGICEL Powder application at TBS through 30-Day Follow-Up:
All non-serious AEs, whether attributable to the device/procedure or not, will be reported from time of SURGICEL Powder application at TBS until completion of the 30-day follow-up. For all non-serious AEs, the study site is expected to complete the Adverse Event eCRF within 2 weeks of becoming aware of the event. Supporting documentation may be requested, as needed.

Reporting Unanticipated Adverse Device Effects to the Sponsor
The study site must report all UADEs to the Sponsor as soon as possible, but no later 72 hours of becoming aware.

Information not available at the time of the initial report (e.g., an end date for the UADE) must be updated within [redacted]. In the event of a fatal or life-threatening event, any required follow-up information must be submitted to the Sponsor immediately, but no later than 10 calendar days of the initial report.

If the Sponsor determines an UADE presents an unreasonable risk to subjects, the Sponsor shall terminate all or a portion of investigations as soon as possible so as not to jeopardise the health of any subject.

Termination shall occur no later than 5 working days after the Sponsor makes this determination and no later than 15 working days after the Sponsor first receives notice of effect. Resumption of terminated studies can occur only with IRB/EC and Health Authority approval.

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 or as a result of user error. The Investigator must contact the Sponsor should this occur.

11 PRODUCT COMPLAINT DEFINITION

A product complaint is defined as any written, electronic or oral communication that alleges A product complaint is defined as any written, electronic or oral communication that alleges deficiencies related to the identity, labelling, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution. A product complaint may or may not be associated with an AE/SAE.

Product complaints may include, but are not limited to:

- Product contamination;
- Defective components;
- Poor packaging or product mix-up;
- Questionable stability;
- Device malfunction (the failure of a device to perform as intended for this study);
- Labelling concerns;
- User errors.

11.1 Reporting Product Complaints

Product complaints related to or possibly related to the study devices must be reported to the Sponsor by completing the Product Complaint form in a timely manner. For all UADEs, the Sponsor must be notified within 72 hours of the site becoming aware. If an Ethicon representative is made aware of a product complaint related to the study device, the event should be reported within 24 hours of their awareness.

Product Complaint forms related to the study device should be emailed to:
[redacted]

Alternatively, product complaint information may also be reported by calling [redacted]).

12 REGULATORY OBLIGATIONS

12.1 Informed Consent

Regulations concerning the protection of subjects require that informed consent be obtained before a subject may participate in any clinical investigation. Regulations concerning the protection of subjects require that informed consent be obtained before a subject may participate in any clinical investigation. Screening assessments that are part of standard-of-care (SOC) may occur prior to consent; however, the data may not be collected for study purposes until the ICF has been signed by the subject. A subject will be considered enrolled upon signing the study site's ICF. Treated subjects are those that receive SURGICEL Powder at a TBS.

An IRB/EC approved informed consent must be sought from each subject and must be appropriately documented in the subject's medical record prior to initiating the study. It is the Investigator's responsibility to obtain written informed consent from the subject, however, the Investigator may delegate this responsibility if appropriately documented.

The informed consent process involves the following: giving a subject adequate information concerning the study, providing adequate time for the subject to consider all available options, responding to the subject's questions, ensuring that the subject has comprehended this information and finally, obtaining the subject's written consent to participate in this study. All subjects in this study should be completely informed about the purpose, risks, benefits, and other pertinent details of this study. The informed consent process is careful to avoid the perception of any coercion or undue influence on, or inducement of, the subject to participate, and does not waive or appear to waive the subject's legal rights. The ICF is presented in native, non-technical language that is understandable to the subject.

Prior to a subject's participation in this study, an ICF will be signed and dated by the subject and person who conducted the consent discussion. The subject will be provided a copy of the signed ICF. The ICF and any other written materials provided to the subject to assist in the decision to participate must be revised whenever new information becomes available that may be relevant to their willingness to participate or continue participation in this study. Revision to the ICF and other written materials will receive IRB/EC approval before implementation. Each subject will be

required to sign any amended ICF (as required by the IRB/EC) and will receive a copy of the signed ICF.

12.2 Institution Approval / Ethics Committees

Participating Investigators will ensure that this protocol, Informed Consent Form (ICF), and if applicable, any protocol amendments or other written information provided to the subjects that assist in the decision to participate are reviewed by an Institutional Review Board (IRB) or Ethics Committee (EC) that complies with governmental requirements. The approving IRB/EC will be responsible for the initial and continuing review and approval of this clinical investigation. Participating Investigators will be required to promptly report to the IRB/EC as required by the IRB/EC's policies. Additionally, Investigators will be required to refrain from making any changes in the clinical investigation plan without Sponsor and IRB/EC approval of an amended protocol, except where necessary to eliminate apparent immediate hazards to study subjects or others.

12.3 Data Management

12.3.1 Electronic Data Capture (EDC)

An EDC system will be used by site personnel to transfer data from source records (medical records and/or source document worksheets) onto common eCRFs. This system is a web-based, secure electronic software application [redacted].
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 data at the site. Designated site personnel will be responsible for entering subject 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 [redacted] staffed by the outsourced vendor will also be available to respond to site and monitor questions.

12.3.2 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 electronic CRFs provided by Sponsor in accordance with the parameters set forth in ICH Topic E6 for GCP (1.5.96) Guidelines - Responsibilities of Sponsor, Monitor and Investigator. All data on the eCRFs should be recorded with 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. The 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.

12.3.3 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]

Investigators must keep accurate separate records (other than the CRFs) of all subjects' phone calls, 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 documented.

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

12.3.4 Source Documentation

Investigators must keep accurate separate records (other than the eCRFs) of all subjects' phone calls, ensuring the inclusion of 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 screening failures). This confidential subject identification # provides the link between named subject source records in the subject file and anonymous eCRF data provided to Sponsor.

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. If regional regulations differ, the Investigator must retain

study related documents by whichever is longer. Study documents should not be destroyed without prior written agreement between the Investigator and Sponsor. The Sponsor must be notified if the Investigator wishes to assign the study records to another party, or move them to another location.

12.4 Data Quality Assurance

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

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate sites, review of protocol procedures with the Investigator and associated personnel prior to the study, and periodic monitoring phone calls or visits by the Sponsor. The Sponsor will review eCRFs for accuracy and completeness during on-site monitoring; any discrepancies will be resolved with the Investigator or designees, as appropriate.

Any deviations from the protocol or procedures should be recorded in the source documents.

All protocol amendments must be issued by the Sponsor, signed and dated by the Investigator, and should not be implemented without prior IRB/EC approval, except where necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)). The Investigator reports the protocol amendments to the IRB/EC as per their local requirements. The Investigator reports the protocol amendments implemented without prior Sponsor or IRB approval (i.e. where necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study) to the Sponsor as soon as possible.

Investigator Training

Prior to screening subjects for this study, the PI, sub-Investigators, study coordinators, and other designated staff (as applicable) will be provided information on study execution, data collection, and procedures specific to this clinical protocol.

Monitoring

This study will be monitored by the Sponsor to ensure the following:

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

The extent and nature of monitoring will be predetermined and agreed to by the Sponsor and Investigators. Monitors will comply with established written standard operating procedures as well as procedures (i.e., monitoring plan) specified by the Sponsor for monitoring this study as characterised in the monitoring plan.

12.5 Protocol Deviation

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

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate sites, the review of protocol procedures with the Investigator and associated personnel prior to the study, and periodic monitoring visits by the Sponsor. The Sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits; any discrepancies will be resolved with the Investigator or designees, as appropriate.

Any deviations from the protocol or procedures should be recorded in the source documents.

12.6 Sponsor Obligations

12.6.1 Study Monitoring and Auditing

The Sponsor monitor or designee will contact the Investigator regularly and will be allowed, on request, to inspect the various records of the trial. The monitor will contact the site as soon as possible following surgery of the first treated subject and at regular intervals during the study as deemed necessary. It will be the monitor's responsibility to inspect the source documents 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 during these monitoring phone calls or visits are resolved.

The study may be subject to audit by the Sponsor or by regulatory authorities. If such an audit occurs, the Investigator must agree to allow access to required subject records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives, and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation.

12.6.2 Regulatory Requirements

This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

12.6.3 Liability and Insurance Conditions

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

13 INVESTIGATOR OBLIGATIONS

The Investigator is responsible for ensuring that this study is conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the ICH GCP, the signed Clinical Study Agreement, this Protocol, the institution's IRB/EC policies and procedures, requirements. And applicable regulatory and country-specific requirements.

Prior to the initiation of this clinical investigation at each site, the responsible Principal Investigator will approve this Protocol by signing the signature page. This signature confirms that the clinical trial will be performed in compliance with the Protocol.

The following documents must be provided to the Sponsor prior to study start:

1. A copy of the formal written notification to the Investigator regarding approval of the protocol by an IRB/EC that is in compliance with regulatory guidelines.
2. A copy of the IRB/EC approved ICF and other adjunctive materials (e.g., advertising) to be used in the study, including written documentation of IRB/EC approval of these items.
3. Name and address of the IRB/EC, and a current list of the IRB/EC members. If accompanied by a letter of explanation from the IRB/EC, a general statement may be substituted for this list, or a general assurance number.
4. Applicable local regulatory documentation.
5. Signed and dated protocol Investigator Signature page.
6. Signed confidentiality agreement between the Investigator and the Sponsor Signed confidentiality agreement between the Investigator and the Sponsor.
7. Signed and dated clinical study agreement, including financial agreement.
8. Up-to-date signed and dated curriculum vitae for each investigator and sub-investigator.

13.1 Financial Disclosure

The Investigator is responsible for updating the Sponsor if there are any changes that would affect their Financial Disclosure during the conduct of the study.

13.2 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.

13.3 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, and enrolment 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.

13.4 Record Retention

The Investigator must maintain all documentation related to the study until notified by the Sponsor. The Investigator will allow representatives of the Sponsor and all other government regulatory agencies to inspect all study records, eCRFs, and corresponding portions of the subject's office and/or hospital medical records at regular intervals during the study. These inspections are to verify adherence to the protocol, integrity of the data being captured on the eCRFs, and compliance with applicable regulations.

Study reports will not identify subjects by name. These reports may be submitted to regulatory authorities.
If custody of the clinical study records is transferred, notice of such a transfer should be given to the Sponsor no later than 10 working days after the transfer occurs.

14 CHANGES TO THE PROTOCOL

14.1 Protocol Amendments

All protocol amendments are required to be submitted for information / consideration to the regulatory authorities, IRBs and ECs. Documentation of approval is required before implementation of amendments.

All protocol amendments must be issued by the Sponsor, signed and dated by the Investigator, and should not be implemented without prior IRB/EC approval, except where necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study [e.g., change in monitor(s), change of telephone number(s)].

The Investigator will report the protocol amendments to the IRB/EC as per their local requirements. The Investigator will report any protocol amendments implemented without prior Sponsor or IRB approval (e.g., where necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study) to the Sponsor as soon as possible.

14.2 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, Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subjects' interests and safety.

14.3 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 relating to the continued development of the SURGICEL Powder 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.

In addition, publication of the results of this study will be governed by J&J publication policies, including current and applicable Medical Device Publication Policy. Any presentation, abstract, or manuscript will be made available for review by operating company prior to submission. Licensing agreements or copyrights applying to tools, work products or intellectual property used during the study should be observed and clearly displayed on study documentation and publications, wherever appropriate.

The Investigator understands not to use the name of Johnson & Johnson (J&J), Ethicon, Ethicon Biosurgery, 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.

15 APPENDICES

15.1 Appendix 1: Ethicon Contact Details

15.2 Appendix 2: United States 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.

15.3 Appendix 3: Adverse Event Causality Assessment Guide

Not Related	Relationship to the device or procedures can be excluded when: - the event is not a known[1] side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the event can be attributed to another cause (e.g. an underlying or concurrent illness / clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis[2], when applicable; - harms to the subject are not clearly due to use error; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

[1] When the event is not a known side effect of the product category the device belongs to or of similar devices and procedures, generally is considered "not related". Yet, the unexpected effect shall not be excluded from evaluation and reporting.

[2] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition.

Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that • the investigational device or procedures are applied to; • the investigational device or procedures have an effect on; - the event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis[3] when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

[3] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition.

15.4Appendix 4: Glossary

List of Abbreviations and Acronyms

Acronyms / Abbreviations	Terms
ADE	Adverse Device Effect
AE	Adverse Event
aPTT	Activated Partial Thromboplastin Time
BIOS	Biosurgery
CI	Confidence Interval
CTC	Common Terminology Criteria
DVT	Deep Vein Thrombosis
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EUQ	Ease of Use Questionnaire
GCP	Good Clinical Practice
HEOR	Health Economics and Outcomes Research
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFU	Instructions for Use
INR	International Normalised Ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
J&J	Johnson & Johnson
MedDRA	Medical Dictionary for Regulatory Activities
OC	Oxidised Cellulose
ORC	Oxidized Regenerated Cellulose
OTC	Over the Counter
PE	Pulmonary Embolism
PMCF	Post Market Clinical Follow-up
PP	Per-Protocol
PSC	Product Safety Committee
PT	Prothrombin Time
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMP	Safety Management Plan
SOC	Standard of Care
TBS	Target Bleeding Site
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

16 REFERENCES

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