[ESC-201701]

A Prospective, Multicenter, Randomized Controlled Study to Evaluate the Effect of Absorbable Adhesion Barrier in Preventing the Abdominal Incision Adhesions

INTERCEED

Name of investigational medical device	INTERCEED™ Absorbable Adhesion Barrier
Model/Specification	M4345; M4350; M4350N
Management category of investigational medical device	Class III medical device that needs the approval for clinical trial Y□ N√ Similar product in same Category in China Y√ N□
Protocol version number	5.0
Protocol date	Apr 27 2020
Clinical trial Leading institution	Beijing Friendship Hospital, Capital Medical University
Lead Investigator	Zhang, Zhongtao
Sponsor	Ethicon SARL
Agent	Johnson & Johnson Medical (Shanghai) Ltd.

Revision Record

Revised version	*Revision date*	*Description of changes*
1.1	*Nov 1 2017*	*1. The change of the name of study device: change all "GYNIECARE INTERCEED™ Absorbable Adhesion Barrier" to "INTERCEED™ Absorbable Adhesion Barrier".* *2. Use the abbreviation of the study device in the text of the protocol: change all "GYNIECARE INTERCEED™ Absorbable Adhesion Barrier" to "INTERCEED™".* *3. The change of study site: delete "Jiangsu Province Hospital" and add "The First Affiliated Hospital of Nanchang University", "Xiangya Hospital Central South University" and "The affiliated Hospital of Xuzhou Medical University" into the list.* *4. Other changes: Study Objectives: "The primary objective of this study is to evaluate the efficacy and safety of INTERCEED™ in reducing the incidence of adhesions at the abdominal incision site in patients undergoing laparoscopic colorectal surgery." Changed to "The primary objective of this study is to evaluate the efficacy and safety of INTERCEED™ Absorbable Adhesion Barrier (hereafter called INTERCEED™) in reducing the incidence of adhesions at the abdominal incision site in patients undergoing laparoscopic colorectal surgery."*
2.0	*Mar 7 2018*	*1. The change of study site: delete "Tangdu Hospital" and add "Shanghai Tenth People's Hospital" into the list.* *2. The change of the number of study site in the synopsis: from 8 to 10.* *3. Other changes: Section 13.1, add "All Aes need to be recorded in the EDC system in 2 weeks".*
3.0	*Jun 25 2018*	*1. The follow-up period of evaluating the Primary Endpoint (Phase 2 operation): from 6-9 months after phase 1 operation to 3-7 months after phase 1 operation.* *2. The change of study site: add "The Second Xiangya Hospital of Central South*

		University" , "The First Affiliated Hospital of Zhengzhou University" and "Ruijin Hospital" into the list. ***3. The change of the number of study site in the synopsis: from 10 to 13*** ***4. Exclusion Criteria: from "• Patient with a history of mechanical bowel obstruction" to "Patient with a history of mechanical bowel obstruction, but except the mechanical bowel obstruction caused by the colorectal cancer treated in the Phase I operation"*** ***5. Visit: Add "Visit 7" and revise the description of "study completion"*** ***6. Adverse event: Postoperative pain, fever and laboratory abnormalities is expected and will not be documented as an adverse event unless the Investigator considers the pain or fever to exceed that normally anticipated following the surgery or related to study devices. Also, the adverse event, not including the serious adverse event and ileus event, which is "not relative" or "unlikely related" to the study device and occurred 1. between 30 days after Phase 1 operation and the hospitalization for Phase 2 operation or 2. between Visit 6 and Visit 7 should not be documented.*** ***7. Serious adverse event: The rehospitalization events only for receiving the scheduled chemotherapy/radiotherapy between Phase 1 operation and Phase 2 operation will not be documented as an adverse event.***
4.0	***Jun 25 2019***	***1. The follow-up period of evaluating the Primary Endpoint (Phase 2 operation): from 3-7 months after phase 1 operation to 3-9 months after phase 1 operation.*** ***2. The change of study site: withdraw "Beijing Cancer Hospital" from the list.*** ***3. The change of the number of study site in the synopsis: from 13 to 12.*** ***4. Withdrawal of Subjects: from "The subject undergoes a second abdominal operation that doesn't meet the definition of Phase 2 operation (see Section 3.2) within the follow-up period, such as:" to "The subject undergoes a second abdominal operation that doesn't meet the definition of Phase 2 operation (see Section 3.2) within the follow-up period and without the image data as described in the Section 7.1.2.. The***

		abdominal operation included but not limited to:" 5. ***Overall duration of clinical trial: from 42 to 47.*** 6. ***Maximum Number of Subjects in Each Clinical Trial Institution: delete "The number of patients recruited in any site should not exceed 54." .*** 7. ***Email: from"gzhu15@its.jnj.com" to "RA-JNJSG-InterceedCN@ITS.JNJ.com".*** 8. ***Ethical concern: Delete "The control product should ensure the safety for the subjects to the full extent.".*** 9. ***Reporting Procedure, Contact Information: Delete "From randomization of the subject, all adverse events related to the subject's participation in this study should be followed up until the event is resolved, or if the event causes the permanent damage, it should be followed up until the event is stable and the clinical outcome is determined.".*** 10. ***Study Design: delete " from the ostomy site abdominal wall opening before submersion of the bowel loop into the peritoneal cavity and abdominal wound closure".*** 11. ***Contents of Clinical Trial: from "patients" to "subjects".*** 12. ***Secondary Endpoint: form "Complaints of study product" to "Defects of study product".*** 13. ***Measures to Reduce and Avoid Bias: from "All medical records (source documents) documenting the adhesion barrier application procedure through hospital discharge and all follow-ups will not be blinded because the operation record will indicate whether the anti-adhesion product is applied." to "All medical records (source documents) documenting the adhesion barrier application procedure through hospital discharge and all follow-ups will not be blinded, because the operation record will not indicate whether the anti-adhesion product is applied.".*** 14. ***Criteria and Procedure of Withdrawal of Subjects from Study: "Discontinuation" to "Withdrawal".*** 15. ***Visit 1: add "adverse events ".*** 16. ***Device Defect: from "The investigator should***

		record all adverse events occurred and device defects found in the process of clinical trial" to "The investigator should record all adverse events required in protocol and device defects found in the process of clinical trial" . ***17. Reporting Procedure, Contact Information: "The investigator must submit the serious adverse events occurred in the study and the device defects that may cause serious adverse event to the sponsor and CFDA (or designated person) immediately after being informed of the event" to "The investigator must submit the serious adverse events occurred in the study and the device defects that may cause serious adverse event to the sponsor and the regulatory authorities at every level (or designated person) immediately after being informed of the event"***

5.0	***27 Apr 2020***	***1. The placement of drainage tube: from "The drainage tube (if applicable) must be placed on the left side of the patient and is recommended to be lateral to the left midclavicular line." to "The drainage tube (if applicable) could be placed on either side of the patient according to the standard of care of the participating site and should be at the discretion of the investigator away from the target incision as much as possible."*** ***2. Study design: Add "An ad-hoc interim analysis is proposed based on feedback received from the investigators who observed very low rate of adhesions at the second procedure for ostomy reversal. The ad-hoc interim analysis is planned to be performed while at least 61% of the total number of participants with evaluable primary endpoints are available. If the conditional power (CP) is ≤ 60%, the observed adhesion rate difference magnitude is much less than the assumed difference magnitude of 0.25, therefore, the study will be terminated due to low adhesion rate and small effect size between INTERCEED and control arms. Otherwise, the study will continue until the study completion as planned."*** ***3. Update "Criteria and Reason for Terminating the Trial based on the Statistical Results" section as per interim analysis plan.*** ***4. Update "Reporting Procedure of Deviation from Original Statistical Plan" section as per interim analysis plan.*** ***5. Update "Likelihood Analysis of Failure" section as per feedback from the investigator and interim analysis plan.*** ***6. Serious Adverse Event: from "The rehospitalization events only for receiving the scheduled chemotherapy/radiotherapy between Phase 1 operation and Phase 2 operation will not be documented as an adverse event." to "The rehospitalization events after Phase 1 operation only for receiving the chemotherapy/radiotherapy which planned after the diagnosis of the primary disease will not be documented as an adverse event".***

		7. Removed the Approval Page. ***8. Updated Expected overall duration of clinical trial and reasons for determination: from "The expected overall duration is about 47 months" to "The expected overall duration is about 60 months"***

A Prospective, Multicenter, Randomized Controlled Study to Evaluate the Effect of INTERCEED™ Absorbable Adhesion Barrier in Preventing the Abdominal Incision Adhesions

Protocol Number: ESC-201701

Approval: Refer to TV-eFRM-02922 Protocol Approval Form

COMPLIANCE STATEMENT

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

TABLE OF CONTENTS

SYNOPSIS

Study Title	A Prospective, Multicenter, Randomized Controlled Study to Evaluate the Effect of Absorbable Adhesion Barrier in Preventing the Abdominal Incision Adhesions
Study Objectives	The primary objective of this study is to evaluate the efficacy and safety of INTERCEED™ Absorbable Adhesion Barrier (hereafter called INTERCEED™) in reducing the incidence of adhesions at the abdominal incision site in patients undergoing laparoscopic colorectal surgery.
Number of Study Sites	12 Sites
Number of Subjects	220 Subjects
Study Design	This is a prospective, randomized controlled study. The study population will include 220 subjects scheduled to undergo laparoscopic radical resection of rectal carcinoma with preventive ileostomy (Phase 1 operation). During the Phase 1 operation, when the definite decision to create a temporary ostomy is made, patients will be randomized in 1:1 ratio to either the treatment arm (INTERCEED™) or the control arm (standard of care treatment: no adhesion barrier, no placebo). In subjects assigned to the treatment arm, the INTERCEED™ must be applied beneath the target incision site (the midline incision mainly for the removal specimen). The subjects will return 3-9 months after the phase 1 operation (colorectal resection with temporary ileostomy) for phase 2 operation, to have their diverting ostomy taken down (ileostomy reversal). During the phase 2 operation (ileostomy reversal), the incidence, extent and severity of adhesions will be evaluated through the laparoscope. An ad-hoc interim analysis is proposed based on feedback received from the investigators who observed very low rate of adhesions at the second procedure for ostomy reversal. The ad-hoc interim analysis is planned to be performed while at least 61% of the total number of participants with evaluable primary endpoints

	are available. If the conditional power (CP) is ≤ 60%, the observed adhesion rate difference magnitude is much less than the assumed difference magnitude of 0.25, therefore, the study will be terminated due to low adhesion rate and small effect size between INTERCEED and control arms. Otherwise, the study will continue until the study completion as planned.
Study Endpoints	**The primary endpoint** is defined as the proportion of subjects free of adhesions at the target incision site in each study group. The assessment of adhesions will be conducted during the second laparoscopy for ileostomy reversal (phase 2 operation). **Secondary endpoints of the study include**: a) extent and severity of adhesions at the target incision site and four abdominal quadrants; b) incidence of mechanical ileus; c) Incidence of surgical site infections; d) Incidence of postoperative all-layer wound dehiscence; e) incidence of delayed wound healing; f) any adverse events and g) study product defects.
Test Product	This product is a sterile, single-use-only, absorbable, off-white knitted fabric; Size 7.6cm x 10.2cm.
Inclusion Criteria	• Subjects ≥ 18 years of age who require laparoscopic colorectal resection with the formation of a temporary diverting loop ileostomy and a planned closure of diverting ileostomy within 3 to 9 months; • The subjects should be willing to participate in the study, comply with study requirements, follow-up schedule, and give written informed consent prior to any study-related procedures; • The target incision length ≤ 8cm allowing the INTERCEED™ (product length 10.2cm) to overlap at least 1cm beyond each pole of the incision; • The subject is believed to have life expectancy ≥ 12 months after Phase 1 operation, based on investigators' assessment.
Exclusion Criteria	• Female patients who are pregnant or lactating at the time of screening; • Patient with a history of mechanical bowel obstruction, but except the mechanical bowel obstruction caused by the colorectal cancer treated in the Phase I operation; • Subjects with history of mid and lower abdominal region or

	pelvic surgery; • Patients for whom it is known that loop ileostomy closure within 3 to 9 months is not feasible • Patients with a history of active intra-abdominal infection such as peritonitis or abdominal abscess; • Patients with a history of intestinal fistulae; • Patients with a history of endometriosis; • Intended use of intraoperative lavage/irrigation with any anti-adhesion solutions other than saline (e.g., dextran, heparin, corticosteroids, icodextrin) or an adhesion barrier other than INTERCEED™; • Use of immune system suppressants deemed by the investigator to interfere with wound healing; • Impaired immune system function or coagulation disorders deemed by the surgeon to interfere with wound healing; • Bevacizumab use within 30 days prior to surgery; • Subjects with any intra-operative findings identified by the surgeon that may preclude conduct of the study procedures; • Patients with evidence of distant metastasis of the primary colorectal cancer; • Patients who underwent abdominal radiotherapy before Phase 1 operation; • Adhesions (Grade 2-3 adhesion[1]) and/or gross contamination (e.g., caused by tumor perforation) present in the abdominal cavity at the Phase 1 operation; • The rectal carcinoma radical resection (R0 resection) + preventive ileostomy are not performed in Phase 1 operation; • Expected resection of other organs (e.g., bladder, uterus, etc.) during Phase 1 operation; • Use of topical haemostatic products, local chemotherapeutic products or other drugs and/or medical device in abdominal/pelvic cavity which may impact the study primary endpoint judged by the investigator; • Patient is participating in other investigational drug or device study within 30 days or 5 half-lives of an investigational drug; • A known history of severe multiple drug allergies or known allergy to cellulose or cellulose derived products; • Any medications, treatments and/or implanted devices (except INTERCEED™) that on investigator's opinion may

	be adhesiogenic or may potentially affect the observation of postoperative adhesions; • Any physical or psychological conditions that at discretion of investigators may impair study participation; • A medical condition or other serious conditions that will interfere with compliance and/or ability to complete this study protocol; or • Any other situation or reason that at discretion of investigators is unsuitable for study participation.

1. SPONSOR INFORMATION

(1) Name of sponsor

Ethicon SARL

(2) Address of sponsor

Puits Godet 20, Neuchatel CH-2000, Switzerland.

(3) Contact of sponsor

Email: rkochar1@its.jnj.com

(4) Related qualification documents of sponsor

See the CE certification attached to the protocol

(5) Name, address, contact and related qualification documents of agent

Johnson & Johnson Medical (Shanghai) Ltd.

Section C, Floor 1,2,3, No. 439, Futuxi Road, China (Shanghai) free trade zone.

Email: RA-JNJSG-InterceedCN@ITS.JNJ.com

Tel: +86021-33378888

Address: Building A, Xinyan Mansion, No. 65, Guiqing Road, Xuhui District, Shanghai, China.

See the business license attached to the protocol.

2. LIST OF CLINICAL TRIAL INSTITUTIONS AND INVESTIGATORS

Code of clinical trial institution	Name of clinical trial institution	Investigator (signature)	Title	Contact
1*	Beijing Friendship Hospital, Capital Medical University	Zhongtao Zhang	Director	010-63014411
2	Peking University People's Hospital	Yingjiang Ye	Director	010-88326666
3	Chinese PLA General Hospital	Lin Chen	Director	010-68182255
5	The First Hospital of Jilin University	Jian Suo	Director	0431-88782222
6	Changhai Hospital	Wei Zhang	Director	021-31166666
7	Shanghai Tenth People’s Hospital	Donglei Zhou	Director	021-66303643
8	The First Affiliated Hospital of Nanchang University	Zhengrong Li	Director	0791-88692748

9	Xiangya Hospital Central South University	Zhikang Chen	Director	0731-84328888
10	The affiliated Hospital of Xuzhou Medical University	Jun Song	Director	0516-85609999
11	The Second Xiangya Hospital of Central South University	Hongliang Yao	Director	0731-85295888
12	The First Affiliated Hospital of Zhengzhou University	Weitang Yuan	Director	0371-66913114
13	Ruijin Hospital	Aiguo Lu	Director	021-64370045

**Information of leading site and principal investigator*

3. OBJECTIVE AND CONTENTS OF CLINICAL TRIAL

3.1. Objective of Clinical Trial

The primary objective of this study is to evaluate the efficacy and safety of INTERCEED™ in reducing the incidence of adhesions at the abdominal incision site in patients undergoing laparoscopic colorectal surgery.

3.2. Contents of Clinical Trial

The study population will enroll 220 subjects schedulled to undergo laparoscopic colorectal carcinoma radical resection with preventive ileostomy. The enrolled subjects will be randomly divided in two groups in a 1:1 ratio: the study group and control group, of which the INTERCEED™ is applied in the study group, and no adhesion barrier for subjects in the control group.

In this study, a follow-up period of 9 months will be required for the eligible subjects. The primary endpoint is defined as the proportion of subjects free of adhesions at the target incision site in each study group. The target incision site in this study is a midline incision mainly for removal the specimen. The assessment of adhesions will be conducted during the second laparoscopy for ileostomy reversal. The study hypothesis is that the occurrence of postoperative target incision site adhesions in the study group using INTERCEED™ would be lower than that in the control group.

The Phase 1 operation is defined as laparoscopic rectal carcinoma radical resection (R0 resection) with preventive terminal ileostomy; and the Phase 2 operation is defined as ileostomy reversal and laparoscopic exploration between 3 months to 9months after Phase I operation.

Secondary endpoints of the study include: a) extent and severity of adhesions at the target incision site and four abdominal quadrants; b) incidence of mechanical ileus; c) Incidence of surgical site infections; d) Incidence of postoperative all layer wound dehiscence; e)

incidence of delayed wound healing; f) any adverse events and g) study product defects.

4. BACKGROUND INFORMATION OF CLINICAL TRIAL

4.1. Introduction to the Condition

4.1.1. Explanation for the Condition

Postoperative adhesion formation is a common complication after abdominal and pelvic operations. Abdominal and pelvic adhesions may be present after most of the operations. It may cause serious complications such as ileus, chronic pain and female infertility, etc., which may have strong impact on the patient's quality of life, resulting in significant medical and health resources utilization [2-5]. The incidence of postoperative adhesions is currently considered a complex process related to the injury of the intraperitoneal endothelial layers of visceral and abdominal wall, starting to form within a week after the operation [6]. The early epidemiological data showed that the incidence of adhesions after the abdominal and pelvic operations might be up to 95% in some cases [7]. Other recent controlled studies also demonstrated that their incidence could range between 60 and 85% [8-12]. The formation of adhesions after surgical procedures may be suspected based on clinical symptoms but can only be definitely confirmed by looking inside the peritoneal cavity either during subsequent laparoscopic or open procedure. Routine assessment of incidence of adhesions after surgery is not typical because it requires a "second-look" procedure. However, there are few surgical procedures where a second look laparoscopy is part of the planned treatment process, e.g. a phased bowel reconstruction such the reversal of temporary loop ileostomy or split colostomy.

4.1.2. Therapeutic Option and Prognosis

Currently, several products available for application in abdominal/pelvic cavity to prevent the occurrence of postoperative adhesions, such as INTERCEED™, Seprafilm, etc. Multiple studies have shown that applying these products to the incision site or wrapping around the visceral organs in the abdominal and pelvis operations can effectively reduce the occurrence of abdominal adhesions [7-11].

4.2. Application of Investigational Product and Control Product

INTERCEED™ (Oxidized Regenerated Cellulose) is a sterile, single-use-only, absorbable off-white knitted fabric prepared by the controlled oxidation of regenerated cellulose. It has been applied in clinical practice for many years. It already has some clinical and non-clinical evidences.

Based on the existing clinical literatures, the application of the investigational product is as follows (Table 1):

Table 1 Clinical data of INTERCEED™

Author	Method	Result	Conclusion
Sekiba K[13]	INTERCEED™ (TC7) was evaluated in a randomized, multicenter clinical study.	Significantly more adhesions were observed at second laparoscopy on the control	The author conclude that INTERCEED™

	Sixty-three infertility patients had bilateral pelvic sidewall adhesions removed at laparotomy. One pelvic sidewall was covered by INTERCEED™ (TC7) and the other was left uncovered. The deperitonealized areas (N = 205) of all sidewalls were divided into three groups: less than 100 mm2, N = 72; 100-1000 mm2, N = 95; and more than 1000 mm2, N = 38. The effectiveness of INTERCEED™ (TC7) was evaluated at laparoscopy 10-98 days after laparotomy.	pelvic sidewalls (48 of 63, 76%) than on the treated sides (26 of 63, 41%) (P less than .0001). The INTERCEED™ (TC7)-treated sidewalls also had significantly less area involved with adhesions at laparoscopy (P less than .05, P less than .001, and P less than .001 in the three groups, respectively). Twenty-eight women with severe endometriosis also had significantly more adhesions on the control side (23 of 28, 82%) than on the treated side (14 of 28, 50%) (P less than .05).	(TC7) effectively reduced the incidence and extent of postoperative adhesions, even in patients with severe endometriosis.
Azziz R[14]	Prospective, multicenter, randomized, blinded, controlled study involving134 patients. Treatment side INTERCEED™ Barrier; control side good surgical technique. Evaluation method at second look laparoscopy, 10 days to 14 weeks post-surgery. Measurements include incidence of adhesions and extent of adhesions.	2nd-look laparoscopy: Adhesions present: INTERCEED™ 10/134* Control side 46/134 Both sides 56/134 None 22/134 *p<0.0001	INTERCEED™ Barrier is twice as effective in preventing the incidence of adhesions as good surgical technique alone.
Li TC, Cooke ID. [15]	A prospective, randomised, controlled study was conducted. Twenty-eight women who underwent pelvic microsurgery for infertility or for chronic pelvic pain and who had bilateral pelvic adhesions and deperitonealised areas following adhesiolysis. Following microsurgical adhesiolysis, one side of the	The use of INTERCEED™ resulted in a significant reduction of adhesion reformation over and above that achieved by conventional microsurgical techniques with hydrocortisone as an adjuvant.	INTERCEED™ , an absorbable adhesion barrier, is of value in the prevention of adhesion reformation and may be used in conjunction with hydrocortisone instilled intraperitoneally at

	pelvis was randomised to have its deperitonealised areas covered with INTERCEED™ , whereas the contralateral side served as the control. A second look laparoscopy was carried out 3 to 14 weeks after microsurgery to evaluate adhesion reformation.		the conclusion of microsurgery.
Tinelli A, Malvasi A, Guido M, Tsin DA, Hudelist G, Hurst B, Stark M, Mettler L. [8]	Prospective blinded observational study was conducted. A total of 694 women undergoing laparoscopic or abdominal myomectomy were randomized for placement of oxidized regenerated cellulose absorbable adhesion barrier to the uterine incision or for control subjects without barriers. The presence of adhesions was assessed in 546 patients who underwent subsequent surgery.	There was a higher rate of adhesions in laparotomy without barrier (28.1%) compared with laparoscopy with no barrier (22.6%), followed by laparotomy with barrier (22%) and laparoscopy with barrier (15.9%). Additionally, the type of adhesions were different, filmy and organized were predominant with an adhesion barrier, and cohesive adhesions were more common without an adhesion barrier.	Oxidized regenerated cellulose reduces postsurgical adhesions. Cohesive adhesions reduction was noted in laparoscopy.
Chapa H O, Venegas G.[9]	This was a retrospective study of patients in whom an absorbable adhesion barrier was/was not used at their primary CS. Mean and excessive blood loss, the need for adhesiolysis, and postoperative fever were compared between those in whom a barrier was used at first CS and those in whom a barrier was not used. Visceral injury at repeat cesarean was also compared between the two groups.	No statistically significant difference in mean blood loss was noted between the two groups. However, significantly more patients in whom a barrier was not used had excessive intraoperative blood loss (barrier group, 1/53 [1.9%]; no-barrier group, 6/59 [10.1%]; P = 0.04). All seven cases of excessive blood loss had adhesiolysis. Significantly more patients in the no-barrier group underwent adhesiolysis (no-barrier group, 35/59 [59.3%]; barrier group, 7/53 [13.2%]; P = 0.03). No statistical difference in postoperative metritis was noted (1/59 [1.8%] in the barrier group and 1/59 [1.7%]	Those in whom a barrier was not used at primary CS were more likely to have adhesiolysis and excessive blood loss (.1250 mL) at repeat CS. No significant difference in postoperative metritis/fever was noted between groups. Adhesion barrier at primary CS may reduce some aspects of maternal morbidity at repeat CS.

		in the no-barrier group; P = 0.99). Only one deserosalization of the bladder dome occurred in a patient in the no-barrier group.	
Chapa HO, Venegas G, Vanduyne CP, Antonetti AG, Sandate JP, Silver L.[16]	A retrospective, two-arm cohort, chart review of primary and subsequent first repeat cesarean sections from January 1, 2006-December 31, 2009 was performed. Exclusion criteria were incomplete operative report, history of prior abdominal-pelvic surgery, pelvic inflammatory disease, chorioamnionitis, emergency cesarean delivery or use of corticosteroids within 2 weeks. Adhesion incidence/severity as well as skin incision to newborn delivery times were analyzed. Effects of peritoneal closure and suture types were examined.	Of 262 primary cesareans performed, 43% (N= 112) had repeat cesarean section. With barrier, 74% had no adhesions at repeat surgery, versus 22% in the no barrier group (p = 0.011). Eleven percent had grade 2 adhesions with barrier, while 64% had grade 2-3 in the no barrier group (p = 0.012). The barrier group had no grade 3 adhesions. Those with parietal peritoneal closure had less incidence (p = 0.02) and mean adhesion severity (p = 0.03); no significant difference was found per suture type. No statistical difference in time from skin incision to newborn delivery was noted between primary and barrier group (p = 0.006); those without barrier had a statistically longer delivery interval (p = 0.35).	Use of an absorbable adhesion baóóórrier reduces the incidence and severity of adhesions at cesarean.
Haney AF, Hesla J, Hurst BS, Kettel LM, Murphy AA, Rock JA, Rowe G, Schlaff WD.[17]	A multicenter, nonblinded, randomized clinical trial was performed. Each barrier was allocated randomly to the left or right sidewall of every patient. Thirty-two women with bilateral pelvic sidewall adhesions undergoing reconstructive surgery and second-look laparoscopy. Adhesion score (on a 0- to 11-point scale), the area of adhesion (cm2), and the likelihood of no adhesions.	The use of both barriers was associated with a lower adhesion score and area of adhesion postoperatively. However, those sidewalls covered with PTFE had a significantly lower adhesion score (0.97 +/- 0.30 versus 4.76 +/- 0.61 points, mean +/- SEM) and area of adhesion (0.95 +/- 0.35 versus 3.25 +/- 0.62 cm2). Overall, more sidewalls covered with PTFE had no adhesions (21 versus 7) and, when adhesions were present on the contralateral sidewall, the number of sidewalls covered with PTFE	Expanded polytetrafluoroethylene was associated with fewer postsurgical adhesions to the pelvic sidewall than oxidized regenerated cellulose.

		without adhesions was greater than those covered with oxidized regenerated cellulose (16 versus 2).	
Franklin RR[18]	In a multicenter randomized study, 55 patients with bilateral ovarian disease were treated at initial laparotomy. At the end of the procedure, one ovary was assigned randomly to be wrapped with INTERCEED™ and the other was left uncovered. A second-look laparoscopy was performed 10-98 days later to evaluate the occurrence and severity of adhesions and the raw ovarian surface area exposed after lysis of adhesions.	At second-look laparoscopy, 26 of 55 INTERCEED™ -treated ovaries were free of adhesions, compared with 14 of 55 untreated control ovaries, a statistically significant difference (P = .028, Fisher exact test). At second-look laparoscopy, ovaries treated with INTERCEED™ formed adhesions less extensively (1.66 +/- 0.34 cm2) than did untreated ovaries (2.75 +/- 0.60 cm2) and with a greater reduction of raw ovarian surface area (difference in area differential -1.89 +/- 0.96 cm2; P = .055, paired t test). Adhesion scores at second-look laparoscopy were reduced significantly for ovaries treated with INTERCEED™ compared with untreated ovaries (P = .02, Wilcoxon signed-rank test). No adverse events were recorded during the course of the study.	Treatment of ovaries with INTERCEED™ significantly reduced the occurrence and severity of postsurgical ovarian adhesions.
Nordic Adhesion Prevention Study Group[19]	Prospective, randomized, multicenter, controlled clinical study was performed. Sixty-six women suffering from infertility due at least in part to bilateral tubal disease with bilateral adhesions attached to ovaries, fallopian tubes, and fimbriae. Adhesiolysis bilaterly through laparotomy with microsurgical techniques, application of INTERCEED™ on one of the sides randomly assigned not known by the surgeon before application, follow-up	When the initial scores registered at the operation for fertility were compared with those registered at the second-look laparoscopy, the results indicated that gentle microsurgical techniques resulted in a significant reduction of postoperative adhesions. Adnexa, which were covered with INTERCEED™ , had significantly lower adhesion scores than the control adnexa, representing an improvement of 39% compared	In a prospective, randomized, multicenter, controlled clinical study using a protocol in which other adjuvants have been shown not to be efficacious, INTERCEED™ was shown to reduce significantly the incidence and severity of

	laparoscopy 4 to 10 weeks postoperatively, with each patient serving as her own control. Adhesion severity scores at all sites and number of adhesion free organs after laparotomy and follow-up laparoscopy.	with microsurgery alone (control) in reducing adhesion reformation scores. When combined with microsurgical techniques, INTERCEED™ reduced adhesion reformation scores by 70%. The number of ovaries, fallopian tubes, and fimbriae without adhesions at the time of second-look laparoscopy was significantly increased by approximately twofold when organs were covered with INTERCEED™ .	adhesion reformation to the ovary, fallopian tube, and fimbria after infertility surgery.
Mais V, Ajossa S, Piras B, Guerriero S, Marongiu D, Melis GB.[20]	To evaluate the effectiveness of the oxidized regenerated cellulose absorbable barrier (INTERCEED™ , TC7) in the prevention of de-novo adhesion formation after laparoscopic myomectomy, a prospective and randomized study was performed at the Department of Obstetrics and Gynaecology of the University of Cagliari, Cagliari, Italy. A total of 50 pre-menopausal non-pregnant women, aged 23-42 years, who submitted to laparoscopic myomectomy from January 1993 to June 1994, were randomized to surgery alone (control group, n = 25) or surgery and oxidized regenerated cellulose barrier (INTERCEED™ group, n = 25). Neither group received any other treatment for adhesion prevention. A second-look laparoscopy was performed 12-14 weeks after laparoscopic myomectomy.	The numbers of adhesion-free patients were three out of 25 (12%) in the control group and 15 out of 25 (60%) in the treatment group ($P < 0.05$).	In conclusion, the oxidized regenerated cellulose absorbable barrier significantly reduced de-novo adhesion formation after laparoscopic myomectomy.
Mais V, Ajossa S, Marongiu	Thirty-two premenopausal nonpregnant women who had severe endometriosis and	Twelve of 16 (75%) women treated with the oxidized regenerated cellulose barrier	The oxidized regenerated cellulose

D, Peiretti RF, Guerriero S, Melis GB.[21]	complete posterior cul-de-sac obliteration and were undergoing laparoscopic surgery were randomly assigned to either surgery alone or surgery and INTERCEED™ . None of the subjects received any other treatment for adhesion prevention. Second-look laparoscopy was performed 12-14 weeks after laparoscopic surgery by an investigator blinded to the treatment, and the incidence of adhesion-free subjects was assessed.	were free of adhesions, compared with two of 16 (12.5%) controls, a statistically significant difference (P < .05).	absorbable barrier significantly reduces adhesion reformation after laparoscopic surgery for endometriosis.

As described in the above table, INTERCEED™ has been applied in clinical practice for more than 30 years so far. There are a large number of publications showed that it can significantly reduce the occurrence of postoperative adhesions.

4.3. Product registration and the reason for clinical trial registration in China

INTERCEED™ first passed the BSI Design Examination in November 2002 and obtained the EC Design-Examination Certificate. The “Design-Examination Certificate” was extended in February 2015.

This product has been applied in clinical practice in many countries around the world, including many EU, USA, Canada, Latin American countries, Asia-Pacific countries, Middle Eastern and African countries.

This product has not been used in general abdominal operations in Chinese population. Therefore, the clinical study is designed to support the registration of the product in China.

5. Features, structural composition, operation principle, mechanism of action and study population

5.1. Features

5.1.1. Design Features of Study Product

INTERCEED™ is a sterile, single-use-only, absorbable off-white knitted fabric prepared by the controlled oxidation of regenerated cellulose. INTERCEED™ is applied dry in general abdominal and gynecological operations, after meticulous hemostasis has been achieved, in order to reduce the occurrence of postoperative adhesions.

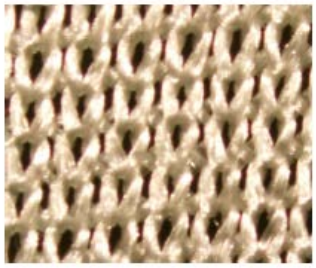
INTERCEED™ reduces the formation of adhesions by physically separating the surfaces of tissues that are adjacent to each other during the reperitonealization phase.

When used as directed, INTERCEED™ is easy to apply and is absorbed from the site of implantation within four weeks. Absorption rate depends upon several factors, including the amount used and implantation site.

5.1.2. Material Features of Study Product

INTERCEED™ is a sterile, single-use-only, absorbable off-white knitted fabric prepared by the controlled oxidation of regenerated cellulose. The oxidized regenerated cellulose knitted fabric is weaved of 60D and 24-strand lustrous rayon. See **Fig. 1** below.

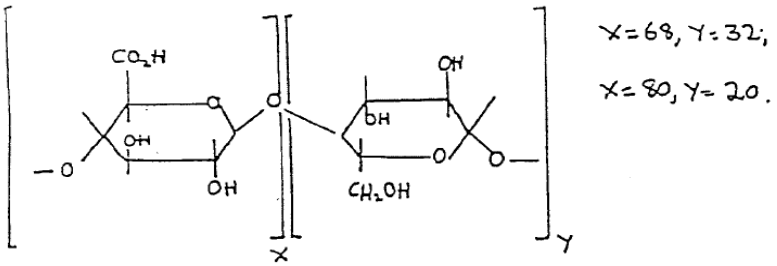
Fig. 1 Picture of INTERCEED™



INTERCEED™ Enlarged view of knitted fabric

The oxidized regenerated cellulose is a copolymer composed of 68-80 mole percentage of uronic acid and 20-32 mole percentage of glucosyl group. The carboxyl group content is 12%-18%.

The chemical structural formula is as follows.



5.2. Structural Composition, Operation Principle and Mechanism of Action

5.2.1. The study product is a sterile, single-use-only, absorbable off-white knitted fabric prepared by the controlled oxidation of regenerated cellulose.

5.2.2. The operation principle and mechanism of action of the study product are to reduce the formation of adhesions by physically separating the surfaces of tissues that are adjacent to each other during the reperitonealization phase.

5.3. Study Population

The study population will include 220 subjects scheduled to undergo laparoscopic radical resection of rectal carcinoma with preventive loop ileostomy.

6. INDICATIONS AND CONTRAINDICATIONS, PRECAUTIONS

6.1. Indications:

INTERCEED™ is indicated as an adjuvant in general abdominal and gynecological pelvic surgery for reducing the incidence, extent and severity of postoperative abdominal adhesions after meticulous hemostasis has first been achieved.

6.2. Contraindications:

INTERCEED™ is contraindicated in the presence of frank infection.

INTERCEED™ is not indicated as a hemostatic agent. Appropriate means of achieving hemostasis must be employed.

6.3. Precautions:

Use only a single layer of INTERCEED™, since multiple layers of packing or folding will not enhance the adhesion barrier characteristics and may interfere with the absorption rate of INTERCEED™. Care should be exercised in applying INTERCEED™ to a pelvic or abdominal organ not to constrict or restrict it.

Wrapping directly around gastrointestinal anastomoses is not recommended.

If the product comes in contact with blood prior to completing the procedure, it should be discarded, as fibrin deposition cannot be removed by irrigation and may promote adhesion formation.

The safety and effectiveness of using INTERCEED™ in combination with other adhesion-prevention treatments have not been clinically established.

INTERCEED™ is supplied sterile. As the material is not compatible with autoclaving or ethylene oxide sterilization, INTERCEED™ must not be resterilized.

Foreign-body reactions may occur in some patients.

Interactions may occur between INTERCEED™ and some drugs used at the surgical site.

Pathologists examining sites of INTERCEED™ placement should be made aware of its usage and of the normal cellular response to INTERCEED™ to facilitate proper evaluation of specimens.

There is no evidence to suggest, or reason to believe, that the use of INTERCEED™ has any deleterious effect on the mother or fetus when used during pregnancy or that the product or its breakdown products would have an effect on lactation. However, ectopic pregnancies have been associated with fertility surgery of the female reproductive tract. No adequate and well-controlled studies have been conducted in women who become pregnant within the first month after exposure to INTERCEED™. No data exist to establish the effect, if any, of INTERCEED™ on the occurrence of ectopic pregnancies. No teratogenic studies have been performed. Therefore, an avoidance of conception should be considered during the first complete menstrual cycle after use of INTERCEED™.

7. OVERALL DESIGN

7.1. Trial Design

7.1.1. Trial Objective

The primary objective of this study is to evaluate the efficacy and safety of INTERCEED™ in reducing the incidence of adhesions at the target incision site in patients undergoing laparoscopic colorectal surgery.

7.1.2. Trial Endpoint

Primary Endpoints

The primary endpoint is defined as the proportion of subjects with adhesions at the target incision site in each study group.

The assessment of adhesions will be conducted during the second laparoscopy for ileostomy reversal.

The primary endpoint will be assessed by means of reviewing the imaging data by independent central reviewers who will be blinded to the study treatment groups. The image data is defined as the video which is not shorter than 30 seconds taken through laparoscopy during Phase 2 operation and allowing an observation of the entire product application site and surrounding areas in the treatment group or the target incision site in the control group.

Secondary Endpoints

a. **Extent of adhesions** (including severity):

   The extent of adhesions to the incision and abdominal wall between organs will be evaluated by the following grading scale[1] respectively:

   Severity

   — Grade 1: filmy thickness, avascular

   — Grade 2: moderate thickness, limited vascularity

   — Grade 3: dense thickness, vascularized

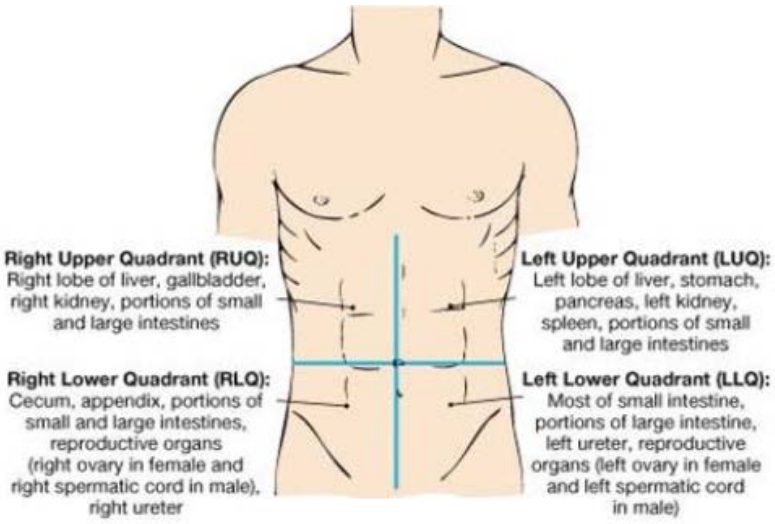
   Extent (percentage of the area covered by adhesion)

   — Grade 1: mild, covering up to 25% of the total area and length

   — Grade 2: moderate, covering 26%–50% of the total area and length

   — Grade 3: severe, covering over 50% of the total area and length

For quantifying the extent of adhesions to the abdominal wall and between organs, the abdominal cavity will be divided into four abdominal quadrants as follows:



b. **Incidence of patients with mechanical ileus**: defined as the mechanical ileus judged by investigators, which occurred 1 week after Phase 1 operation:

c. **Incidence of patients with surgical site infections (SSI) following surgery**: according to the criteria of the US Centers for Disease Control (CDC) and Prevention of [22] as follows:

CDC Definition of SSI

1. **Superficial incisional SSI:**

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

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

   Do not report the following conditions as superficial SSI:

   - Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration);
   - Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).

2. **Deep incisional SSI:**

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

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

Notes:

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

3. **Organ/Space SSI**:

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to, be related to the operation and infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation and at least one of the following:

- Purulent drainage from a drain that is placed through a stab wound into the organ/space;
- Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space;
- An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination;

Diagnosis of an organ/space SSI by a surgeon or attending physician.

d. Incidence of postoperative all layer wound dehiscence of the target incision;

e. Incidence of delayed wound healing of the target incision;

f. Any adverse event;

g. Defects of study product.

7.1.3. Trial Method Selection and Its Rationale

The following investigational study method is used per the regulatory requirements of “Guidance for Absorbable Adhesion Barrier Devices for Use in Abdominal and/or Pelvic Surgery; Guidance for Industry”.

This is a prospective, multicenter randomized controlled trial. Its rationale is as follows:

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

Controlled: the measures and methods maintain the comparability between groups in other factors and conditions except whether the anti-adhesion product is used.

Prospective: the prospective study may reduce the bias.

The trial will also estimate the appropriate sample size as needed according to the statistical hypotheses, using conservative assumed proportions of primary endpoint failures in the test group and control group, and the permissible Type I and II error, ensuring the statistical significance of the results.

7.1.4. Measures to Reduce and Avoid Bias

The randomization method is used in the study. The subjects are randomly allocated to the test group and control group according to the same inclusion and exclusion criteria so that the various factors including the unknown confounding factors to be evenly distributed in each group, eliminating the confounding effect. The selection bias and confounding bias can be reduced by the method of randomized trial.

Blinding practices for this study will include the following:

Patients: Patients will be informed of the 1:1 randomization to determine whether the study product will be implanted, but will remain blinded for study treatment (INTERCEED™ or Control) until they have completed all study follow-up.

Implanting surgeon: Given the difference between the INTERCEED™ treatment and Control (no adhesion barrier), it will not be possible for the surgeon to be blinded to the treatment. Therefore, to avoid any bias in the conduct of the surgical procedure, randomization will take place during the primary procedure only after colorectal resection and prior to formation of the temporary loop ileostomy.

In addition, the surgeon who performs assessment of adhesions after the second procedure (ostomy takedown) will be independent from the surgeons who performed the surgical procedures, including the Phase I and Phase 2 operations.

Medical Records: All medical records (source documents) documenting the adhesion barrier application procedure through hospital discharge and all follow-ups will not be blinded, because the operation record will not indicate whether the anti-adhesion product is applied.

Central reviewers: the image data in the Phase 2 operation will be submitted to the site reviewers for evaluation to determine the primary endpoints and secondary endpoints, who will remain blinded throughout the study.

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

The study will also collect the data of objective indicators. The study related data will be recorded in the original Medical Records as much as possible, and checked in the monitoring process. The training for the investigators should be enhanced so as to assure the scientific attitude of investigators. The Investigator should communicate further with the subjects to improve the subject compliance. This will help to reduce the informational bias.

The Central Registration System will be used to record all patients with informed consent and screening process and results. All reasons for the withdrawal of subjects from study will be properly documented.

7.1.5. Selection of Subjects:

1) Inclusion Criteria

- Subjects ≥ 18 years of age who require laparoscopic colorectal resection with the formation of a temporary diverting loop ileostomy and a planned closure of diverting ileostomy within 3 to 9 months;
- The subjects should be willing to participate in the study, comply with study requirements, follow-up schedule, and give written informed consent prior to any study-related procedures;
- The target incision length ≤ 8cm allowing the INTERCEED™ (product length 10.2cm) to overlap at least 1cm beyond each pole of the incision;
- The subject is believed to have life expectancy ≥ 12 months after Phase 1 operation, based on investigators' assessment.

2) Exclusion Criteria

- Female patients who are pregnant or lactating at the time of screening;
- Patient with a history of mechanical bowel obstruction, but except the mechanical bowel obstruction caused by the colorectal cancer treated in the Phase I operation;
- Subjects with history of mid and lower abdominal region or pelvic surgery;
- Patients for whom it is known that loop ileostomy closure within 3 to 9 months is not feasible
- Patients with a history of active intra-abdominal infection such as peritonitis or abdominal abscess;
- Patients with a history of intestinal fistulae;
- Patients with a history of endometriosis;
- Intended use of intraoperative lavage/irrigation with any anti-adhesion solutions other than saline (e.g., dextran, heparin, corticosteroids, icodextrin) or an adhesion barrier other than INTERCEED™;

- Use of immune system suppressants deemed by the investigator to interfere with wound healing;
- Impaired immune system function or coagulation disorders deemed by the surgeon to interfere with wound healing;
- Bevacizumab use within 30 days prior to surgery;
- Subjects with any intra-operative findings identified by the surgeon that may preclude conduct of the study procedures;
- Patients with evidence of distant metastasis of the primary colorectal cancer;
- Patients who underwent abdominal radiotherapy before Phase 1 operation;
- Adhesions (Grade 2-3 adhesion[1]) and/or gross contamination (e.g., caused by tumor perforation) present in the abdominal cavity at the Phase 1 operation;
- The rectal carcinoma radical resection (R0 resection) + preventive ileostomy are not performed in Phase 1 operation;
- Expected resection of other organs (e.g., bladder, uterus, etc.) during Phase 1 operation;
- Use of topical haemostatic products, local chemotherapeutic products or other drugs and/or medical device in abdominal/pelvic cavity which may impact the study primary endpoint judged by the investigator;
- Patient is participating in other investigational drug or device study within 30 days or 5 half-lives of an investigational drug;
- A known history of severe multiple drug allergies or known allergy to cellulose or cellulose derived products;
- Any medications, treatments and/or implanted devices (except INTERCEED™) that on investigator's opinion may be adhesiogenic or may potentially affect the observation of postoperative adhesions;
- Any physical or psychological conditions that at discretion of investigators may impair study participation;
- A medical condition or other serious conditions that will interfere with compliance and/or ability to complete this study protocol; or
- Any other situation or reason that at discretion of investigators is unsuitable for study participation.

3) Any other situation or reason that at discretion of investigators is unsuitable for study participation. Criteria and Procedure of Withdrawal of Subjects from Study

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

observations as thoroughly and timely as possible. The primary reason for early withdrawal will be recorded on the electronic case report form (eCRF). The criteria for withdrawal of subjects from study including but not limited the following:

Withdrawal of consent: Any method of contact with the subject in which they state they no longer want to participate in the study specific activities constitutes withdrawal of consent for participation in the study. This decision must be “self-determination” and should be documented in the electronic case report form (eCRF);

Physician’s determination: the investigator may determine the withdrawal of subjects from study according to the reasonable medical judgement;

Adverse event: the adverse event or serious adverse event may not cause the subjects to discontinue the study treatment. If the investigator decides to withdraw a subject from the study, this subject must be followed up, until the adverse event is resolved or until the stable clinical endpoint is reached;

Death: The cause of death will be documented; If the cause of death is related to incisional adhesions which is judged by investigators, the subject will not be withdrawn from the study.

Loss to follow-up: All subjects should be able to participate in all scheduled clinical follow-ups, providing the appropriate contact information. If a subject can’t return to undergo the scheduled clinical visit, attempts to contact the subject by phone should be done for 3 times to ask the subject to participate in all scheduled clinical follow-ups. Each attempt to contact should be recorded in the source document. If the subject makes no response to all three times of telephone contact, the investigator must send a registered mail to the subject. If the subject makes no response to the registered mail and makes no further contact, the subject is considered loss to follow-up; the eCRF at the end of study must be completed now.

Termination by the Sponsor, Data Safety Monitoring Board or health authorities;

Other:

1. Tumor recurrence or intra-abdominal metastasis of primary rectal cancer within the follow-up period;
2. The subject undergoes a second abdominal operation that doesn’t meet the definition of Phase 2 operation (see Section 3.2) within the follow-up period and without the image data as described in the Section 7.1.2.. The abdominal operation included but not limited to:
    a. Operation for an obstructive ileus or other critical anatomical structure (e.g. vessel, nerve) compression;
    b. Other abdominal operations before the scheduled Phase 2 operation;
    c. The Phase 2 operation conducted sooner than 3 months or didn’t conduct within 9 months after Phase 1 operation;
3. The subject experienced anastomotic leakage (Class B and C) after Phase 1 operation [23];
4. The subject recieved postoperative radiotherapy after Phase 1 operation;

5. Any intervention that may affect adhesion formation or wound healing at the target incision site judged by the investigator.

Procedure for Subject's Withdrawal from the Study Treatment:

The subjects should continue to receive treatments before the completion of 9-month follow-up specified in the study protocol. If the subject is withdrawn from the study early, the reasons for termination should be documented in the source document and site files, and submitted via the electronic case report form (eCRF).

The subjects withdrawn from the study early will be included in the analysis of results; however, no new subjects will be recruited to replace the subjects withdrawn from the study.

Criteria of Sponsor's Discontinuation of the Trial are as follows:

The sponsor has the right to temporarily or early terminate the studies of single site, multiple sites or all sites. Reasons may include, but are not limited to: safety issue or ethical issue, inaccurate or incomplete data record, non-compliance or dissatisfactory quality or quantity of the recruited subjects.

Flow of Sponsor's Discontinuation of the Trial:

If this study is terminated or discontinued early, the sponsor or its representative should inform investigator/affiliated unit and regulatory authority of this study having already been terminated or discontinued and the reasons for study termination or discontinuation according to the applicable supervision requirements. The sponsor or investigator/affiliated unit should also inform EC and submit the reasons for termination or discontinuation according to the applicable supervision requirements. In addition, all unused study devices and other materials should be returned according to the study procedures of sponsor.

4) Enrolment

Subjects will be considered enrolled into the study upon satisfaction of the following criteria:

- Completion of the informed consent process
- It is determined by the investigator that the subject meets all inclusion criteria and does not meet any exclusion criteria

No operation procedures related to the study should be conducted prior to signing the informed consent.

5) Expected overall duration of clinical trial and reasons for determination

The expected overall duration is about 60 months, including the time that Ethics Committee of each institution takes to sign the trial protocol, duration of follow-up, time for data management and statistical analysis and time to write the report.

6) Expected duration of participation of each subject

The duration of each subject's participation in the study will be around 6-9 months according to the follow-up schedule specified in the protocol.

7) Number of subjects required for clinical trial

Two hundred and twenty subjects will be included in this study, including 110 for test group and 110 for control group. See Section 8 “Calculation of sample size” for the basis for selecting this sample size.

7.1.6. Efficacy Evaluation Method

1) Description of efficacy parameters

The primary endpoint is defined as the proportion of subjects free of adhesions at the target incision site in each study group.

In addition, the secondary parameters will also be collected in this study, including:

Extent and severity of adhesions;

Incidence of patients with mechanical ileus.

2) Selection of method and time to evaluate, record and analyze the efficacy parameters

The primary effective parameter in this study will be assessed by the central reviewers according to the image data, which will be collected in the Phase 2 operation, and recorded on the e-CRF. The effective data is compared between groups when performing data analysis.

Extent and severity of adhesions will be assessed by the central reviewers according to the image data as described in the Section 7.1.2., which will be collected in the Phase 2 operation, and recorded on the e-CRF according to the investigator’s record, the incidence of patients with mechanical ileus will be assessed by medical record, investigator report and physical examination, which are collected at each follow-up visit after Phase 1 operation. The secondary parameters will be compared between groups when performing data analysis.

7.1.7. Safety Evaluation Method

1) Description of safety parameters

The safety parameters in this study are the incidence of surgical site infections, wound dehiscence, delayed wound healing, any adverse events and defects of study product.

2) Selection of method and time to evaluate, record and analyze the safety parameters

The safety parameters are recorded on the e-CRF according to the investigator’s record, medical record and inspection result, which are collected at each follow-up visit. The safety data is compared between groups when performing data analysis.

7.2. Study Process

7.2.1. Study Flowchart

The list of time and events of trial is as follows:

Item	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7 [h]

Time point	Screening/Baseline: performed whthin 14 days before Phase 1 operation	Randomization:performed during the Phase 1 operation	Phase 1 operation	Post-Op (Phase 1) through Discharge	Phase 2 operation: performed between 3-9 months after Phase 1 operation [a]	3 days after Phase 2 operation or Discharge	6-7months after Phase 1 operation
Informed consent	X						
Demographic information	X						
Randomization		X					
Inclusion/Exclusion Criteria	X	X					
Urine/blood pregnancy test	X						
Medical/Surgical history [b]	X				X		X
Concomitant therapy[c]	X		X	X	X	X	
Physical examination [d]	X			X	X	X	
Concomitant medications[e]	X		X	X	X	X	
Procedural data [f]			X		X		
Mechanical ileus				X	X	X	X
SSI				X	X	X	X
Incision dehiscence				X	X	X	X
Delayed wound healing events				X	X	X	X
Adverse event	X		X	X	X	X	X
Defectts of study product			X	X	X	X	
Study completion [g]						X	X

a. Other information except operative data should be collected from admission to hospital to the day before operation.

b. The surgical history should be collected carefully in the two visits.

c. The neoadjuvant radiotherapy information should be collected at Screening/Baseline visit, if any. The radiotherapy information includes dose and site.

d. Including height, weight and abdominal sign.

e. Only including the medicine related to adverse events and which is used beyond two weeks. The neoadjuvant/postoperative chemotherapy protocol and period should also be collected.

f. The information about the procedure time, hemorrhage volume, use of sterile gloves, target incision, application of study product in the study group should be collected at the visits of Phase 1 operation; the image data and the treatment for

adhesion (if any) should be collected in the Phase 2 operation.

g. If Visit 6 occurs 6-9 months after Phase 1 operation, the study completion would be in Visit 6. If not, the study completion would be in Visit 7.

h. Phone contact. If Visit 6 occurs 3-6 months after Phase 1 operation, the Visit 7 need to be conducted.

7.2.2. Standard Operating Procedures of Medical Device

According to IFU and technical manual of the product, the requirements for the use of study product are as follows:

a. Indications and scope of application

INTERCEED™ is indicated as an adjuvant in general abdominal and gynecological pelvic surgery for reducing the incidence, extent and severity of postoperative abdominal adhesions after meticulous hemostasis has first been achieved.

b. Recommended operating mode

1) To minimize the formation of postoperative adhesions and to optimize the performance of the study product, the following surgical techniques, as appropriate, are recommended: use of magnification; use of fine-caliber microsurgical instruments; use of fine suture material of low tissue reactivity; achievement of meticulous hemostasis; minimization of tissue handling; prevention of desiccation of tissues; avoidance of introduction of foreign bodies, such as talc, in the operative field; and precise reapproximation of tissue planes;

2) This product should be applied just before closure of the surgical area in order to minimize possible dislodging during the remainder of the surgical procedure.

3) Meticulous hemostasis must be achieved before application.

4) Remove all irrigation fluid and instillates from the peritoneal cavity. If Trendelenburg positioning was used during the procedure, place patient in reverse Trendelenburg position, if possible, to remove as much of the irrigation fluid as possible from the cul-de-sac.

5) After obtaining meticulous hemostasis, the following steps are recommended in applying the study product.

   a. Remove the sheet of study product from the product packaging.

   b. Cut pieces of study product to desired size, which should be sufficient to completely cover the area at risk.

   c. Apply the study product dry, in a single layer. After expanding the omentum majus to the greatest extent, lay the study product above the omentum majus and below the target surgery incision. Do not fold, wad, or apply multiple layers. Most importantly, do not conjoin or coat adjacent structures within one layer as this will hold these surfaces together and may potentially promote adhesion formation. Since the study product adheres well to serosal tissue, it is not necessary to suture in place. Moistening the study product with 1 to 2 ml of irrigating solution after positioning will further ensure adherence and conformance of the study product to the application

site. If moistening is desirable, this should be done 1) only after the study product is placed on the deperitonealized serosal area and 2) caution is exercised to prevent the fabric from floating off the surface. If the latter occurs, the piece of the study product should be discarded and a new piece used. If the product comes in contact with blood prior to use, it should be discarded, as fibrin deposition cannot be removed by irrigation and may promote adhesion formation.

d. Hold the study product in place at site of application to ensure adherence.

e. Assess the site after the application of study product for discoloration of the device. The study product that is dark brown or black indicates incomplete hemostasis. If discoloration occurs, it will occur within 1 to 2 minutes following application of the study product. This will render the product ineffective as an adhesion barrier and may promote adhesion formation. Should this discoloration occur, remove the study product and achieve hemostasis. Apply new piece of the study product as specified above.

c. Warnings and precautions

Use only a single layer of INTERCEED™, since multiple layers of packing or folding will not enhance the adhesion barrier characteristics and may interfere with the absorption rate of INTERCEED™. Care should be exercised in applying INTERCEED™ to a pelvic or abdominal organ not to constrict or restrict it.

If the product comes in contact with blood prior to completing the procedure, it should be discarded, as fibrin deposition cannot be removed by irrigation and may promote adhesion formation.

The safety and effectiveness of using INTERCEED™ in combination with other adhesion-prevention treatments have not been clinically established.

INTERCEED™ is supplied sterile. As the material is not compatible with autoclaving or ethylene oxide sterilization, INTERCEED™ must not be resterilized

Foreign-body reactions may occur in some patients.

Interactions may occur between INTERCEED™ and some drugs used at the surgical site.

Pathologists examining sites of INTERCEED™ placement should be made aware of its usage and of the normal cellular response to INTERCEED™ to facilitate proper evaluation of specimens.

There is no evidence to suggest, or reason to believe, that the use of INTERCEED™ has any deleterious effect on the mother or fetus when used during pregnancy or that the product or its breakdown products would have an effect on lactation. However, ectopic pregnancies have been associated with fertility surgery of the female reproductive tract. No adequate and well-controlled studies have been conducted in women who become pregnant within the first month after exposure to INTERCEED™. No data exist to establish the effect, if any, of INTERCEED™ on the occurrence of ectopic pregnancies. No teratogenic studies have been performed. Therefore, an avoidance of conception should be considered during the first complete menstrual cycle after use of INTERCEED™.

7.2.3. Study Procedure

Laparoscopic rectal carcinoma radical resection (R0 resection) + preventive terminal ileostomy:

This surgery is the Phase 1 operation in this study. It is suggested that no more than three groups of surgeons at each site perform this surgery, including the implantation of study product and the wound closure procedure of target incision to minimize bias and variability. The laparoscopic rectal carcinoma radical resection (R0 resection) will be performed per each institutional requirements or specific guidelines. The target incision should be the mid-line incision and is recommended to be about 5-8cm, but not longer than 8cm. The stoma should be on the right side of the patient and is recommended to be lateral to the right midclavicular line. The drainage tube (if applicable) could be placed on either side of the patient according to the standard of care of the participating site and should be at the discretion of the investigator away from the target incision as much as possible.

Implantation of study product and the closure procedure of incision in laparoscopic surgery:

The absorbable suture should be used for all subjects to close target incision (except the skin layer). For the patients who are randomized to receive the study product (INTERCEED), the physician will implant the study product in the abdominal cavity beneath the target incision. See below for the specific implantation method of the study product.

Application of INTERCEED™ to the target incision site:

- The size of INTERCEED™ should be sufficient to completely cover the target area (the incision size ≤ 8cm);
- Apply INTERCEED™ dry, in a single layer;
- It should be placed on denuded/injured surface (target incision site) to mechanically prevent this area from adhering to visceral surfaces, thus minimizing resultant adhesion formation;
- Do not fold, plug or apply multiple layers;
- INTERCEED™ adheres well to serosal tissue; it is not necessary to suture in place;
- Hold INTERCEED™ in place at site of application to ensure adherence;
- Moistening the INTERCEED™ with 1- 2 ml of irrigating saline solution (NaCl 0.9%) after positioning will further ensure its adherence and conformance to the application site;
- If moistening is desirable, this should be done only with solution (NaCl 0.9%) after INTERCEED™ is placed on the de-peritonealized serosal area cautiously keeping the fabric from floating off the surface;
- If floating off the surface occurs, the piece of INTERCEED™ should be discarded and a new piece used;
- If the product comes in contact with blood prior to use, it should be discarded because fibrin deposition on INTERCEED™ (ORC fabric) cannot be removed by irrigation and may promote adhesion formation;
- INTERCEED™ will be applied at the target incision to minimize possible dislodging during the remainder of the surgical procedure;

- Discoloration of the device to dark brown or black indicates incomplete hemostasis;
- If such discoloration occurs, it will happen within 1-2 minutes following application of INTERCEED™ and will reduce its effectiveness as an adhesion barrier and may promote adhesion formation;
- Should this discoloration occur, the device should be removed and complete hemostasis achieved before new piece of INTERCEED™ can be applied.

Postoperative Care:

Postoperative care will be performed per institutional requirements for clinical practice or specific guidelines regarding postoperative care. Patient status is monitored closely until discharge. Changes in concomitant medications including analgesics will be recorded throughout inpatient stay.

Neoadjuvant radiation/chemotherapy and postoperative chemotherapy:

The neoadjuvant radiation/chemotherapy and postoperative chemotherapy will be performed per institutional requirements for clinical practice or specific guidelines, except, abdominal radiotherapy between primary procedure and ostomy takedown (reversal). Patient status is monitored closely until discharge. The scope of neoadjuvant radiation is limited to pelvic cavity.

Ileostomy reversal + laparoscopic exploration：

This surgery is the Phase 2 operation in this study. It is suggested that no more than three groups of surgeons at each site perform this surgery. During the surgery, the image data of the target incision of Phase 2 operation through laparoscopy should be recorded. The image data is defined as the videos which is not shorted than 30 seconds taken through laparoscopy

Screening

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

- Completion of the informed consent process and signing the ICD;
- Verification of the eligibility criteria (Section 7.1) by the PI and/or authorized investigators. The verification must be conducted by the PI and/or authorized investigators prior to randomization.

Screening Failures

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

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

Randomization

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

Each case will be randomized to one of two groups in a 1:1 ratio. The only difference between the groups will be the use of INTERCEED™ or not. The plan is to randomize at least 110 subjects for each of the two groups. The randomization will be used in this study so that the patients cannot guess the upcoming assigned group.

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

In the event a potential subject fails intra-operative criteria, and is not randomized to the study, the unused randomization envelope should be returned to the series, and used for the next subject per its original sequence

Visit 1 – Baseline/Screening Visit

The following screening activities will occur prior to the study procedure:

- The subject must be given ample time to review and sign the ICD;
- Collection of demographic information (year and month of birth, race, gender, ethnicity, etc);
- Review and collection of medical/surgical history; especially the surgical history;
- Review/collection of inclusion/exclusion criteria and determination as to whether the subject is eligible for participation;
- Urine/blood pregnancy test;
- Physical Examination, including height, weight and abdominal sign;
- Concomitant therapy: including the dose and site of neoadjuvant radiotherapy;
- Concomitant medications: Only including the which used beyond two weeks. The neoadjuvant chemotherapy protocol and period should also be captured.
- Adverse Events;

Visit 2 – Randomization

The following must be obtained in this visit:

- Radomization: whether the patients recieved neoadjuvant radiotherapy will be the factor of the stratified randomization.
- Confirm inclusion and exclusion criteria

Visit 3 – Phase 1 Operation

The following must be obtained prior to the surgical procedure:

- Update to medical/surgical history
- Device usage data: The code and quantity of the used study product, placement position and placement method of the study product;
- Procedure time: the time beginning with the opening of the first incision to the closure of the last incision.
- Blood loss
- During this operation, adhesions assessment (extent and severity) and any treatment of adhesions will be recorded
- Quantity of surgical gloves used: including the surgical sterile gloves used by the doctors and instrument nurses;
- Length and closure method of the target incision: the sutures and closure method also should be recorded.
- Intra-operative device failure;
- Concomitant medications: Only including the medicine related to adverse events and which used beyond two weeks.;
- Concomitant therapy;
- Adverse Events;
- Defects of study product.

Visit 4 – Post-Op through Discharge

The following must be obtained in this visit:

- Concomitant medications: Only including the medicine related to adverse events and which used beyond two weeks. The postoperative chemotherapy protocol and period should also be captured (if any);
- Concomitant therapy;
- Adverse Events (Concomitant medication associated with AEs will also be collected);
- Defects of study product;
- Mechanical ileus;
- Physical Examination, including abdominal sign.
- SSI;
- All layer Wound dehiscence;
- Delayed wound healing events;.

Visit 5 – Phase 2 Operation

The following information must be obtained in this visit:

- Review and collection of medical/surgical history: the sugical history should be collected carefully;
- Concomitant therapy;
- Physical Examination including abdominal sign;
- Concomitant medications: Only including the medicine related to adverse events and which used beyond two weeks. The postoperative chemotherapy protocol and period should also be captured (if any);
- SSI;
- All layer Wound dehiscence;
- Delayed wound healing events;
- Adverse Events (Concomitant medication associated with AEs will also be collected);
- Defects of study product;
- Mechanical ileus;
- Operative data: the image data of operation needs to be recorded as follow: starting from the upper left quadrant and proceeding clockwise to the lower left quadrant. If the incisional adhesion was found, whether and how the treatment for the adhesion performed should be recorded.

Visit 6 – Post-Op through Discharge

The following must be obtained in this visit:

- Concomitant medications: Only including the medicine related to adverse events and which used beyond two weeks;
- Concomitant therapy;
- Adverse Events;
- Defects of study product;
- Mechanical ileus;
- Physical Examination including abdominal sign.
- SSI;
- All layer Wound dehiscence;
- Delayed wound healing events;

- Study completion: If this visit occurs 6-9months after Phase 1 operation, study completion would be conducted in this visit.

Visit 7 – 6-7 months after Phase 1 operation (Phone contact)

If Visit 6 occurs 3-6 months after Phase 1 operation, this visit should be conducted. The following must be obtained in this visit:

- Review and collection of medical/surgical history: the sugical history and the diagonosis which may related to abdominal adhesions should be collected carefully;
- Adverse Events;
- Defects of study product;
- Mechanical ileus;
- SSI;
- All layer Wound dehiscence;
- Delayed wound healing events;
- Study completion.

7.3. Monitoring Plan

This study is performed according to the Good Clinical Practice for Medical Device Trials and related international laws and regulations, criteria, etc., such as ISO 14155, the Declaration of Helsinki.

The sponsor bears the monitoring responsibility for the clinical trial and will select the qualified monitor to execute the monitoring responsibility.

The monitor should comply with the related laws and regulations and the standard operating procedure established by the sponsor with regard to the monitoring to monitor each phase of this study.

The monitor should contact and visit the investigators at a regular basis and make the field visit/monitoring for the study. The monitor should make a visit when the first subject is enrolled, and make a necessary visit at a regular basis (about every 4 or 6 weeks) during the study period.

The monitoring includes the visit to clinical trial institution, verification of CRF data, communication with investigators and clinical trial institution, ensuring that this study will be performed strictly in compliance with the trial protocol and the requirements of regulations of Good Clinical Practice, etc.

The on-site inspection of CRF includes verifying the source document and checking whether original data is true, accurate, complete and clear, the original document of each subject is complete.

This study may be subject to the audit by the sponsor or regulatory authority. If such audit is

performed, the investigator must agree the auditor to look up the records of subjects. The investigator agrees the sponsor or its appointed representative and regulatory authority to monitor all project-related study documents on site by signing on the signature page of this trial protocol.

See the attached monitoring plan for the detailed monitoring plan.

8. STATISTICAL CONSIDERATIONS

8.1. Statistical Design, Method and Analysis Procedure

This study is a prospective, multicenter, randomized controlled study to evaluate the superiority of INTERCEED™ compared to blank control in reducing the incidence of postoperative incision adhesions in laparaoscopic surgery.

The primary effectiveness endpoint is the proportion of subjects free of abdominal incision adhesions at primary target incision site observed in the two treatment groups (INTERCEED™ and Control). The assessment of adhesions will be conducted during the second laparoscopy for ileostomy reversal.

The statistical hypotheses for the primary endpoint are as follows:

- H_0: $P_I \leq P_C$ tested against the alternative hypothesis
- H_a: $P_I > P_C$

where P_I is the proportion of subjects free of adhesions in the INTERCEED™ group and P_C is the proportion of subjects with adhesions in the Control group.

The proportion of subjects free of adhesions will be summarized for each treatment group and will be calculated as the number of subjects free of adhesions divided by the total number of subjects randomized to that treatment. Within-treatment group two-sided 95% confidence intervals for the proportions of subjects free of adhesions will be provided using Clopper-Pearson method. In addition, a one-sided Wald 97.5% confidence interval for the difference in two independent proportions (INTERCEED™ minus Control) will be constructed and used for testing the null hypothesis of superiority stated above. If the lower limit of the confidence interval is greater than 0, then it will be concluded that INTERCEED™ is superior to Control.

The primary endpoint will be analyzed using the Intent-to-Treat (ITT) and Per-Protocol (PP) sets. The ITT analysis will be considered primary, while the PP analysis will be considered supportive. The analysis sets for this study are defined in section 8.9.

The following secondary effectiveness endpoints will be summarized descriptively by treatment group for the ITT analysis set:

- Extent and severity of adhesions--at the incision site and four abdominal quadrants;
- Incidence of subjects with mechanical ileus.

In addition, the following safety endpoints will be summarized descriptively by treatment group for the Safety analysis set:

- Incidence of subjects with surgical site infections (SSI) of target incision after Phase 1 operation;

- Incidence of postoperative all layer wound dehiscence of target incision after Phase 1 operation;
- Incidence of subjects with delayed wound healing events of target incision after Phase 1 operation;
- Any adverse event;
- Defects of study product.

All continuous variables will be summarized by number of subjects, mean, standard deviation, median, minimum and maximum. All categorical data will be summarized by frequencies and associated percentages.

All analyses/summaries will be produced using SAS® (Version 9.1 (EG) or later).

8.2. Calculation of Sample Size

8.2.1. Total Sample Size: 220 patients.

The relevant literature review revealed observed percentages of subjects with pelvic wall adhesions of 41% and 49.3% for INTERCEED™ and of 76% for Control[12,13]. As a consequence, for the sample size determination, the assumption was conservatively made that the proportions of subjects with adhesions in INTERCEED™ and Control groups would be 0.5 and 0.75, respectively. With a one-sided significance level of 0.025, a sample size of 77 subjects in INTERCEED™ group and 77 subjects in Control group are required to achieve 90% power to detect a difference of 0.25 between the two group proportions using a one-sided Chi-square test. In order to adjust for a 30% dropout rate, a total of 110 subjects in INTERCEED™ group and 110 subjects in Control group, for a total of 220 subjects, will be enrolled.

8.2.2. Minimum and Maximum Number of Subjects in Each Clinical Trial Institution and Reasons for determination

A total of 220 Chinese patients undergoing rectal cancer surgery and needing second stage reposition of preventive terminal ileostomy will be enrolled in 12 study sites in China.

8.3. Significance Level and Power of Clinical Trial

The power of the statistical test at which the sample size for the primary effectiveness endpoint was calculated is 90%, and the significance level of the test was set to 0.025 (one-sided).

Within-treatment group two-sided 95% confidence intervals for the proportions of subjects with adhesions will be provided using Clopper-Pearson method. In addition, a one-sided Wald 97.5% confidence interval for the difference in two independent proportions (INTERCEED™ minus Control) will be constructed and used for testing the null hypothesis of superiority stated in section 8.1. If the upper limit of the confidence interval is smaller than 0, then it will be concluded that INTERCEED™ is superior to Control.

8.4. Expected Drop-out Rate

The expected dropout rate in this study is 30%.

8.5. Criterion of Acceptability/Unacceptability of Clinical Trial Result

For the primary efficacy endpoint, a one-sided Wald 97.5% confidence interval for the difference in proportions of subjects with adhesions (INTERCEED™ minus Control) will be constructed and used for testing the null hypothesis of superiority stated in section 8.1. If the upper limit of the confidence interval is smaller than 0, then it will be concluded that INTERCEED™ is superior to Control.

8.6. Criteria and Reason for Terminating the Trial based on the Statistical Results

An ad-hoc interim analysis is proposed based on feedback received from the investigators who observed very low rate of adhesions at the second procedure for ostomy reversal.

The conditional power (CP) is the probability that the final result will be significant, given the data obtained up to the time of interim look. The table as below shows the CP per different adhesion rate difference of INTERCEED vs Control arms at the interim look.

Given the assumed 30% drop-out rate, it was planned that a total of 154 participants (77 per arm) with evaluable primary endpoint are available by the study completion. The interim analysis will be performed while at least 94 participants (at least 61% of the total number) have their primary endpoints evaluated in the electronic data collection system. If the CP is ≤ 60%, the observed adhesion rate difference magnitude between two arms is only around 0.10, which is much less than the assumed difference magnitude of 0.25 used for sample size calculation. Therefore, the study will be terminated due to low adhesion rate and small effect size between INTERCEED and control arms. Otherwise, the study will continue until the study completion as planned.

There is a database lock for this interim analysis. All data for the analysis will be cleaned with 100% source data validation. The statistical analysis will be conducted per updated and approved protocol and SAP to determine if the interim results meet the pre-specified threshold of early discontinuation (CP≤ 60%).

Table: Conditional power per different treatment effect size observed at interim look

Observed adhesion difference between INCTERCEED vs control at interim look	Data availability at interim look Percentage of participants with evaluable primary endpoint (number of participants)				
	61% (94)	66% (102)	70% (108)	72% (112)	75% (116)
-0.02	0.19	0.11	0.07	0.04	0.02
-0.06	0.35	0.26	0.2	0.16	0.12
-0.08	0.45	0.37	0.3	0.26	0.21
-0.1	0.55	0.48	0.42	0.38	0.34
-0.11	0.59	0.54	0.49	0.45	0.41
-0.12	0.64	0.6	0.56	0.52	0.49
-0.13	0.69	0.65	0.62	0.6	0.57
-0.14	0.73	0.7	0.68	0.66	0.64
-0.15	0.77	0.75	0.74	0.72	0.71

-0.16	**0.81**	**0.8**	**0.79**	**0.78**	**0.78**
-0.18	**0.87**	**0.87**	**0.87**	**0.87**	**0.87**

8.7. Statistical Method of All Data, together with the Handling Method of Missing, Unused and Error Data (including Termination and Withdrawal Halfway) and Unreasonable Data

All study endpoints will be analyzed using the available data. There will be no missing data imputation in this study.

8.8. Reporting Procedure of Deviation from Original Statistical Plan

Any changes from the original planned statistical analyses will be specified in the protocol revisions, if applicable, and/or in a final or amended statistical analysis plan.

The statistical analysis plan will be updated accordingly per the ad-hoc interim analysis.

8.9. Selection Criteria and Reason of Subjects Included in the Analysis

All subjects that meet the inclusion/exclusion criteria are considered to meet the requirements for recruitment.

The following three analysis sets are defined in this study:

- The Intent-to-Treat (ITT) set will contain all randomized subjects.
- The Per-Protocol (PP) set will contain all subjects in the ITT set who have no major protocol deviations.
- The Safety set will contain all subjects who receive study device.

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

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

In all cases, treatment allocation will be based on randomization for the primary effectiveness endpoint using the ITT. If more than 11 subjects are mis-randomized, then an additional confirmatory analysis based on treatment received will be performed for the primary effectiveness endpoint, using the ITT.

The secondary effectiveness endpoint will be analyzed using the ITT set, while the safety endpoints will be analyzed using the Safety set.

9. Data management

The individual subject data collected during the period of this trial will be recorded in the corresponding database. The data is audited by the data management group after collecting the data. Any unexpected or missing data points will generate inquiry and the unexpected or missing data will be forwarded to the site for solving it. When all subjects have the opportunity to complete

all follow-up evaluation, this study will be closed and the data analysis will be performed.

10. FEASIBILITY ANALYSIS

10.1. Likelihood Analysis of Success

INTERCEED™ was first marketed in America in 1989, which was used in gynecological pelvic surgery to prevent the occurrence of postoperative adhesion. It was approved in Europe in 2002 to be used in abdominal operation. It was introduced in the Chinese market in 2004 and approved to be used in gynecological pelvic surgery. It has been widely used at home and abroad for nearly 30 years.

INTERCEED™ is a sterile, single-use-only, absorbable off-white knitted fabric prepared by the controlled oxidation of regenerated cellulose. INTERCEED™ reduces the formation of adhesions by physically separating the surfaces of tissues that are adjacent to each other during the reperitonealization phase.

The currently existing clinical literatures regarding the study product showed that INTERCEED™ could reduce the occurrence of postoperative adhesion when compared to the blank control [6,7,11-19]. Especially the two papers (e.g. Sekiba and Azziz) [13,14] studying the tissue, pelvic wall similar to abdominal wall clearly pointed out that the incidence of adhesions in pelvic wall was about 76% when INTERCEED™ was not used, while the incidence of adhesions was reduced to 40%-50% when INTERCEED™ was used. It can be seen that INTERCEED™ has a prominent impact on preventing the occurrence of adhesions [11,12].

10.2. Likelihood Analysis of Failure

Although a large amount of clinical literature showed that INTERCEED™ could reduce the occurrence of postoperative adhesion when compared to the blank control, most of these studies were limited to uterus and ovary, no clinical literatures related to the application in abdominal cavity or abdominal wall.

An ad-hoc interim analysis is proposed based on feedback received from the investigators who observed very low rate of adhesions at the second procedure for ostomy reversal. The ad-hoc interim analysis is planned to reevaluate the study assumptions used for hypothesis testing. If the assumptions don’t hold, the likelihood analysis of failure may increase to be moderate.

11. QUALITY CONTROL OF CLINICAL TRIAL

During the clinical study, the sponsor and investigator should execute their respective responsibilities according to the Good Clinical Practice for Medical Device Trials and applicable related Chinese and international regulations. They should also strictly follow the clinical trial protocol in order to ensure the quality of clinical trial.

The sponsor should organize the training on clinical trial protocol and the use and maintenance of investigational medical device for all investigators participating in the trial, so as to ensure the consistency in the implementation of clinical trial protocol, the use of investigational medical device.

During the implementation of study, the sponsor is responsible for monitoring each phase of clinical trial. The clinical monitor employed by the sponsor or appointed representative should comply with the related standard operating procedure (SOP) and clinical trial protocol that are

established by the sponsor to monitor the clinical trial, so as to ensure the complete, accurate, true and reliable data.

To ensure the quality of study, the sponsor may authorize the eligible QA auditor to audit the clinical trial as needed. The investigator should allow the auditors to look up the original data and documents related to this study after receiving the notification.

When the food and drug regulatory authority, competent department of health and family planning or other regulatory agencies send the inspection personnel to carry out the inspection, the clinical trial institution and investigator should cooperate and immediately notify the sponsor.

12. CLINICAL TRIAL-INVOLVED ETHICAL ISSUES AND INFORMED CONSENT

12.1. Ethical Concerns

In the whole study process, the study protocol (and update), informed consent form (and update) and other applicable documents related to the study must be submitted to the relevant Ethics Committee and can't be implemented until the written approval is obtained.

Before the subjects participate in the clinical trial, the investigator must fully explain this study and answer all questions raised by subjects. Each subject (or legally authorized representative) must voluntarily sign and date the informed consent form (and other documents as per local regulations) that is approved by the Ethics Committee prior to implementing any study-related operations. The process of obtaining the informed consent needs to be clearly documented in the original record of the subject. The subject may request to withdraw the informed consent at any time in the study process. This withdrawal will not affect the subsequent therapy of the investigator for the subject.

The production of investigational product should meet the relevant requirements of applicable quality management system for medical devices; the processing and storage of investigational product should meet the requirements of specifications and related standard operating procedure; the investigational product should be used according to the approved protocol and related operation instructions.

The collection, use and disclosure of all personal data (including the patient health and medical information) should comply with the applicable laws and regulations with regard to the personal data protection and security. When collecting and processing such personal data, appropriate measures are to be taken to maintain the confidentiality of patient health and medical information and to prevent access by unauthorized persons.

12.2. Approval of Trial Protocol

The trial protocol should be internally approved and filed according to the company's standard operating procedure (SOP) prior to submitting to the external agency (including but not limited to the government regulatory agencies, Ethics Committee).

The clinical trial protocol should not be implemented until the written approval is obtained from the Ethics Committee according to the relevant requirements of laws and regulations.

12.3. Process of Informed Consent and Text of Informed Consent Form

12.3.1. Process of Informed Consent

The informed consent of all potential subjects must be obtained prior to performing any study operations/procedures. Once the investigator determines that the patients are suitable for participating in this study, the investigator must explain the background of the study presented and the benefits and risks of surgery and study to the patients and answer the questions raised by patients. Only the patient who signs the informed consent form that is approved by the Ethics Committee (EC) prior to participating in the study is eligible to participate in this study. The patient who doesn't sign the written informed consent form is not eligible to participate in this study.

Each subject (or legally authorized representative) must sign and date the informed consent form that is approved by the (EC) (and other documents as per local regulations) prior to implementing any study-related items or operations not belonging to the standard treatment and after the nature of this study is fully clarified.

The process of obtaining the written informed consent needs to prove that the subjects volunteer to participate in this study. All aspects of this study must be clarified to the subjects prior to signing the informed consent form. The process of obtaining the informed consent must be clearly documented by the investigator and/or designated person in the original clinical trial documents of subjects. The investigator has responsibilities to ensure the process of obtaining the informed consent is implemented according to the Good Clinical Practice for Medical Device Trials and related regulations, such as ISO 14155, the Declaration of Helsinki.

12.3.2. Text of Informed Consent Form

See the Informed Consent Form attached to the protocol.

13. REGULATIONS OF ADVERSE EVENT AND DEVICE DEFECT REPORTING

13.1. Adverse event

An AE is defined as any untoward medical occurrence in the process of clinical trial, regardless of its relationship to the investigational medical device.

The investigator should determine whether an AE occurs and determine its relationship to the study device or surgery at each evaluation for the subjects recruited for the clinical study.

All AEs, study device faults and other product problems must be recorded in the medical record and entered in the CRF. All AEs need to be recorded in the EDC system in 2 weeks.

Postoperative pain, fever and laboratory abnormalities is expected and will not be documented as an adverse event unless the Investigator considers the pain or fever to exceed that normally anticipated following the surgery or related to study devices. Also, the adverse event, not including the serious adverse event and ileus event, which is "not relative" or "unlikely related" to the study device and occurred 1. between 30 days after Phase 1 operation and the hospitalization for Phase 2 operation or 2. between Visit 6 and Visit 7 should not be documented.

The severity of adverse event is graded into the following levels:

Mild: Existing signs or symptoms have no impact on the usual activities of the subjects, or transient, no treatment required, with no sequel.

Moderate: Have an impact on the usual activities of the subjects, with no interference, with possible need of treatment.

Severe: Cause the symptom of severe discomfort, resulting in major impact on the usual activities of the subjects, medical intervention or treatment required.

The causal relationship of adverse events should be determined as follows:

Not related: The event is definitely not related to the use of product

Unlikely related: The time sequence between the use of product and the event shows that the event is unlikely associated,

Possibly related: The time sequence between the use of product and the event shows that the event is likely associated, or AE may also be caused by the disease or concomitant treatment of the subjects,

Probably related: The time sequence shows the event has temporal relationship to the use of investigational product, or the event is alleviated at the end of use of product, or it is unable to give reasonable explanation to this event according to the disease of the patient,

Definitely related: The time sequence shows the event has temporal relationship to the use of investigational product, or the event is alleviated after the withdrawal of product, or the event occurs again when the product is reused (reactivated).

13.2. Serious Adverse Event

A Serious Adverse Event is any AE that results in a death or a serious deterioration in the health of the subject during the clinical trial, including a life-threatening illness or injury, a permanent impairment of a body structure or a body function, in-patient hospitalization or prolongation of existing hospitalization, medical or surgical intervention to prevent permanent impairment of a body structure or a body function; or results in fetal distress, fetal death or congenital abnormality, congenital anomaly, etc. The rehospitalization events after Phase 1 operation only for receiving the chemotherapy/radiotherapy which planned after the diagnosis of the primary disease will not be documented as an adverse event.

13.3. Device Defect

The device defect is defined as unreasonable risk occurred under normal use of medical device during the clinical trial, which may do harm to the human health and life safety, such as label error, quality problem, fault, etc.

For the device defect that may cause serious adverse event, the sponsor should report to the CFDA and the competent department of health and family planning at the same level where the device is registered within 5 workdays after being informed. The sponsor should also inform other clinical trial institutions and investigators that participate the trial, and timely inform the Ethics Committee of such clinical trial institution through its administrative department for clinical trial of medical device. The investigator should record all adverse events required in protocol and device defects found in the process of clinical trial, work with the sponsor to analyze the causes of the events, form the written analysis report, present the comments on the continuation, discontinuation or termination of the trial, and report to the Ethics Committee by the administrative department for clinical trial of medical device of clinical trial institution for review.

13.4. Reporting Procedure, Contact Information

The investigator should ensure to provide the sufficient treatment for Any adverse event of any

subjects, including the laboratory detection value with clinical significance and related to this study.

The adverse event is reported from the start of signing the informed consent to the end of the study of subjects. All adverse events should be followed up, until the adverse event is resolved, stable or the study is completed.

The investigator should record the nature, severity, treatment and outcome of serious adverse event, and determine whether it is related to the study device, drug administration or surgery specified in the study protocol. The investigator will report the adverse event to the sponsor via the Case Report Form (CRF).

The investigator must submit the serious adverse events occurred in the study and the device defects that may cause serious adverse event to the sponsor and the regulatory authorities at every level (or designated person) immediately after being informed of the event; if required by the sponsor, the further information should be provided.

All serious adverse events need to be followed up until the event is resolved (with or without sequela). When the event is not resolved or stable at the end of study, the medical monitor in this clinical study will decide whether it is necessary to collect the further follow-up information.

The investigator and sponsor should report the serious adverse events occurred in the study and the device defects that may cause serious adverse event to the regulatory authorities at every level according to the requirements of laws and regulations.

The study device with device defect should be returned to the sponsor according to the instructions given in Section 13.3 of this study. Once a device defect is found, the site should inform the sponsor as soon as possible, and report the device related information on the relevant CRF.

The contact person to report adverse event and device defect is as follows:

Adverse event: RA-JNJSG-InterceedCN@ITS.JNJ.com

Device defect: JJMC-productcomplaint-Ethicon@its.jnj.com

14. DEVIATION FROM CLINICAL TRIAL PROTOCOL AND REGULATIONS FOR CLINICAL TRIAL PROTOCOL AMENDMENT

The study protocol deviations are defined as the circumstances that fail to comply with the requirements of clinical trial protocol intentionally or unintentionally.

All protocol deviations should be reported as protocol deviations to the sponsor. The records include the date of and reason for protocol deviations. The investigator should also report the protocol deviations to the EC according to the procedures and in combination with the requirements and procedures of the EC.

If protocol amendment occurs, the sponsor or designated person should submit the change data of study protocol to the investigator, regulatory authority, and the Ethics Committee, etc. according to the relevant laws and regulations. All major amendments must be approved by the Ethics Committee and regulatory authority (if needed) prior to implementing any changes to study procedures.

If an amendment likely has major impact on the following items, this amendment belongs to the major amendment:

- Safety or physical or mental health of subjects;
- Scientific value of trial;
- Implementation or management of trial;
- Quality or safety of investigational medical device specified in the trial.

15. DIRECT ACCESS TO SOURCE DATA AND DOCUMENT

The source data is defined as all information in the original record and its approved copy with regard to the clinical findings, observations and other activities in the clinical trial, which can be used for reproduction and evaluation of clinical trial. The source documents are documents on which the source data is recorded, including printed, paper or electronic documents.

The subject's medical record and other study related documents (source documents) must be maintained and retained by the Investigator. The investigator should allow the monitors and auditors/inspectors to look up, at least including but not limited to the following information:

- Medical/physical condition of the study subject that meets the inclusion criteria prior to participating this study;
- Process of informed consent;
- Operational description of use and implantation of the study product;
- All inspection results and follow-ups;
- Examined printed output file or report (for example, X-ray film) that is dated and signed;
- Image data of Phase 2 operation;
- Description of adverse event and follow-ups of adverse event (description of event, severity, date of occurrence, duration, correlation with the study device, study procedure, outcome and treatment of adverse event, concomitant medications when an adverse event occurs);
- Description of device defect;
- Study subject's status at the end of the study or withdrawn from the study.

The sponsor expects that the appropriate study coordinator and/or investigator, appropriate source documents and appropriate environment are available for reviewing the study related documents during the period of monitoring and visit.

16. FINANCES AND INSURANCE

See the relevant study contract and insurance document.

17. CONTENTS THAT THE CLINICAL TRIAL REPORT SHOULD COVER

According to the regulatory requirements, the clinical trial report should be consistent with the clinical trial protocol, mainly including:

.1. General information;

.2. Synopsis;

.3. Introduction;

.4. Clinical trial objective;

.5. Clinical trial method;

.6. Clinical trial contents;

.7. General clinical data;

.8. Investigational medical device and control device or control diagnosis and treatment method;

.9. Statistical analysis method and evaluation method used;

.10. Clinical evaluation criteria;

.11. Organizational structure of clinical trial;

.12. Ethical description;

.13. Clinical trial results;

.14. Adverse events found in the clinical trial and their treatment;

.15. Analysis and discussion of clinical trial results, especially the indications, scope of application, contraindications and precautions;

.16. Conclusion of clinical trial;

.17. Existing problems and improvement suggestion;

.18. List of investigators;

.19. Other conditions that need to be described.

.20. For multicenter clinical trial, it also includes the summary of clinical trial of each sub-site

18. CONFIDENTIALITY

The personal data of the subject partipicating in the trial is confidential; however, the Ethics Committee, food and drug administration, competent department of health and family planning or the sponsor and its authorized representative may look up the personal data of the subject partipicating in the trial for the demand of work according to the established procedure.

The personal data of the subject should be kept confidential during the entire period of clinical trial, and it should be ensured that the source data can be verified through the supporting information. So, a unique ID number of the subject (site number and subject number) is used to identify all data of each subject reported. If the data is kept strictly confidential and it is ensured that the privacy of the subject has been protected, the data related to this study is available for the third party (for example, under the audit of regulatory authority).

19. AGREEMENT ON THE PUBLICATION OF TRIAL RESULTS

If needed, a article for multicenter trial will be prepared and published in the prestigious scientific

journal at the end of the study. No major results of experience of any individual site in this study are allowed to be published before the multicenter trial results are prepared and published. The exception from this regulation needs an prior approval from the sponsor. Other endpoints analysis specified preoperatively and non-preoperatively will be implemented in the data management department. Such secondary analysis and other proposed investigations need to be approved by the sponsor. To timely extract the statement and publish, the second publication will be entrusted to the corresponding principal authors. The final anlaysis and review of all multicenter trial data are requried to be approved by the sponsor.

20. RESPONSIBILITIES THAT EACH PARTY SHOULD BEAR

20.1. Responsibilities of the sponsor

1) The sponsor is responsible for the initiation, application, organization and monitoring of clinical trial.

2) The sponsor is responsible for the organization to establish and modify the investigator's brochure, clinical trial protocol, informed consent form, Case Report Form, relevant standard operating procedure and other relevant documents, carry out the training required for the clinical trial, and provide these documents to the investigators before the study starts.

3) The sponsor should select the qualified trial instituion and investigators.

4) The sponsor should sign a written agreement with the clinical trial institution and the investigator with regard to the clinical trial.

5) The sponsor should provide qualified study product according to the regulatory requirements. The sponsor should be responsible for the safety of investigational medical device in the clinical trial. The adverse event, serious adverse event and the device defect that may cause serious adverse event should be collected and reported in accordance with the provisions.

6) The sponsor should inform the regulatory authority at every level when the sponsor decides to suspend or terminate the clinical trial or at the end of the study.

7) The sponsor should ensure the investigator should perform the study strictly in compliance with the clinical trial protocol, timely correct the protocol deviations and reserve the rights to report to the regulatory authority.

8) The sponsor should bear the treatment cost and relevant economic compensation for the clinical trial-related injury or death of subjects, with the exception of damages due to the fault of medical instituion and medical staff in the diagnosis and treatment.

9) The sponsor should select the qualified monitor for monitoring and organize the inspection appropriately.

20.2. Responsibilities of Clinical Trial Institution and Investigator

1) The clinical trial institution should evaluate the relevant recources according to the features of investigational medical device prior to the clinical trial, so as to decide whether to perform this clinical trial.

2) The clinical trial institution should properly keep the records and documents of clinical trial according to the agreement with the sponsor.

3) Make sure that the investigators responsible for the clinical trial should have the qualifiication in accordance with the requirements of related laws and regulations.

4) The administrative department for clinical trial of medical device of clinical trial institution should cooperate with the sponsor to apply to the Ethics Committee and submit the relevant documents prior to the clinical trial according to requirements.

5) The investigator should ensure that the relevant workers participating in the trial have the enough resources and proper training, and keep the training related documents.

6) The investigator should ensure to use the investigational medical device only for the subjects of this clinical trial, and may not charge any fee.

7) The investigator should strictly follow the clinical trial protocol, with the exception of emergency circumstances when the subject faces the direct risk and needs immediate clinical measures, which can be reported later in a written form.

8) The investigator is responsible for recruiting the subjects, communicating with the subject or its legal representative before signing the informed consent.

9) The investigator should protect the rights, safety and health of the subjects.

10) In case of adverse event occuring in the clinical trial, the investigator should protect the safety of the subjects and timely report the event to the regulatory authority.

11) The investigator should record all adverse events occurring and device defects found in the process of clinical trial, work with the sponsor to analyze the causes of the events, form the written analysis report, present the comments on the continuation, discontinuation or termination of the trial, and report to the Ethics Committee by the administrative department for clinical trial of medical device of clinical trial institution for review.

12) The investigator should make sure that the clinical trial data is accurately, completely, clearly and timely recorded in the Case Report Form.

13) The clinical trial institution and investigator should make sure that the data, documents and records generated in the clinical trial are true, accurate, clear and safe.

14) The clinical trial institution and investigator should accept and cooperate with the monitoring and audit of the sponsor, the supervision of the Ethics Committee, and the inspection of the food and drug administration, competent department of health and family planning, etc., and provide all required records related to the trial.

15) If the clinical trial needs to be suspended or terminated, the subjects should be informed of, and it should be ensured that the subjects to receive the proper care and follow-up. The clinical trial institution and investigator should also report in accordance with the regulations, provide the detailed written explanation.Relevant report should be submitted to the local food and drug administration at the provincial, autonomous regional and municipal level if necessary.

16) The clinical trial institution and investigator reserve the rights to report to the regulatory authority at every level when the sponsor violates relevant laws and regulations.

17) The investigator should ensure to complete all records and reports at the end of clinical trial.

The investigator should also ensure that the received investigational medical devices are properly handled and recorded according to the requirements.

20.3. Responsibilities of other interested parties

See the study-related contract

STATEMENT OF INVESTIGATOR

I agree to:

1. Conduct this clinical trial in strict accordance with the requirements of the Declaration of Helsinki, China's current laws and regulations and trial protocol.
2. Record all required data correctly in the case report form (CRF) and complete the clinical trial report on schedule.
3. Use the investigational medical device only for this clinical trial, accurately and completely record the investigational medical device receiving and use condition during the clinical trial, and keep record.
4. Allow the CRA and inspectors authorized and dispatched by the sponsor and regulatory authority to monitor, inspect and audit this clinical trial.
5. Strictly implement the terms in the clinical trial contract/protocol signed by all parties.

I have read thoroughly the clinical trial protocol, including the above statements, and I agree to all the above contents.

Comments of sponsor Signature (Stamp) Date: DD/MM/YYYY

Comments of investigator Signature Date: DD/MM/YYYY

Comments of clinical trial institution of medical device Signature (Stamp) Date: DD/MM/YYYY

APPENDIX 1:

REFERENCES

1. Kusunoki M, Ikeuchi H, Yanagi H, Noda M, Tonouchi H, Mohri Y, et al. Bioresorbable hyaluronate-carboxymethylcellulose membrane (Seprafilm) in surgery for rectal carcinoma: a prospective randomized clinical trial. Surg Today. 2005;35(11):940-5.

2. Ellis H, Moran BJ, Thompson JN, Parker MC,Wilson MS, Menzies D, et al. Adhesion-related hospital readmissions after abdominal and pelvic surgery: a retrospective cohort study. Lancet 1999; 353:1476–80.

3. Trimbos-Kemper TCM, Trimbos JB, van Hall EV. Adhesion formation in tubal surgery: results of the eight day laparoscopy in 188 patients. Fertil Steril 1985; 43:395–400.

4. Bronson RA, Wallace EE. Lysis of periadnexal adhesions for correction of infertility. Fertil Steril 1977; 28:613–9.

5. Ray NF, Denton WG, Thamer M, Henderson SC, Perry S. Abdominal adhesiolysis: inpatient care and expenditures in the United States in 1994. J Am Coll Surg. 1998 Jan;186(1):1-9.

6. Matthews BD, Pratt BL, Backus CL, Kercher KW, Heniford BT. Comparison of adhesion formation to intra-abdominal mesh after laparoscopic adhesiolysis in the New Zealand White rabbit. Am Surg. 2002 Nov;68(11):936-40; discussion 941.

7. Menzies D, Ellis H. Intestinal obstruction from adhesions--how big is the problem? Ann R Coll Surg Engl. 1990 Jan;72(1):60-3.

8. Tinelli A, Malvasi A, Guido M, Tsin DA, Hudelist G, Hurst B, et al. Adhesion formation after intracapsular myomectomy with or without adhesion barrier. Fertil Steril. 2011 Apr;95(5):1780-5.

9. Chapa H O, Venegas G. Maternal morbidity at first repeat cesarean: a sub-analysis of INTERCEED barrier placed at primary cesarean section. Open Access Surgery, 2013, 2013(default):7-12.

10. Vrijland WW, Tseng LN, Eijkman HJ, Hop WC, Jakimowicz JJ, Leguit P, et al.. Fewer intraperitoneal adhesions with use of hyaluronic acid-carboxymethylcellulose membrane: a randomized clinical trial. Ann Surg. 2002 Feb;235(2):193-9.

11. Kusunoki M, Ikeuchi H, Yanagi H, Noda M, Tonouchi H, Mohri Y, et al. Bioresorbable hyaluronate-carboxymethylcellulose membrane (Seprafilm) in surgery for rectal carcinoma: a prospective randomized clinical trial. Surg Today. 2005;35(11):940-5.

12. Salum M, Wexner SD, Nogueras JJ, Weiss E, Koruda M, Behrens K, et al. Does sodium hyaluronate- and carboxymethylcellulose-based bioresorbable membrane (Seprafilm) decrease operative time for loop ileostomy closure? Tech Coloproctol. 2006 Oct;10(3):187-90; discussion 190-1.

13. Sekiba K. Use of INTERCEED (TC7) absorbable adhesion barrier to reduce postoperative adhesion reformation in infertility and endometriosis surgery. The Obstetrics and Gynecology Adhesion Prevention Committee. Obstet Gynecol. 1992 Apr;79(4):518-22.

14. Azziz R. Microsurgery alone or with INTERCEED Absorbable Adhesion Barrier for pelvic sidewall adhesion re-formation. The INTERCEED (TC7) Adhesion Barrier Study Group II. Surg Gynecol Obstet. 1993 Aug;177(2):135-9.

15. Li TC, Cooke ID. The value of an absorbable adhesion barrier, INTERCEED, in the prevention of adhesion reformation following microsurgical adhesiolysis. Br J Obstet Gynaecol. 1994 Apr;101(4):335-9.

16. Chapa HO, Venegas G, Vanduyne CP, Antonetti AG, Sandate JP, Silver L. Peritoneal adhesion prevention at cesarean section: an analysis of the effectiveness of an absorbable adhesion barrier. J Reprod Med. 2011 Mar-Apr;56(3-4):103-9.

17. Haney AF, Hesla J, Hurst BS, Kettel LM, Murphy AA, Rock JA, et al.. Expanded polytetrafluoroethylene (Gore-Tex Surgical Membrane) is superior to oxidized regenerated cellulose (INTERCEED TC7+) in preventing adhesions. Fertil Steril.1995 May;63(5):1021-6.

18. Franklin RR. Reduction of ovarian adhesions by the use of INTERCEED. Ovarian Adhesion Study Group. Obstet Gynecol. 1995 Sep;86(3):335-40.

19. The efficacy of INTERCEED (TC7)* for prevention of reformation of postoperative adhesions on ovaries, fallopian tubes, and fimbriae in microsurgical operations for fertility: a multicenter study. Nordic Adhesion Prevention Study Group. Fertil Steril. 1995 Apr;63(4):709-14.

20. Mais V, Ajossa S, Piras B, Guerriero S, Marongiu D, Melis GB. Prevention of de-novo adhesion formation after laparoscopic myomectomy: a randomized trial to evaluate the effectiveness of an oxidized regenerated cellulose absorbable barrier. Hum Reprod. 1995 Dec;10(12):3133-5.

21. Mais V, Ajossa S, Marongiu D, Peiretti RF, Guerriero S, Melis GB. Reduction of adhesion reformation after laparoscopic endometriosis surgery: a randomized trial with an oxidized regenerated cellulose absorbable barrier. Obstet Gynecol. 1995 Oct;86(4 Pt 1):512-5.

22. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Committee. American Journal of Infection Control 1999: 27:97-132.

23. Rahbari NN, Weitz J, Hohenberger W, Heald RJ, Moran B, Ulrich A, Holm T, Wong WD, Tiret E, Moriya Y, Laurberg S, den Dulk M, van de Velde C, Büchler MW. Definition and grading of anastomotic leakage following anterior resection of the rectum: a proposal by the International Study Group of Rectal Cancer. Surgery. 2010 Mar;147(3):339-51.

APPENDIX 2: LIST OF MODELS/SPECIFICATIONS

M4345; M4350; M4350N