

# INVESTIGATIONAL NEW DEVICE CLINICAL PROTOCOL

LUBRICOAT® 0.5% Ferric Hyaluronate Gel  
PROTOCOL No. PTL-0013, Rev. 1

CLINICAL EVALUATION OF LUBRICOAT 0.5% FERRIC HYALURONATE GEL  
FOR THE REDUCTION OF ADHESIONS FOLLOWING PERITONEAL CAVITY  
SURGERY, A MULTICENTER STUDY OF SAFETY AND EFFICACY

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## I. INTRODUCTION

Postoperative adhesions, a frequent abdominal surgical complication, may result in patient complaints ranging from abdominal discomfort to bowel obstruction and infertility. An adhesion, in this protocol, is defined as fibrous tissue or band(s) interconnecting at least two organs or sites. Adhesions can form following surgery at sites which had no pre-existing adhesions. These are termed "*de novo* adhesions". *De novo* adhesions can form at sites of surgical trauma, a "surgical site *de novo* adhesion", or at sites which had no surgical intervention, a "non-surgical *de novo* adhesion". Pre-existing adhesions which are lysed, i.e. the organ or site is freed from the other structure to which it was attached, can also reform. These are termed "reformed adhesions". Reformed adhesions can be further classified depending on the size (extent) and tenacity (severity) of the original adhesion which was lysed as well as the size (extent) and tenacity (severity) of the adhesion which reforms. Thus, as with *de novo* adhesions, reformed adhesions can be classified according to the extent of surgery or injury which occurred at a particular site.

Numerous products have been used for the purpose of reducing adhesion formation; among these, saline peritoneal lavage, antibiotic therapy and HYSKON®. Thus far, clinical experience with these treatments has been equivocal. FDA-approved INTERCEED®(TC7) Absorbable Adhesion Barrier has been proven efficacious, but as is inherent with barrier fabric or film products, the effect is localized and therefore site specific. Interest therefore continues in the development of an intraperitoneal device which functions more broadly as a post-surgical adhesion prophylactic.

Sodium hyaluronate (HA), present throughout the body, is a naturally-occurring polydisperse molecular weight mucopolysaccharide comprised of sodium D-glucuronate and N-acetyl-D-glucosamine which are linked as disaccharides by beta 1-3 linkages. The subunits are joined by beta 1-4 glycosidic bonds. It is hydrolyzed to disaccharide or tetrasaccharide units by the action of the enzyme hyaluronidase. HA has been shown to significantly reduce adhesion formation in animal models and is believed to function through a physical effect by providing a viscous, lubricious coating on the peritoneal surfaces. In clinical evaluations conducted by ETHICON, Inc., sodium hyaluronate, supplied by Lifecore Biomedical Inc., was found to be safe but only marginally effective, with the greatest effect coming from a reduction in *de novo* adhesions.

LUBRICOAT 0.5% Ferric Hyaluronate Gel is an aqueous solution of sodium hyaluronate which has been ionically crosslinked by the addition

of a ferric chloride solution. Crosslinking between the carboxylate groups on the HA and the trivalent iron ( $Fe^{+3}$ ) is ionic in nature, resulting in a significant increase in solution viscosity compared to the starting HA solution. The ionically crosslinked LUBRICOAT 0.5% Ferric Hyaluronate Gel prevents or reduces adhesion formation in preclinical animal models where HA has little or no effect. It is hoped that the new device will be superior in reducing post operative peritoneal adhesion formation in humans as well.

LUBRICOAT 0.5% Ferric Hyaluronate Gel is an amber, viscous liquid formulated to a specific viscosity range. It is packaged in 100 mL Type I borosilicate amber vials with 20 mm flip tear-off seals, and is a sterile, nonpyrogenic gel of a highly purified medium molecular weight hyaluronate adjusted to isotonicity with sodium chloride.

A pilot study to assess study methodology and to make a preliminary assessment of the safety of LUBRICOAT Gel was carried out. This single center study was conducted in an open-label, randomized, controlled design. Female patients undergoing peritoneal cavity surgery by laparotomy for infertility, with a planned second-look laparoscopy, received either 300 mL of LUBRICOAT Gel or Lactated Ringer's Solution as an intraperitoneal instillate prior to closure. This volume was based on clinical studies conducted with non-crosslinked sodium hyaluronate solution and is believed to be sufficient to coat the entire surface of the peritoneal cavity. No safety concerns were identified. A total of 23 patients, 13 LUBRICOAT Gel and 10 Lactated Ringers Solution, were enrolled in the study, and 21 second-look laparoscopies, 11 LUBRICOAT Gel and 10 Lactated Ringer's Solution, were completed. No unusual lesions were observed grossly upon second-look laparoscopy, and no clinically significant differences in laboratory values, concomitant medications, or adverse events were noted between treatment and control groups.

## II. OBJECTIVE

The objective of this multicenter study is to assess the safety and efficacy of LUBRICOAT 0.5% Ferric Hyaluronate Gel in preventing or reducing adhesions in patients undergoing peritoneal cavity surgery.

## III. DESIGN CONSIDERATIONS

This multicenter study will be conducted in a third-party blinded, parallel group, randomized, controlled design. Female patients undergoing peritoneal cavity surgery by laparotomy with a planned second-look laparoscopy will be administered 300 mL of LUBRICOAT 0.5% Ferric

Hyaluronate Gel or Lactated Ringer's Solution as an intraperitoneal instillate at the completion of the laparotomy procedure.

The primary indication for surgery will include infertility, pain, and/or irregular vaginal bleeding in patients desirous of retaining their fertility. The principle surgical procedure to be performed at the initial laparotomy will include adhesiolysis, surgical treatment of endometriosis, myomectomy, repair of the Fallopian tube and other pelvic reconstructive surgical procedures, ovarian cystectomy, as well as surgical procedures to facilitate ovulation.

A maximum of twelve (12) centers will participate in this study. A targeted total of two hundred (200) evaluable patients (100 per group) will be included in the study. A maximum of three hundred and fifty (350) patients will be asked to participate, but no more than two hundred and fifty (250) patients, including those who are not evaluable, will be entered into the study, with a corresponding maximum of forty (40) patients for any individual center. An evaluable patient will be defined as one who has completed her scheduled second-look laparoscopy targeted for six (6) to twelve (12) weeks from the initial surgical procedure (minimum of six (6) weeks, maximum not to exceed eighteen (18) weeks).

Study blind will be maintained by a third party or a surgical assistant. The study device or control solution, as determined by the randomization schedule, will be administered into the peritoneal cavity by a surgical assistant (third party) after the surgeon has completed the primary surgical procedure, achieved complete hemostasis, aspirated all irrigants, removed all packs and sponges, and has left the operating area. The surgeon will then conduct the second-look laparoscopy at the appropriate time interval. Alternatively, the initial surgical procedure and the second-look laparoscopy may be carried out by different surgeons.

The assessment of safety will be based on the preoperative and postoperative laboratory test values, concomitant medications / conditions, adverse events, and gross evaluation at second-look laparoscopy.

The primary efficacy variable will be a total adhesion score using the Adhesion Scoring Method of the American Fertility Society<sup>1</sup> (AFS)

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<sup>1</sup> American Fertility Society. The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Mullerian anomalies and intrauterine adhesions. *Fertil.Steril.* 49:944-955, 1988.

applied to 24 anatomical sites including both pelvic and upper abdominal locations. Scores from all potential adhesion sites will be averaged to yield a total adhesion score (0 to 16 range). Adhesions will be characterized as *de novo* if the site had no pre-existing adhesions and as reformed if the site had adhesions that were lysed during the original surgery. Sites with *de novo* adhesions will also be characterized as surgical versus non-surgical. These analyses will be conducted for all sites as well as for pelvic and abdominal site groupings.

The proportion of sites with adhesions will be analyzed as a secondary efficacy variable. This will be a mean proportion based on the number of sites with adhesions divided by the number of possible adhesion sites. As above, adhesions will be characterized as *de novo* versus reformed, surgical versus nonsurgical, and pelvic versus abdominal. Additional secondary variables will include the extent and severity of all categories of adhesions.

In addition, adhesion sites will be categorized by the presence or absence of endometriosis, use of sutures and the method of adhesiolysis (sharp dissection, blunt dissection, cautery, laser). Each anatomical site will also be analyzed.

This study may be stopped prior to completion and combined with a similar European Multicenter Study (Protocol No. PTL-0022) to achieve two hundred (200) evaluable patients (100 per group). The inclusion and exclusion criteria, including both preoperative and intraoperative exclusions, have been narrowly defined to ensure that treatment regimens, i.e. preoperative procedures, and primary indications for laparotomy and second-look laparoscopy, are similar for all centers, regardless of whether they are in the European or US study. This includes intraoperative exclusions to ensure that some centers will not be entering patients which other centers would not consider candidates for second-look laparoscopy.

Additional discussion and details of the statistical analyses, including the assessment of combinability of the U.S. and European Studies, are presented in Section X.

#### IV. PATIENT SELECTION

##### A. Inclusion Criteria (Preoperative)

1. female patients 18 to 45 years of age requiring peritoneal cavity surgery via laparotomy with preservation of fertility (patients with endometriosis can be included)
2. patients who are able to be scheduled for the Day 7-28 post-surgical laboratory determinations
3. patients who will be scheduled for a second-look laparoscopy as part of their treatment plan targeted for 6 weeks to 12 weeks after the initial surgical procedure (minimum of 6 weeks, maximum not to exceed 18 weeks)
4. patients giving written, witnessed informed consent to participate in the study (This informed consent must be given prior to any study-mandated determinations or procedures to be performed with the exception of the physical examinations as discussed on page 8.)

##### B. Exclusion Criteria / Preoperative

1. pregnant (including ectopic pregnancy) or lactating patients
2. patients undergoing tubal sterilization, reversal of sterilization, or tubal implantation
3. patients currently receiving cancer therapy including drugs and radiation, i.e. within the last 4 weeks
4. patients who have lymphatic ( $WBC \geq 12.5 \text{ K/mm}^3$ ), hematologic or coagulation disorders ( $HGB \leq 8.0 \text{ g/dL}$ ), or patients who are taking anticoagulants
5. patients with a history of hemochromatosis
6. patients with hepatic ( $AST \geq 50 \text{ U/L}$  or  $ALT \geq 50 \text{ U/L}$ ) or renal ( $BUN \geq 25 \text{ mg/dL}$  or  $Creatinine \geq 1.5 \text{ mg/dL}$ ) disorders
7. patients who are taking oral or parenteral hypoglycemic agents for diabetes
8. patients whose preoperative laboratory values are outside 20% of the normal range and considered clinically significant
9. patients who are immunocompromised or possess autoimmune disorders
10. patients who are unable to process large fluid loads, such as patients with congestive heart failure

### C. Exclusion Criteria / Intraoperative

1. patients receiving any peritoneal instillate containing corticosteroids, NSAID's, or HYSKON® (Dextran) (During the procedure, irrigants which may or may not contain heparin and/or antibiotics may be used if completely aspirated.)
2. patients in whom any absorbable hemostat is left in the abdominal / peritoneal cavity (Surgicel® Avitene®, Gelfoam®, etc.)
3. patients receiving any adhesion prevention adjuvant (INTERCEED®(TC7) Absorbable Adhesion Barrier , GoreTex® Surgical Membrane)
4. patients who will need to receive postoperative hydrotubation
5. patients presenting with pelvic or abdominal infection
6. patients who will undergo peritoneal grafting as part of their operative procedure
7. patients in whom fibrin glue or other thrombogenic agents are used
8. any surgical procedure at the time of the initial laparotomy that involves opening of the gastrointestinal or urinary tract
9. patients with 12 or more of the 24 anatomical sites involved with adhesions as noted during the initial operative procedure (refer to Section VI for a discussion of the 24 anatomical sites)
10. patients who have one or more of their anatomical sites removed during the initial operative procedure (refer to Section VI for a discussion of the 24 anatomical sites)

### V. DURATION OF STUDY

The total study duration will be up to 12 weeks, from the initial surgical procedure to the second-look laparoscopy (maximum not to exceed 18 weeks). Total enrollment will be expected to take approximately one year.

### VI. STUDY DESIGN

The study will be conducted as a third-party blinded, parallel group, randomized, controlled design. Each patient asked to participate in the study will be assigned sequentially, by means of a computer-generated random number scheme, to one (1) of two (2) equal groups: LUBRICOAT 0.5% Ferric Hyaluronate Gel (study device), or Lactated Ringer's Solution (control solution).

Patients who would like to participate in the study will undergo the following evaluations and procedures:

A. Preoperative Procedures

1. Inclusion criteria
2. Exclusion criteria
3. Demographics/Medical history
4. Surgical history
5. Physical examination / Vital signs
6. Concomitant medications
7. Laboratory evaluation(s)
8. Comments / Principal Investigator signature

Within the two (2) weeks prior to the initial surgical procedure, general background information including surgical history, current medications (prescription, non-prescription, and iron or iron-containing supplements) and checklists for inclusion/exclusion (including witnessed informed consent) will be obtained.

Each patient will have her vital signs (oral temperature, body weight and height, respiration rate, blood pressure and pulse) measured and will undergo a physical examination. Since these examinations (vital signs and physical examination) represent standard pre-operative practice, they may be performed prior to the patient's signing of the consent form, as long as the examinations are performed within the three (3) weeks prior to the initial surgical procedure.

Serum electrolytes, hematology (CBC with differential), blood chemistries and urinalysis (including a urine pregnancy test) will also be performed within the two (2) weeks prior to the initial surgical procedure.

B. Initial Operative Procedures

1. Adhesion assessment
2. Surgical intervention / Suture use / Endometrial Tissue
3. Operative procedures / Endometriosis / Transfusions
4. Abdominal diagrams
5. Device label check
6. Concomitant medications
7. Adverse events
8. Comments / Principal Investigator signature

Approximately two (2) hours prior to the scheduled surgery, the patient will be assigned the next available study number.

At the time of initial surgical procedure and prior to any adhesiolysis, the investigator will assess the presence of adhesions at each of the 24 anatomical sites listed below, with the exception of the anterior peritoneum incision, i.e. the laparotomy incision, which becomes a site of assessment at second-look:

| Anatomical Site                         | Descriptor   |
|---|--|
| caudal anterior peritoneum              | caudal with respect to the fundus of the uterus                        |
| cephalad anterior peritoneum right      | cephalad with respect to the fundus of the uterus & right of midline   |
| cephalad anterior peritoneum left       | cephalad with respect to the fundus of the uterus & left of midline    |
| anterior peritoneum incision            | the laparotomy incision for this procedure                             |
| small bowel                             |  |
| anterior uterus                         |  |
| posterior uterus                        |  |
| omentum                                 |  |
| large bowel right                       | right of midline   |
| large bowel left                        | left of midline  |
| rectosigmoid portion of the large bowel |  |
| cul-de-sac                              | posterior cul-de-sac, medial to the uterosacral ligaments              |
| right pelvic sidewall                   | lateral to right ureter  |
| left pelvic sidewall                    | lateral to left ureter   |
| right ovary- lateral aspect             |  |
| right ovary- medial aspect              |  |
| right ovarian fossa                     | portion of the broad ligament normally in contact with the right ovary |
| left ovary- lateral aspect              |  |
| left ovary- medial aspect               |  |
| left ovarian fossa                      | portion of the broad ligament normally in contact with the left ovary  |
| right tube                              | tube proximal to ampulla   |
| right ampulla                           | including the infundibulum and fimbriae                                |
| left tube                               | tube proximal to ampulla   |
| left ampulla                            | including the infundibulum and fimbriae                                |

An adhesion, in this protocol, is defined as fibrous tissue or band(s) interconnecting at least two organs or sites. If an adhesion is present, this information will be captured on the appropriate assessment and diagram case report forms. If an adhesion is lysed, i.e. the organ or site is completely freed from the other structure, this information will also be recorded, along with the method of adhesiolysis. The severity and extent of the adhesion(s) will be assessed utilizing the following classifications:

| Severity | Description                                   |
|----------|---|
| Mild     | filmy, avascular adhesion                     |
| Severe   | dense, organized, cohesive, vascular adhesion |

  

| Extent    | Description  |
|-----------|--|
| Localized | less than $\frac{1}{3}$ of the site covered        |
| Moderate  | $\frac{1}{3}$ to $\frac{2}{3}$ of the site covered |
| Extensive | more than $\frac{2}{3}$ of the site covered        |

However, the extent of adhesions will not be determined for the small bowel, omentum, and large bowel right and left, since their size precludes adequate visualization or evaluation.

Areas of additional surgical intervention, and/or use of sutures as well as the presence of endometriosis (along with the American Fertility Society classification and method of lysis) will also be recorded. The investigator will also list the actual surgical procedures performed, the types of sutures used, estimate the amount of blood loss and operative time, note any transfusions, and record all concomitant medications used.

All adhesions seen prior to adhesiolysis will be sketched (at the time of the initial surgical procedure, or shortly thereafter -within 24 hours) with careful attention paid to clearly identifying the anatomical site of attachment, extent, and severity for each adhesion. Any adhesions not lysed will be so indicated on **ASSESSMENT OF ADHESIONS I** as well as the **ABDOMINAL DIAGRAM-I(s)**. Although the drawings are two-dimensional, they can be used to depict adhesions in other planes including anterior to posterior by careful labeling of each adhesion. All incisional lines will also be recorded on the appropriate diagrams.

**NOTE: AN OPTIONAL WORKSHEET IS PROVIDED AS AN AIDE FOR RECORDING THE ADHESION ASSESSMENT IN THE OPERATING ROOM.**

The study device or control solution, as determined by the randomization schedule, will be administered into the peritoneal cavity by the surgeon or surgical assistant (depending on the method of blinding being employed) after the surgeon has completed the primary surgical procedure, achieved complete hemostasis, aspirated all irrigants, and has removed all packs and sponges, providing the intraoperative exclusions do not apply. The Principal Investigator will identify the surgeon and surgical assistant (if applicable, depending on the method of blinding) on the **DEVICE LABEL CHECK** case report form. (Additional discussion of this procedure can be found in Section VII.)

**C. Initial Post-Operative Procedures**

1. Laboratory evaluations
2. Adverse events
3. Concomitant medications
4. Abdominal auscultation and percussion
5. Comments / Principal Investigator signature

Prior to the patient's discharge from the hospital or within 3 days of the initial surgery, serum electrolytes, hematology (CBC with differential) and blood chemistries will again be performed.

The investigator will record any adverse experiences noted by the patient and/or observed by the staff, i.e., post-operative pain, nausea, infection, etc. The patient will be examined for the presence of significant accumulation of abdominal fluid or ascites, by abdominal auscultation and percussion in all four quadrants. The date of discharge will also be noted.

The patient will also be provided with a diary to document medications taken following discharge and to comment on their general status.

**D. Post-Operative Day 7 - 28 Evaluations**

1. Laboratory evaluations
2. Adverse events
3. Concomitant medications
4. Abdominal auscultation and percussion
5. Comments / Principal Investigator signature

Serum electrolytes, hematology (CBC with differential) and blood chemistries will again be performed at the initial postoperative visit at day 7 to 28.

The investigator will also record any adverse experiences noted by the patient and/or observed by the staff, i.e., post-operative pain, nausea, infection, etc. The patient will also be examined for the presence of significant accumulation of abdominal fluid or ascites, by abdominal auscultation and percussion in all four quadrants.

The patient's diary will be retrieved and a new one provided. Prior to completing this visit, the patient must be interviewed regarding any ongoing or new adverse experience(s).

E. Second-Look Laparoscopy

1. Laboratory evaluations (prior to surgery)
2. Adverse events
3. Concomitant medications
4. Adhesion assessment
5. Abdominal diagrams
6. Gross Observations
7. Comments / Principal Investigator's signature

The patients will undergo a second-look laparoscopy targeted for six (6) weeks to twelve (12) weeks following the laparotomy (minimum of six (6) weeks, maximum not to exceed eighteen (18) weeks).

Prior to the surgery, serum electrolytes, hematology (CBC with differential), blood chemistries, and urinalysis (including a urine pregnancy test) will again be performed.

The patient's diary will be retrieved, and the patient will be interviewed regarding any ongoing or new adverse experience(s).

The second-look laparoscopy procedure will be videotaped. During the surgical procedure, the investigator will perform a gross examination of the peritoneal cavity, note any unusual lesions or the presence of ascites, and will repeat the assessment of the presence, severity and extent of adhesions at the same 24 anatomical sites. Specific adhesion sites will again be indicated on the abdominal drawings and recorded on the case report form.

If any tissues or biopsies are taken during this procedure, the histology information will be recorded.

**NOTE: AN OPTIONAL WORKSHEET IS PROVIDED AS AN AIDE FOR RECORDING THE ADHESION ASSESSMENT IN THE OPERATING ROOM.**

## VII. MATERIALS AND METHODS

### A. Supplies

The study device and control will be provided without charge by LIFECORE BIOMEDICAL, INC. The study device and control solution will be packaged in sealed cartons so that there is one (1) carton for each patient appropriately labeled with this protocol number and patient number (from the randomization schedule). Each carton will contain one (1) of the following:

1. LUBRICOAT 0.5% Ferric Hyaluronate Gel, three (3) separate vials each containing 100 mL , or
2. Lactated Ringer's Solution, one package containing at least 300 mL.

The study device will be provided with two (2) part labels affixed to each bottle, a permanently affixed part and a tear-off part. Both parts of the label have appropriate spaces for the patients initials to be entered. The tear-off part of the label, which is to be affixed to CRF **DEVICE LABEL CHECK** contains the concealed identity and lot number, which can be revealed by rubbing off the silver paint in the event of an emergency. The control solution will be labeled with the manufacturers label and the study label. Two (2) additional tear off labels will also be provided, such that three (3) labels can be affixed to the CRF for either treatment or control.

### B. Storage

All study device and control solution vials are to be stored in their cartons in a refrigerator kept at 2-8°C (35.6 - 46.4°F).

### C. Dispensing of Solution

Approximately two (2) hours prior to the scheduled surgery, the patient will be assigned the next available study number, and the appropriate carton will be removed from the refrigerator and

allowed to warm to room temperature. The carton may be placed in a 40° C warming oven to facilitate the warming process.

**NOTICE: DO NOT REMOVE THE VIALS FROM THEIR PROTECTIVE SEALED CARTON DURING THE WARMING PROCESS.**

When the patient has been confirmed as a suitable study candidate, the pre-warmed study device or control solution will be dispensed following normal operating room aseptic technique by the surgeon or surgical assistant (depending on the method of blinding being employed) after the surgeon has completed the primary surgical procedure as discussed below. All 300 mL of the study device or 300 mL of control solution are to be delivered into the abdominal cavity. The amount of material to be administered (300 mL) is sufficient to coat the surfaces of the peritoneal cavity. A slight excess (3 to 8 mL) will remain in each of the study device vials. This excess amount has been added to each study device vial. Excess control solution (200 mL) will also remain.

The patient's initials will be recorded on both parts of the label, i.e. the tear-off portion and permanently affixed portion. All three (3) tear-off labels are to be attached by means of the adhesive backing to the white copy of the **DEVICE LABEL CHECK** case report form.

If at the time of surgery the patient is determined not to be eligible to be included in the study, the sealed carton should be returned to storage and quarantined from the remaining study clinical supplies. At that time, a reason for the patient's disqualification will also be recorded. The principal investigator will also complete the **FINAL STATUS** case report form.

**NOTICE: DO NOT BREAK THE SEALS ON THE CARTON**

All used and/or unused solution bottles and cartons must be accounted for by the Principal Investigator. Lifecore Biomedical, Inc. will provide instruction for either returning supplies or disposal of supplies upon study completion.

**NOTICE: DO NOT RESTERILIZE OR REUSE FOR ANOTHER PATIENT**

#### D. Application of Solution

The study device or control solution will be administered into the peritoneal cavity by the surgeon or surgical assistant (depending on the method of blinding being employed) after the surgeon has completed the primary surgical procedure, achieved complete hemostasis, aspirated all irrigants, and has removed all packs and sponges.

Because the outside of each study device and control solution bottle is not sterile, the contents will be transferred to the sterile field by usual aseptic operating room techniques. Large (60 mL catheter tip or luer lock) syringes fitted with 5 mm diameter (urological catheter or luer lock) irrigation canulas are recommended for removing the gel from the vials for instillation.

The following procedures are recommended when actually administering the study materials:

1. The first application should be approximately 180 mL administered either directly into the pelvis or through an irrigation canula while the small bowel is still out of the operative field. Special attention should be given to direct the study device or control solution to cover all operative sites including the broad ligament, ovarian fossae, pelvic sidewall, tubes and ampullae. Distribution throughout the peritoneal cavity can be facilitated by the surgeon's hand or probe. Special attention should be given to directing the device over the peritoneal surfaces of the left pelvic sidewall and rectosigmoid areas.

2. The remaining material, approximately 120 mL should be administered after the small bowel has been returned to its normal position. During this application, special attention should be given to directing the study device or control solution over the anterior portion of the abdomen including the anterior uterus, omentum and small bowel. Distribution of the solution over the serosal surfaces can be facilitated by the surgeons hand or probe.

VIII. OUTLINE OF PATIENT EVALUATIONS

The evaluations to be performed and the frequency of these evaluations are outlined below.

| SCHEDULE OF EVALUATIONS                               |        |                   |                 |                  |                |
|---|--------|-------------------|-----------------|------------------|----------------|
| EVALUATIONS/PROCEDURES                                | PRE-OP | INITIAL OPERATIVE | INITIAL POST-OP | POST-OP DAY 7-28 | SECOND-LOOK*   |
| Informed Consent                                      | X      |                   |                 |                  |                |
| Inclusion/Exclusion                                   | X      | X                 |                 |                  |                |
| Background Information (Demog., Med. & Surg. History) | X      |                   |                 |                  |                |
| Physical Exam ( &Vital Signs)                         | X      |                   | X**             | X**              |                |
| Concomitant Medications                               | X      | X                 | X <sup>†</sup>  | X <sup>‡</sup>   | X <sup>†</sup> |
| Blood Chemistries                                     | X      |                   | X               | X                | X              |
| Hematology  | X      |                   | X               | X                | X              |
| Pregnancy Test / Urinalysis                           | X      |                   |                 |                  | X              |
| Confidential Patient Follow -Up                       | X      |                   |                 |                  |                |
| Device Label Check                                    |        | X                 |                 |                  |                |
| Adhesion Assessment                                   |        | X                 |                 |                  | X              |
| Suture Use, Surg. Intervention                        |        | X                 |                 |                  |                |
| Endometriosis Evaluation                              |        | X                 |                 |                  | X              |
| Abdominal Drawings                                    |        | X                 |                 |                  | X              |
| Adverse Events  |        | X                 | X               | X                | X              |
| Patient Status  |        |                   |                 | X                | X              |
| Principal Investigator Signature & Comment            | X      | X                 | X               | X                | X              |

\* Concomitant Medications, Blood Chemistries, Hematology, and Pregnancy Test / Urinalysis are to be completed prior to undergoing a second-look laparoscopy.

\*\* A limited physical examination prior to discharge and at the Day 7-28 visits is for the purpose of performing an abdominal auscultation and percussion for assessment of the presence of ascites.

<sup>†</sup> Dispense Daily Patient Diary.

<sup>‡</sup> Collect Daily Patient Diary.

Case Report Forms (CRF) for the evaluations presented in Table 1 will be provided in individual binders, one set per patient. The forms are grouped under the "Schedule of Evaluations" column headings, with the exception of the concomitant medications and adverse events. The latter forms are grouped together in the first section of the binder since this information is to be collected during all phases of the study. Additional discussion of these evaluations and the appropriate CRF follow.

A. Concomitant Medications and Adverse Events

Beginning with the pre-operative phase, all baseline and concomitant medications (with the exception of IV hydrating solutions, anesthetics, and muscle relaxants administered during the surgical procedure) will be recorded on case report form **CONCOMITANT MEDICATIONS**. A copy of the anesthesiologists report will be collected and kept with the patients case report forms.

Medications which are considered necessary for the patient's welfare and which will not either directly or indirectly modify the actions and assessment of the study solution are permitted at the discretion of the investigator. These medications will also be recorded on the **CONCOMITANT MEDICATIONS** form.

The listing of concomitant and baseline medications, including prescription and non-prescription medications, and iron or iron-containing supplements, will be derived from interviewing the patient as well as from the following source documents:

- Patient history (office chart)
- Pre-operative anesthesia notes
- Anesthesia records
- Post-anesthesia care unit records
- Inpatient medication records

All of the above source documents will be made available at the time of monitoring but will not be removed from the study site.

The patient will also be provided with a **DAILY PATIENT DIARY** to document medications taken following discharge and to comment on their general status. The investigator or study coordinator will instruct the patient concerning the use of the **DAILY PATIENT DIARY** and the need to bring the **DAILY PATIENT DIARY** to each follow-up visit. At these visits, the investigator or

study coordinator will review the patient's **DAILY PATIENT DIARY** for completeness and accuracy. Should the patient fail to return the **DAILY PATIENT DIARY** for a specific visit, this fact will be noted in the comments section for that visit. All data concerning medications and comments related to patient status will be recorded on the **CONCOMITANT MEDICATIONS** and **ADVERSE EVENTS** forms where appropriate.

Beginning with the pre-operative phase, all adverse events and/or intercurrent illnesses occurring during the study including the nature, severity and the relation of the incident to the study solution will be recorded on the **ADVERSE EVENTS** case report form.

**B. Preoperative**

General background information including surgical history and checklists for inclusion/exclusion will be obtained within the two (2) weeks before the initial surgical procedure and recorded on the "Pre-Operative" forms **INCLUSION CRITERIA, EXCLUSION CRITERIA PREOPERATIVE, BACKGROUND INFORMATION - DEMOGRAPHIC INFORMATION / MEDICAL HISTORY, and BACKGROUND INFORMATION - SURGICAL HISTORY.**

Each patient will also have a physical examination, including vital signs (oral temperature, body weight and height, respiration rate, blood pressure and pulse) performed within the three (3) weeks before the initial surgical procedure. Since this examination represents standard pre-operative practice, it may be performed prior to the patient's signing the consent form. The results will be recorded on the case report form **PHYSICAL EXAM.**

Each patient will have the below-listed laboratory tests performed within the two (2) weeks before the initial surgical procedure. These test results will be used as a baseline for evaluating the safety of intraperitoneal administration of the study solution:

1. Serum electrolytes (sodium, potassium, calcium, chloride)
2. Hematology (CBC with differential)
3. Blood Chemistries: BUN, total protein, total bilirubin, phosphorus, creatinine, albumin, SGOT, SGPT, alkaline phosphatase, and uric acid.
4. Urinalysis, including a urine pregnancy test

The investigator is responsible for reviewing the laboratory data and having the information recorded on case report form **PRE-OP LABS**. All values should be within 20% of the normal range. If any values are outside of 20% of the normal range, the investigator should consider whether the value is clinically significant and provide comments on form **PRE-OPERATIVE COMMENTS** regarding their decision to include or exclude the patient. The principal investigator will review and sign the latter form after carefully examining and verifying all of the entries in this section.

C. Initial Operative

Approximately two (2) hours prior to the scheduled surgery, the patient will be assigned the next available study number, and the appropriate carton will be removed from the refrigerator and may be placed in a 40° C warming oven to facilitate warming. At the time of initial surgical procedure and prior to any adhesiolysis, the investigator will assess the presence of adhesions at each of the 24 anatomical sites listed below, with the exception of the anterior peritoneum incision, i.e. the laparotomy incision, which becomes a site of assessment at second-look:

| Anatomical Site                         | Descriptor   |
|---|--|
| caudal anterior peritoneum              | caudal with respect to the fundus of the uterus                        |
| cephalad anterior peritoneum right      | cephalad with respect to the fundus of the uterus & right of midline   |
| cephalad anterior peritoneum left       | cephalad with respect to the fundus of the uterus & left of midline    |
| anterior peritoneum incision            | the laparotomy incision for this procedure                             |
| small bowel                             |  |
| anterior uterus                         |  |
| posterior uterus                        |  |
| omentum                                 |  |
| large bowel right                       | right of midline   |
| large bowel left                        | left of midline  |
| rectosigmoid portion of the large bowel |  |
| cul-de-sac                              | posterior cul-de-sac, medial to the uterosacral ligaments              |
| right pelvic sidewall                   | lateral to right ureter  |
| left pelvic sidewall                    | lateral to left ureter   |
| right ovary- lateral aspect             |  |
| right ovary- medial aspect              |  |
| right ovarian fossa                     | portion of the broad ligament normally in contact with the right ovary |
| left ovary- lateral aspect              |  |
| left ovary- medial aspect               |  |
| left ovarian fossa                      | portion of the broad ligament normally in contact with the left ovary  |
| right tube                              | tube proximal to ampulla   |
| right ampulla                           | including the infundibulum and fimbriae                                |
| left tube                               | tube proximal to ampulla   |
| left ampulla                            | including the infundibulum and fimbriae                                |

An adhesion, in this protocol, is defined as fibrous tissue or band(s) interconnecting at least two organs or sites. If an adhesion is present, this information will be captured on the appropriate assessment and diagram case report forms. If an adhesion is lysed, i.e. the organ or site is completely freed from the other structure, this information will also be recorded, along with the method of adhesiolysis.

The severity and extent of the adhesion(s) will be assessed utilizing the following classifications:

| <u>Severity</u> | <u>Description</u>                            |
|-----------------|---|
| Mild            | filmy, avascular adhesion                     |
| Severe          | dense, organized, cohesive, vascular adhesion |

  

| <u>Extent</u> | <u>Description</u>                                 |
|---------------|--|
| Localized     | less than $\frac{1}{3}$ of the site covered        |
| Moderate      | $\frac{1}{3}$ to $\frac{2}{3}$ of the site covered |
| Extensive     | more than $\frac{2}{3}$ of the site covered        |

However, the extent of adhesions will not be determined for the small bowel, omentum, and large bowel right and left, since their size precludes adequate visualization or evaluation.

These data will be recorded on case report form **ASSESSMENT OF ADHESIONS I**.

**NOTE:** The investigator will answer **YES** to the lysing question for each anatomical site only if 100% of the adhesions at that site are lysed, i.e. the organ or site is completely freed from the other structure to which it was adhered. Should less than 100% of the adhesions at a specific anatomical site be lysed, the investigator will then answer **NO** to the lysing question on case report form **ASSESSMENT OF ADHESIONS I**.

The presence of endometriosis, and whether the tissue was excised or fulgurated will also be evaluated at each of the 24 anatomical sites. The investigator will also note suture use and any other surgical intervention for each of the 24 anatomical sites on case report form **SURGICAL INTERVENTION**. The type(s) of sutures used will be noted along with a synopsis of the procedure(s) on the **OPERATIVE COMMENTS** form.

The investigator will also provide data regarding the following:

- the stage of endometriosis (if present) utilizing the AFS scoring system
- listing of the actual surgical procedures (e.g., cystectomy, myomectomy, etc.)
- estimate of blood loss
- transfusion type and amount
- estimate of operative time

These data will be recorded on case report form **OPERATIVE PROCEDURES** and **OPERATIVE COMMENTS**.

All adhesions seen prior to adhesiolysis will be sketched at the time of the initial surgical procedure, or shortly thereafter (within 24 hours) with careful attention paid to clearly identifying the anatomical site of attachment, extent, and severity for each adhesion. Although the drawings are two-dimensional, they can be used to depict adhesions in other planes including anterior to posterior by careful labeling of each adhesion. All incision lines will also be recorded on the appropriate diagrams. These entries will be made on case report forms **ABDOMINAL DIAGRAM-I / POSTERIOR PELVIS**, **ABDOMINAL DIAGRAM-I / ANTERIOR PELVIS**, **ABDOMINAL DIAGRAM-I / LARGE BOWEL**, **ABDOMINAL DIAGRAM-I / RIGHT SAGITTAL**, and **ABDOMINAL DIAGRAM-I / LEFT SAGITTAL**.

**NOTE: AN OPTIONAL WORKSHEET IS PROVIDED AS AN AIDE FOR RECORDING THE ADHESION ASSESSMENT IN THE OPERATING ROOM.**

The study device or control solution, as determined by the randomization schedule, will be administered into the peritoneal cavity by the surgeon or surgical assistant (depending on the method of blinding being employed) after the surgeon has completed the primary surgical procedure, achieved complete hemostasis, aspirated all irrigants, and has removed all packs and sponges, providing the intraoperative exclusions do not apply. The Principal Investigator will identify the surgeon and surgical assistant (if applicable, depending on the method of blinding) on the **DEVICE LABEL CHECK** case report form and complete the **EXCLUSION CRITERIA INTRAOPERATIVE** form.

The tear-off portion of each label is to be removed from all three (3) bottles at the time of surgery and all three (3) labels are to be

attached by means of the adhesive backing to the white copy of the **DEVICE LABEL CHECK** case report form.

If at the time of surgery the patient is determined not to be eligible to be included in the study, the sealed carton should be returned to storage with the seals intact and quarantined from the remaining study clinical supplies. At that time, a reason for the patient's disqualification will also be recorded. The principal investigator will also complete the **FINAL STATUS** case report form.

All used and/or unused solution bottles and cartons must be accounted for by the Principal Investigator. Lifecore Biomedical, Inc. will provide instruction for either returning supplies or disposal of supplies upon study completion.

**NOTICE: DO NOT RESTERILIZE OR REUSE FOR ANOTHER PATIENT**

Additional comments may be made on **OPERATIVE COMMENTS**. The principal investigator will review and sign the latter form after carefully examining and verifying all of the entries in this section.

D. Initial Postoperative

Prior to the patient's discharge from the hospital or within 3 days of the initial procedure, serum electrolytes, hematology (CBC with differential) and blood chemistries will again be performed. These data will be recorded on case report form **POST-OP LABS I**.

The patient will be examined for the presence of significant accumulation of abdominal fluid or ascites, by abdominal auscultation and percussion in all four quadrants. The results from this examination and the date of discharge will be recorded on case report form **POST-OPERATIVE COMMENTS**.

The patient will also be provided with a **DAILY PATIENT DIARY** to document medications taken following discharge and to comment on their general status.

The investigator will also record any adverse experiences noted by the patient and/or observed by the staff, i.e., post-operative pain, nausea, infection, etc. These data will be recorded on case report form **ADVERSE EVENTS**.

Additional comments may be made on **POST-OPERATIVE COMMENTS**. The principal investigator will review and sign the latter form after carefully examining and verifying all of the entries in this section.

E. Postoperative Day 7 - 28

Serum electrolytes, hematology (CBC with differential), and blood chemistries will again be performed at the postoperative visit at day 7 to 28. The patient will also be examined for the presence of significant accumulation of abdominal fluid or ascites, by abdominal auscultation and percussion in all four quadrants. These results will be recorded on case report forms **POST-OP LABS II**, and **DAY 7 -28 COMMENTS** respectively.

The investigator will also record any adverse experiences noted by the patient since the initial operative procedure and/or observed by the staff during the visit, i.e., post-operative pain, nausea, infection, etc. These data will be recorded on case report form **ADVERSE EVENTS**.

The patient's **DAILY PATIENT DIARY** will be retrieved and a new one provided. Prior to completing this visit, the patient must be interviewed regarding any ongoing or new adverse experience(s).

Additional comments may be made on **DAY 7 - 28 COMMENTS**. The principal investigator will review and sign the latter form after carefully examining and verifying all of the entries in this section.

F. Second-Look Laparoscopy

Patients will undergo a second-look laparoscopy as part of their treatment plan targeted for within six (6) weeks to twelve (12) weeks after their initial surgical procedure (minimum of 6 weeks, maximum not to exceed eighteen (18) weeks).

Serum electrolytes, hematology (CBC with differential), blood chemistries, and urinalysis (including a urine pregnancy test) will again be performed prior to the second-look laparoscopy. These data will be recorded on case report form **POST-OP LABS III**.

The patient's **DAILY PATIENT DIARY** will also be retrieved, and the patient will be interviewed regarding any ongoing or new adverse experience(s).

The second-look laparoscopy procedure will be videotaped. During the surgical procedure, the investigator will perform a gross examination of the peritoneal cavity, and note any unusual lesions or the presence of ascites. These observations, along with the name of the surgeon performing the procedure will be recorded on case report form **2<sup>ND</sup> LOOK LAPAROSCOPY COMMENTS**.

The overall presence, severity and extent of adhesions present at this second-look procedure as they appear prior to lysis will be noted for the same 24 anatomical sites. These data will be recorded on case report form **ASSESSMENT OF ADHESIONS II**.

The presence of endometrial tissue at this second-look procedure will also be noted for the same 24 anatomical sites. These data will also be recorded on case report form **ASSESSMENT OF ADHESIONS II**.

The stage of endometriosis (if present) utilizing the AFS scoring system is to be noted on the case report form **2<sup>ND</sup> LOOK LAPAROSCOPY COMMENTS**.

At the time of the second-look procedure, or shortly thereafter (within 24 hours), the investigator will complete the abdominal drawings noting the adhesions as they appear prior to lysis. These drawings will be made on case report form **ABDOMINAL DIAGRAM-II / POSTERIOR PELVIS, ABDOMINAL DIAGRAM-II / ANTERIOR PELVIS, ABDOMINAL DIAGRAM-II / LARGE BOWEL, ABDOMINAL DIAGRAM-I / RIGHT SAGITTAL, and ABDOMINAL DIAGRAM-II / LEFT SAGITTAL**.

**NOTE: AN OPTIONAL WORKSHEET IS PROVIDED AS AN AIDE FOR RECORDING THE ADHESION ASSESSMENT IN THE OPERATING ROOM.**

The investigator will also record any adverse experiences noted by the patient since the previous visit and/or observed by the staff during the visit, i.e., post-operative pain, nausea, infection, etc. These data will be recorded on case report form **ADVERSE EVENTS**.

Additional comments may be made on case report form **2<sup>ND</sup> LOOK LAPAROSCOPY COMMENTS**. The principal investigator will review and sign the latter form after carefully examining and verifying all of the entries in this section.

G. Patient Status

The patient status at the end of study will be recorded upon study completion / discontinuation. Should the patient not complete the entire study, i.e., be determined not to be eligible at the time of the initial surgical procedure or not return for the second-look laparoscopy, she is considered a screen failure or an early termination respectively, and the reason for the discontinuation must be provided. Additionally, at completion / discontinuation, the principal investigator will provide an observation of the patient's condition, and whether any complications were noted. All of the above data will be recorded on case report form **FINAL STATUS**, and the principal investigator will review and sign the latter form after carefully examining and verifying all of the entries in the study binder.

IX. ADVERSE EVENTS

All adverse events and/or intercurrent illnesses occurring during the study including the nature, severity and the relation of the incident to the study solution will be recorded on the **ADVERSE EVENTS** case report form.

Any serious adverse event is to be reported promptly by telephone to the Sponsor even though it may not appear to be device related. A serious adverse event is considered one that results in death, is life-threatening, results in or prolongs hospitalization, results in severe or permanent disability, or involves cancer, a congenital anomaly, or an overdose. LIFECORE BIOMEDICAL, INC. designated contact is:

Gerald L. Klein, M.D.,  
Phone: (619) 941- 4444

There are no anticipated adverse events other than those attendant with the surgery for this indication. The theoretical risks that could be associated with the use of the study solution are ascites, allergic reactions, sepsis, and wound dehiscence, although these were not observed in preclinical animal testing.

## X. STATISTICAL METHODS

### A. PATIENT POPULATIONS

1. The intent-to-treat efficacy and safety populations will consist of all patients who receive LUBRICOAT Gel or Lactated Ringer's Solution.
2. A subset of the intent-to-treat efficacy population will exclude patients who refuse the second-look laparoscopy for reasons unrelated to the device.
3. The evaluable efficacy population will consist of all patients who receive a second-look laparoscopic evaluation.

Patients who are randomized but do not receive treatment will be described but will not be otherwise analyzed. If any patients are incorrectly randomized, alternative analyses will be performed with those patients analyzed in the treatment group or the assigned group.

### B. EFFICACY VARIABLES

The primary efficacy variable will be a total adhesion score using the Adhesion Scoring Method of the American Fertility Society (AFS) applied to 24 anatomical sites. Adhesions occurring at each of the 24 potential adhesion sites will be scored as mild (a filmy avascular adhesion) or severe (a dense organized cohesive vascular adhesion). The extent of adhesions will be graded as Localized (<1/3 of the site covered), Moderate (1/3 - 2/3 of the site covered) or Extensive (>2/3 of the site covered). The extent of adhesions will not be scored for the small bowel, omentum and left and right large bowel since their size precludes adequate visualization. These sites will be assigned a classification of Moderate in order to determine the total adhesion score.

For each adhesion site, the adhesion score will be derived from severity and extent scores as follows:

|                  |                   |    |
|------------------|-------------------|----|
| No Adhesion      |                   | 0  |
| Severity: Mild   | Extent: Localized | 1  |
| Severity: Mild   | Extent: Moderate  | 2  |
| Severity: Mild   | Extent: Extensive | 4  |
| Severity: Severe | Extent: Localized | 4  |
| Severity: Severe | Extent: Moderate  | 8  |
| Severity: Severe | Extent: Extensive | 16 |

Scores from all potential adhesion sites will be averaged to yield a total adhesion score. Adhesions will be characterized as *de novo* if the site had no pre-existing adhesions and as reformed if the site had adhesions that were lysed during the original surgery. Sites with *de novo* adhesions will also be characterized as surgical versus non-surgical.

These analyses will be conducted for all sites as well as for pelvic and abdominal site groupings. Pelvic sites include the caudal anterior peritoneum, anterior and posterior uterus, cul-de-sac, right and left pelvic sidewall and all tube, ampulla and ovarian sites. Abdominal sites include the right and left cephalad anterior peritoneum, small bowel, omentum, right and left large bowel, rectosigmoid and the anterior peritoneum incision.

The proportion of sites with adhesions will be analyzed as a secondary efficacy variable. This will be a mean proportion based on the number of sites with adhesions divided by the number of possible adhesion sites. As above, adhesions will be characterized as *de novo* versus reformed, surgical versus nonsurgical, and pelvic versus abdominal.

In addition, adhesion sites will be categorized by the presence or absence of endometriosis, use of sutures and the method of adhesiolysis (sharp dissection, blunt dissection, cautery, laser). Each anatomical site will also be analyzed.

Additional secondary variables will include the extent and severity of all categories of adhesions. Severity will be scored on a three-point scale where 0 = None, 1 = Mild and 3 = Severe. Extent will be scored on a four-point scale where 0 = None, 1 = Localized, 2 = Moderate and 3 = Extensive.

### C. SAFETY VARIABLES

Safety variables will include the proportions of patients reporting adverse events categorized using COSTART terms. Laboratory values will be presented as mean change from baseline and as transition tables showing the proportions of patients above, below and within the normal range before and after treatment.

### D. DEMOGRAPHIC, PRETREATMENT AND SURGICAL VARIABLES

Age, race, height, weight, blood pressure, previous and concomitant medications (categorized by AHFS codes), presence of endometriosis, surgical procedures (categorized by CPT codes), estimated blood loss, operative time, baseline adhesion scores and length of hospital stay will be analyzed. Use of these variables to determine combinability with a European study (Protocol PTL-0022) is described in Section G.

### E. STATISTICAL ANALYSIS

Second-look adhesion scores will be analyzed using factorial analysis of covariance where one factor is treatment group (LUBRICOAT Gel versus Lactated Ringer's Solution), the other factor is center and baseline adhesion score is a covariate. This will allow analyses of the effect of treatment, the effect of center and the interaction of treatment with center. Homogeneity of slopes will be tested by examination of interactions between baseline adhesion score and treatment group.

If the two groups differ on any important demographic or surgical variables or if these pre-treatment variables appear to strongly predict second-look adhesion scores (as determined using multiple linear regression with treatment group forced into the model as a dummy variable), these variables may be added to the model as covariates. Homogeneity of slopes will be tested by examination of interactions between covariates and treatment group. Pre-treatment variables may be transformed in order to yield homogeneous slopes.

The mean proportion of sites with adhesions at second look will be analyzed in the same fashion as the mean second-look adhesion scores.

Other continuous variables will be analyzed using factorial analysis of variance where one factor is treatment group and the

other factor is center. Analyses to determine combinability will also use continent (US versus Europe) as a factor (see Section G).

Categorical variables will be analyzed using the Cochran-Mantel-Haenszel test with individual sites as strata. Determination of combinability of the US and European data will use categorical models as described in section G. Proportions with small expected event rates (e.g. adverse events) will be analyzed using Fisher's exact test. Laboratory value transition tables will be compared using 2x9 Fisher's exact tests.

Two-sided p values will be reported and p values less than 0.05 will be considered to be statistically significant.

F. INTENT-TO-TREAT ANALYSIS

As requested by FDA, an intent-to-treat analysis will be performed in which patients treated with LUBRICOAT Gel or Lactated Ringer's Solution who do not have a second-look laparoscopy will be considered to be treatment failures. This will be accomplished by assigning them second-look adhesion scores of 16 (the worst possible score). Because this will produce a highly skewed distribution, scores will be transformed to ranks prior to statistical analysis.

G. EVALUATION OF COMBINABILITY

After at least 120 patients have completed the study, the possibility of combining these data with a concurrent European study (Protocol PTL-0022) will be considered. The European study is expected to have enrolled approximately 80 patients by this time. Combinability will be based on three factors.

1. There should be no significant interaction between location (US versus Europe) and treatment efficacy.

2. The US and European population should be similar on demographic and pre-treatment variables and the level of medical care. Variables examined will include:

- Age
- Race
- Body weight
- Baseline adhesion score
- Previous and concomitant medications (AHFS classification<sup>2</sup>)
- Presence of endometriosis
- Surgical procedures performed (CPT classification)
- Estimated blood loss
- Operative time
- Baseline clinical laboratory values
- Length of hospital stay (expected to be longer in Europe)
- Time to second-look laparoscopy
- Number of patients lost to follow-up (by reason for discontinuation)

Continuous variables will be analyzed using factorial analysis of variance where one factor is treatment group (LUBRICOAT Gel versus Lactated Ringer's Solution) and the other factor is location (US versus Europe). All statistically significant effects involving location will be considered as possible sources of non-homogeneity that might preclude combination of the US and European data. Categorical variables will be analyzed using categorical models equivalent to analysis of variance with factors for treatment group, location and the interaction between treatment group and location.

3. The US and European control groups should be similar on second-look adhesion scores. This variable can serve as a proxy for subtle differences in medical treatment. The 95% confidence intervals of the difference between the US and European control groups will be presented.

For each of these factors, data will also be analyzed and presented by individual center within the US and Europe.

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<sup>2</sup> McEvoy, G. K., Ed. American Hospital Formulary Service Drug Information. American Society of Health-System Pharmacists, Inc., Bethesda, MD, 1995.

These data will be presented to FDA and the US and European data will not be combined unless Lifecore, Inc. and FDA agree that there are no clinically significant differences that preclude that combination.

If the US and European centers are combinable, then the study will terminate as soon as that decision is made. All patients currently enrolled in the study will be followed to second-look laparoscopy and added to the database for the final statistical analysis.

If the US and European centers are not combinable, then enrollment in the US protocol will continue until 200 evaluable patients have completed the study.

The decision to stop or continue the study will not be affected by the p values of the difference between LUBRICOAT Gel and Lactated Ringer's Solution. Note that:

1. If the data are not combinable, the U.S. study will not be stopped regardless of the statistical significance of the difference between the treated and control groups (either in the combined US/European study or the US study alone).
2. If the data are combinable, and the difference between the treated and control groups in the combined US/European study is not statistically significant, the study will not be continued, but will be stopped and considered to have failed.

Therefore, p values required to demonstrate statistical significance will not be adjusted.

## H. POWER

Power calculations were performed using the method described by Lachin<sup>3</sup> using an alpha level of 0.05 and a beta level of 0.20 (80% power). Preliminary analysis of a Phase I study indicated a mean adhesion score of 1.7 (Standard deviation: 1.4) for the treated group and 5.7 (Standard deviation: 2.7) for the control group. Assuming that 20% of the treatment group and 10% of the control group are lost to follow-up, scoring these patients as treatment failures would yield a mean adhesion score of 4.6 (Standard deviation: 5.9) for the treated group and 6.7 (Standard deviation: 4.1) for the control group. Assuming a standard deviation of 5.0, 180 patients would be required. Thus the 200 evaluable patients (approximately 250 total patients) appears to provide sufficient power to reject the null hypothesis if the observed trends are maintained.

## XI. PATIENT DROPOUT RATIONALE

Study enrollment has been planned to allow for a worse case 30% screen failure rate and 20% loss to follow-up rate. This correlates with our request for 350 patients to be asked to participate in the study, with 250 expected to receive treatment, and 200 to complete second-look laparoscopy. All patients assigned study numbers and receiving treatment will be carefully followed and all screen failure and loss to follow-up patients documented. All efforts will be made to keep these to a minimum.

Any patient who fails to return for the Day 7 - 28 laboratory determination and/or the second-look laparoscopy will be contacted and interviewed if possible as to her reason for not returning and her medical status ascertained relative to the effects of the study device. All attempts to contact the patient will be documented on case report form **FINAL STATUS**.

A patient may be discontinued from the study at any time in the event of a serious or intolerable adverse event, the need for an excluded medication, an intercurrent illness, a protocol violation or at the patient's request.

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<sup>3</sup> Lachin JM. Introduction to sample size determination and power analysis for clinical trials. Controlled Clinical Trials 2:93-113, 1981.

## XII. MODIFICATION OF PROTOCOL

Neither the investigator nor Lifecore Biomedical, Inc. will modify this protocol without obtaining the concurrence of the other. The party initiating a modification will confirm it in writing. Lifecore Biomedical, Inc. will submit protocol modifications to the Food and Drug Administration as required.

## XIII. MONITORING PROCEDURES

At the time the study is initiated, the monitor will thoroughly review the protocol and Case Report Forms with the investigators and their staff.

During the course of the study, the Sponsor will be available to discuss by telephone, questions regarding adverse experiences, removal of patients from the study, conduct of the study, etc.

At the time of each monitoring visit, the monitor will review the case report forms of each patient in the study to make certain that all items have been completed and that the data provided are accurate and obtained in the manner specified in the protocol. The patients' clinical records will be reviewed to confirm that (1) the case report form data are consistent with the surgeon's clinical records, (2) the background clinical and laboratory data and concurrent medication are documented in the case report forms, and (3) that there is an accurate account of the use of the study device in surgery. The patient's clinical records will be reviewed to determine whether recording of adverse effects has been omitted on the case report forms. If this is found to be so, then the case report forms will be returned to the investigator and corrected to include this information.

The protocol requires Investigators to complete the drawings related to adhesions and surgical procedures within 24 hours of the operation. Following the second-look laparoscopy procedure, these data will be carefully reviewed by the monitor, and then forwarded along with the videotape of the second-look procedure and a copy of the operative dictation notes to an independent masked Medical Review Officer, who will review the videotape and drawings to ensure the data has been accurately represented and transcribed on the key CRF's. Any questions from this medical review will be directed to the monitor for discussion with the surgeon. The surgeon will have final authority in resolving any discrepancies. If the surgeon can not resolve any questions by review of the drawings, operative dictation notes, or videotapes, the data point(s) in question may be dropped. The final drawings are considered the primary source document.

**XIV. PATIENT CONFIDENTIALITY**

The investigators agree to keep patient identification on the **CONFIDENTIAL PATIENT FOLLOW-UP FORM** or a similar form, which will be used for the purpose of long-term follow-up, if needed. This form will be treated as confidential and will be filed with restricted access by the principal Investigator. Otherwise, all reports and communications relating to the study will identify patients by initials and patient number only.

**XV. RECORDS RETENTION**

Federal law requires that a copy of all records (e.g., informed consent documents, laboratory data slips, source documents, safety reports, study device dispensing record, etc.) which support case report forms for this study, must be retained in the files of the responsible investigator for a minimum of two years following notification by Lifecore Biomedical that all investigations (not merely the investigator's portion) are completed, terminated, and discontinued, or that the Food and Drug Administration has approved the Premarket Approval Application.

If the principal investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Lifecore Biomedical must be notified in writing of the name and address of the new custodian.

**XVI. ON-SITE AUDITS**

The United States Food and Drug Administration, in the person of a scientifically trained and properly authorized employee of the department, may request access to all study records, including source documents, for inspection and copying. Similar auditing procedures may also be conducted by a representative of Lifecore Biomedical.

**XVII. REPORTING AND RECORDING OF DATA**

All information required by the protocol is to be provided or an explanation given for omissions. All case report forms must be made available as soon as they are completed in order that the monitor may verify the validity and completeness of the forms and permit prompt transmittal of the data to the Sponsor.

All data and information on these case report forms are to be neatly recorded in type or legibly printed in black ink for ease of duplication, interpretation and analysis before submission to Lifecore Biomedical.

All corrections on the case report forms should be crossed out neatly with a single line and the new entry initialed and dated by the member of the investigator's staff making the correction.

Prior to retrieval of the case report forms by Lifecore Biomedical personnel or their representative, they should be reviewed for completeness, accuracy and legibility by the principal investigator. Copies of the completed case report forms will be provided for retention by the principal investigator.

#### XVIII. DISCONTINUATION OF THE STUDY

Lifecore Biomedical reserves the right to discontinue any study for administrative reasons at any time, such as, but not limited to, a decision to discontinue further clinical investigation with the device, improper conduct of the study by the investigator(s), inability to obtain the number of patients required by the protocol, etc. Reimbursements for reasonable expenses will be made if such an action is necessary.

#### XIX. PUBLICATIONS

It is hoped that the investigator(s) will consider this study for publication in an acceptable professional journal. Any publication resulting from this study will be reviewed by Lifecore Biomedical in advance of submission for each publication. This review is necessary to prevent premature disclosure of trade secrets or otherwise patent-protected material and is in no way intended to restrict publication of facts or opinions formulated by the investigator(s).

Lifecore Biomedical shall have the right to determine the timing of the publication.

#### XX. DISCLOSURE

All information provided to the investigator(s) dealing with this device or the methodologies used in this study, as well as information obtained during the course of the study will be regarded as confidential. The investigators agree not to disclose any information supplied by Lifecore Biomedical in any way without prior permission of Lifecore Biomedical.

**XXI. DEVICE AND CODE LABELS**

All used and/or unused solution bottles and cartons must be accounted for by the Principal Investigator. Lifecore Biomedical, Inc. will provide instruction for either returning supplies or disposal of supplies upon study completion.

The principal investigator agrees not to supply the study device to any person except those named as investigator(s) and patients in this study.

**XXII. DEVICE SECURITY**

In accordance with federal regulations governing investigational devices, the principal investigator agrees to keep study device in a secure location with restricted access.