

STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

**Use of Hemopatch as a sealant in the pancreaticojejunostomy after
pancreatoduodenectomy to prevent postoperative pancreatic fistula**

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This document is confidential and can not be circulated without the written authorization of the principal investigators.

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1. SYNOPSIS OF THE STUDY.

Principal investigator	Mario Serradilla Martín, MD, FACS Associate Professor at University of Zaragoza Attending Surgeon in General Surgery Division of Hepato-Pancreato-Biliary Surgery Miguel Servet University Hospital Paseo Isabel La Católica, 1-3 50009 Zaragoza, Spain Tel.: +34 636 006 184 Fax: +34 976 765 509 E-mail: marioserradilla@hotmail.com / mserradilla@salud.aragon.es
Title of the study	Use of Hemopatch as a sealant in the pancreaticojejunostomy after pancreatoduodenectomy to prevent postoperative pancreatic fistula
Population	Patients undergoing pancreatoduodenectomy (PD) (due to benign or malignant tumors or chronic pancreatitis) with duct-to-mucosa pancreaticojejunostomy reconstruction
Objetives	Primary objective: <ul style="list-style-type: none">• To demonstrate the effectiveness of Hemopatch in the prevention of postoperative pancreatic fistula after PD with duct-to-mucosa reconstruction against ductomucosal reconstruction without Hemopatch Secondary objectives: <ul style="list-style-type: none">• To assess the safety and tolerance of Hemopatch in patients undergoing PD
Interventions	Performing duct-to-mucosa anastomosis with or without Hemopatch reinforcement after PD
Inclusion and exclusion criteria	Inclusion criteria: patients submitted to PD by laparoscopic or open approach for benign / malignant tumors or chronic pancreatitis; ASA < 4; men and women ≥ 18 and ≤ 80 years of age. Exclusion criteria: patients under 18 and over 80 years old; ASA score ≥ 4 ; subjected to multivisceral resections different from PD; patients with acute necrotizing pancreatitis; immunosuppressed patients; patients who have not signed the informed consent; patient with contraindication of PD performance
Results	Primary point: Type B and C postoperative pancreatic fistula defined according to the criteria of the International Study Group on Pancreatic Fistula (ISGPF) Secondary endpoints: <ol style="list-style-type: none">1) Duration of postoperative hospital stay.2) Length of stay in intensive care unit.3) Measurement of drainage debit.4) Reinterventions including interventional radiology.5) Infection of the surgical site and / or dehiscence of the

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	wound; complications in the deep organ space up to 30 days postoperatively. 6) Delayed gastric emptying. 7) Biliary fistula. 8) Postoperative hemorrhage. 9) Death, regardless of the cause.
Type of study	Prospective randomized double blind unicentric clinical trial
Statistic analysis	For the evaluation of the primary endpoint patients will be dichotomized by the presence or absence of the sealant reinforcement. Further, patients will be categorized by the type of pancreatic fistula rate defined according to the International Study Group of Pancreatic Fistula (ISGPF). Next, a contingency table will be created to calculate positive predictive value, specificity, sensitivity, and c-index. Association between sealant reinforcement and POPF rate will be expressed as odds ratio calculated by logistic regression models with the appropriate covariates. The strength of association between categorical variables will be tested with a chi-square test with Yate's correction. Secondary end points will be analyzed descriptively by tabulation. Chi-square tests will be used to test associations among categorical variables, while Student's t-test or Mann-Whitney U-test will be used to compare continuous normal or non-normal data, respectively. Time dependent variables will be tested by Kaplan-Meier analysis and Cox regression. Statistical analysis will be performed with R.
Sample size	64 patients, 32 in each group
Ethical approval	This study is approved by the Clinical Research Ethics Committee of Aragon (CEICA)
Duration of the study	The study will begin on February 1, 2018. It is estimated a duration of 1.5 years, according to the PD rate of our center (40-50 year). Estimated end date: July 31, 2019.
Participating centers	Division of Hepato-Pancreato-Biliary Surgery, Department of Surgery, Miguel Servet University Hospital

2. PATIENT VISIT AND EVALUATION.

There will be a first visit in an outpatient clinic where the patient will be informed about the study in detail and will be offered to participate in it as long as it meets the selection criteria. Two copies of the informed consent will be signed, one of them for the patient and the other will be kept together with the study documentation. A first evaluation of the patient will be carried out as it appears in the data collection notebook.

3. STRUCTURE OF THE ORGANIZATION.

3.1. Sponsor.

Investigator Initiated Research Grant from Baxter S.L., Chicago, Illinois, United States, convened on March 24, 2017.

3.2. Principal investigators.

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4. SUMMARY.

Pancreatoduodenectomy (PD) is a common surgical procedure to treat carcinoma of the head of the pancreas and other tumors of the periampullary region. Recent advances in surgical techniques and perioperative treatments have reduced the perioperative mortality below 10% in high volume centers [1–4]. However, PD is associated with considerable morbidity in 40–58.5% of patients manifesting postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), postpancreatectomy hemorrhage (PPH), and postoperative pulmonary complications [2, 5, 6].

Several surgical techniques and perioperative care have been studied in order to prevent or decrease the incidence of POPF after PD, including digestive tract reconstruction with pancreaticogastrostomy [7], duct-to-mucosa (DTM) or invagination pancreaticojejunostomy (PJ) [8], prophylactic somatostatin or somatostatin analogues [9], and pancreatic duct stents [10].

Probably the reasons why the pancreaticojejunal anastomosis has greater diffusion are different, starting from the first descriptions of the surgical technique with subsequent inertia, until it is feasible to use 3 anastomosis reconstruction after PD with the same jejunal handle. Currently, there is a growing pancreatic reconstruction trend by pancreaticogastrostomy technique. However, the results of prospective randomized studies as well as meta-analyzes conclude that both techniques are safe and that the rate of fistula is similar in both cases. Despite this, with the pancreaticogastrostomy technique, there is a higher rate of postoperative bleeding and a higher rate of DGE [11-12]. There is another factor in the choice of the technique, which is the consistency of pancreatic remnant. A soft pancreas will always be an added risk for the onset of the fistula. In these cases, many surgeons choose a PJ according Peng's technique [13].

Although perioperative morbidity and mortality associated with a PD has improved significantly over the years, even in high-volume centers, the incidence of POPF is still in the range of 9.9–28.5% [14–16]. Therefore, an ideal pancreatic reconstruction technique or perioperative treatment, which prevents POPF, is still unavailable.

The use of sealants has been one of the approaches performed in order to try to reduce the POPF (Table 1). Some non-controlled or non-randomized studies have shown that the use of fibrin glue based sealants in combinations with patches of felts may lead to a POPF grade B/C of 0-10% [18-21]. Only 2 randomized control trials have been performed with fibrin glue, with opposite results in terms of significant reduction of POPF [17, 22].

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Table 1. Studies with the use of sealants in PD and rates of pancreatic fistula.

Author	Year	Study type	Patients / Surgery	N	CONTROL		TREATMENT		P
					Technique	POPF	Technique	POPF	
Lillemoe [17]	2004	RCT	High risk (soft panc/small duct)	125	Ø (66)	30% ¹	Fibrin glue: Hemaseal (59)	26% ¹	NS
Ochiai [18]	2010	Retrospective	-	54	Ø (36)	38.9% ²	PGA felt + Fibrinogen/ thrombin patch (18)	5.6% ²	0.016
Pozzo [19]	2010	Retrospective non- controlled	-	27	-	-	Tachosil	0% ²	-
Mita [20]	2011	Retrospective non- controlled	Duct-to- mucosa	40	-	-	Tachocomb	7,5% ²	-
Satoi [21]	2011	Prospective (historical control)	-	128	Ø (78)	14% ²	PGA felt + Fibrin glue: Bolheal (50)	10% ²	NS
Martin [22]	2013	RCT	-	57	Ø (32)	43.8% ¹	Fibrin glue: TISSEEL (59)	40% ¹	NS

1- Fistula grade A, B & C; 2- Fistula grade B & C

Hemopatch is an NHS-PEG patch that consists of a soft, thin, pliable, flexible pad of collagen derived from bovine dermis, coated with NHS-PEG (pentaerythritol polyethylene glycol ether tetra-succinimidyl glutarate). It is intended as a surgical sealant for procedures in which control of leakage by conventional surgical techniques is either ineffective or impractical [23], making it a plausible option to use during PD surgical technique in order to decrease POPF.

Preliminary experience with Hemopatch: case serie

In our center we have been using this NHS-PEG patch envolving the pancreaticojejunostomy as a new way to decrease POPF after PD. The results of more than a year of experience have been submitted as an abstract communication to the E-AHPBA congress in Mainz, Germany (May, 2017), and are the following:

Sealing with NHS-PEG patch to prevent postoperative pancreatic fistula after pancreaticojejunostomy

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Background. Postoperative pancreatic fistula (POPF) is a common and most severe complication following pancreaticoduodenectomy (PD) (9.8% to 34.2%). POPF not only prolongs hospital stay and increases healthcare costs, but also plays a central role in the development of life-threatening events such as intra-abdominal abscess and

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postoperative hemorrhage. We present a new way to decrease POPF after PD using a NHS-PEG patch envolving duct-to-mucosa (DTM) pancreaticojejunostomy.

Materials and methods. 26 consecutive PD were performed from July 2015 to October 2016, using the same technique, 13 of them sealing with NHS-PEG patch after DTM. Both groups were statistically homogeneous. Demographic data were collected (age, gender, diagnosis, date of intervention), and rates of postoperative complications (pancreatic fistula, biliary fistula, delayed gastric emptying –DGE-, hemorrhage, exitus, Clavien-Dindo classification, readmission and mean stay).

Results. Postoperative complication rates were (with NHS-PEG patch/without NHS-PEG patch): pancreatic fistula (A: 7.7%/7.7%; B: 0%/7.7%; C: 0%/15.5%); biliary fistula: 7.7%/15.4%; DGE: 7.7%/7.7%; hemorrhage: 7.7%/15.5%; exitus: 0%/7.7%; readmission: 7.7%/46%; mean stay: 21.3/26.1 days; other complications: 61.5%/46.2%.

Discussion. Sealing with NHS-PEG patch to prevent postoperative pancreatic fistula after DTM pancreaticojejunostomy can offer a new possibility to decrease POPF, with less fistula rate B and C, less hospital stay an less healthcare costs. Randomized controlled trials with larger number of patients should be performed to support this theory.

Therefore, we have design the following randomized controlled trial in order to validate our positive experience with Hemopatch in PD.

5. HYPOTHESIS / OBJECTIVE.

This unicentric, double-blind, randomized study investigates the efficacy and tolerance of Hemopatch in the prevention of POPF type B and C after a PD. The goal for Hemopatch is to reduce the risk of POPF type B and C from 30% to 15%.

6. STUDY DESIGN.

6.1. Type of study.

Unicentric, randomized, controlled, double-blind, prospective study with a parallel design of two groups. After giving informed consent, patients will not know to which group they have been assigned (reinforcement with Hemopatch or not). After the last follow-up visit on postoperative day 30, the patients can receive this information if they wish.

This study is also blind on the part of the observer; the final result will be determined by an independent observer, making this a double-blind study.

6.2. Primary objective and secondary objectives.

Primary endpoint: POPF type B and C, according to the definition of the ISGPF (Bassi, Surgery 2005), that is, the secretion of pancreatic fluid externalized through a drain or removed during a reoperation, independently of the color and / or appearance on day 3 or later, whose amylase is 3 times the values of serum amylase or collections (infected or not) detected by fistulography or other imaging techniques (computed tomography, ultrasound, magnetic resonance imaging). See attached table.

Grade	A	B	C
Clinical conditions	Well	Often well	Ill appearing / bad
Specific treatment*	No	Yes / no	Yes
US / CT (if obtained)	Negative	Negative / positive	Positive
Persistent drainage (after 3 weeks)**	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to POPF	No	No	Possibly yes
Signs of infections	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes / no	Yes / no

US, Ultrasonography; CT, computed tomographic scan; POPF, postoperative pancreatic fistula.
*Partial (peripheral) or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or minimal invasive drainage.
**With or without a drain in situ

Secondary endpoints:

- 1) Duration of postoperative hospital stay.
- 2) Duration of stay in intensive care unit.
- 3) Measurement of drainage debit.
- 4) Reinterventions including interventional radiology
- 5) Infection of the surgical site and / or dehiscence of the wound; complications in the deep organ space up to 30 days postoperatively.
- 6) Delayed gastric emptying.
- 7) Biliary fistula.
- 8) Postoperative hemorrhage.
- 9) Death, regardless of the cause.

6.3. Duration of the study.

The study will begin on February 1, 2018. Patients will be recruited at Miguel Servet University Hospital from January 1, 2018 to July 31, 2019. All patients randomly assigned will be followed for 30 days after surgery, or during the total stay in case it is longer than 30 days. They will also be evaluated in external consultations in the postoperative period for 3 months. A period of 4-6 months is considered to evaluate the data and the study will entail 2 years in total.

7. PATIENTS.

7.1. Criteria.

Despite improvements in morbidity after pancreatic resection, POPF after PD remains problematic. The incidence varies markedly in the literature, ranging from 0% to 64%, and 35% are clinically relevant. This great variability is attributed in part to the

indication and extension of the resection, as well as to the comorbidities of the patient. Other factors, such as age, male sex, obesity, prolonged operation time and a soft pancreas, as well as multivisceral resections increase the risk of fistula. The sequelae of pancreatic fistula after PD cover a broad spectrum. These patients often require visits to the emergency department, hospital readmissions, percutaneous drainage guided by interventional radiology, prolonged parenteral antibiotic therapy, radiological surveillance and numerous postoperative visits. The complications derived from the fistula double the cost of hospital treatment and dramatically increase the use of health resources.

7.2. Recruitment.

All patients undergoing PD, either by laparotomy or laparoscopy, are potential participants. Their diagnoses include chronic pancreatitis, benign (for example, cystadenoma) or malignant tumors (adenocarcinoma, NET, metastasis, etc.). They will be invited to participate in the study and will be informed of the possible advantages and disadvantages. The randomization process will begin for any patient who agrees to participate after informed consent.

7.3. Inclusion and exclusion criteria.

Inclusion criteria: patients submitted to PD by laparoscopic or open approach for benign / malignant tumor or chronic pancreatitis; ASA < 4; men and women ≥ 18 and ≤ 80 years of age.

Exclusion criteria: patients under 18 and over 80 years old; ASA score ≥ 4 ; subjected to multivisceral resections different from PD; patients with acute necrotizing pancreatitis; immunosuppressed patients; patients who have not signed the informed consent; patient with a contraindication to PD.

7.4. Intervention techniques and materials.

The indications for performing a PD are multiple. The type of reconstruction to be performed will depend basically on the characteristics of the pancreatic remnant. However, in our center, the usual reconstruction technique is the duct-to-mucosa type pancreaticojejunostomy.

Depending on the randomization, patients will be operated as follows:

- 1) Basic treatment: standard duct-to-mucosa pancreaticojejunostomy.
- 2) Basic treatment plus Hemopatch: standard pancreaticojejunostomy + reinforcement with 2 Hemopatch of 90 x 45 mm, one on each side (lower and upper) as a "scarf".

In both groups, passive external drainage is mandatory for a period of 7 days with drainage placed next to the anastomosis but not in contact with it. The drain can be a Penrose drain, a Jackson-Pratt drain or Blake without active suction. Suction drains are not allowed.

Adjvant procedures

Wrapping, sealing with fibrin or serous patch with another adjacent organ are not acceptable. No resection of adjacent hollow organ is allowed (excepting those included in the standard DPC).

Materials

Hemopatch is a hemostatic-sealant made of collagen that resorbs in 6-8 weeks. The active side is covered with a polyethylene glycol film for better adhesion.

Hemopatch is a medical product with CE certificate (Annex IV - excluding section 4 of Council Directive 93/42 / EEC on medical devices) used for hemostasis. It is not designed for use with heavy or pulsatile bleeding or with acute infections. It also has indication of sealant from March 2016. Hemopatch should not be used intravascularly. It also can not be used for patients who are allergic to any of the materials listed by the manufacturer. The only known side effect is the rare case when Hemopatch can not achieve the desired hemostasis. With documentation of the patient's clinical course, regular blood tests and imaging tests when necessary, any undesirable effects derived from the use of Hemopatch must be diagnosed in a timely manner and appropriate measures will be taken, the coordinator will be immediately informed, the person in charge of the control of the test and, likewise, an immediate communication of the adverse effect to the manufacturer will be sent.

7.5. Postoperative period.

In the postoperative period, the parameters of inflammation, body temperature, visual analog pain scale (VAS), drainage debit and its amylase / lipase content will be documented. To facilitate the healing process, drainage should be left in place for at least 7 days. In the absence of evidence of fistula, the drainage may be withdrawn. If the 7th postoperative day there is evidence of pancreatic fistula according to the ISGPF criteria, the drainage will be maintained until the resolution of the same.

All patients are advised to follow the instructions given at discharge. If there is any reason for the alarm (pain, fever, tachycardia) the patient should go to the hospital where he was treated at any time. A final visit will be scheduled on postoperative day 30 to evaluate any collection of intra-abdominal fluids through the clinical examination and the performance of an ultrasound or CT scan (as is done routinely).

7.6. Complications / failure of the intervention.

POPF are defined according to the definition published in 2005 by the International Study Group on Pancreatic Fistula (ISGPF), which is based on the concentration of amylase in the drainage fluid. A POPF is defined when the concentration of amylase in the drainage fluid is three or more times greater than in serum from the third postoperative day.

Pancreatic fistulas are classified in 3 grades, from A to C:

- **Grade A:** clinically asymptomatic patient, persistent fistula, absence of intra-abdominal fluid collection in imaging test. No therapeutic consequence; the hospitalization is not prolonged.
- **Grade B:** symptomatic patient, requires diagnostic evaluation and therapeutic management. Clinically stable patient, may complain of abdominal pain, fever, nausea and intolerance to oral intake. Normally there is a collection of at least 3 x 3 cm in image tests. Therapeutic consequences: you must start antibiotic treatment and absolute diet. Invasive intervention (percutaneous drainage) may be necessary; hospitalization usually lasts.
- **Grade C:** clinically unstable patient (sepsis). Therapeutic consequences: it requires intensive care, percutaneous drainage or reoperation if the drainage has been removed or is not properly positioned. Hemorrhage is frequent; high expected mortality.

The objective of this study is to evaluate the rate of type B and C fistulas after pancreatic resection with and without Hemopatch.

7.7. Termination conditions / Adverse events / Suspected unexpected serious adverse reaction.

Criteria for withdrawing a patient from the study:

- Patient's desire to be removed from the study.
- Intervention not performed (due to unresectability).
- The investigator suspects a serious threat to the patient's well-being. Adverse events (any sign or symptom that affects the patient's well-being) and serious adverse events (life-threatening, prolongs hospital stay, results in persistent disability or leads to death during the observation period), as cardiopulmonary problems, in the gastrointestinal tract, anaphylactic shock or embolism will be recorded through daily postoperative visits until discharge and during the final visit on the 30th postoperative day. All adverse effects of clinical relevance and all serious adverse effects will be recorded in the case report form along with the degree of the complication (according to the Clavien-Dindo classification). The principal investigator must be informed within 24 hours about the serious adverse effects that occur during the hospital stay. The presence of a causal relationship between adverse effect or serious adverse effect and the intervention of the trial will be judged by the investigator. Serious adverse effects will be reported immediately (ie, within 5 days after recognition) by all investigators to the coordinating investigator. The coordinating researcher must inform the responsible ethics committee and the research sponsor. A list of all serious adverse effects must be compiled.

8. DATA.

8.1. Calculation of the sample size.

The sample size was calculated by comparing two proportions, with a level of statistical significance of 5% (alpha) and a statistical power of 80% (1-beta), and taking into account the preliminary data obtained regarding the rate of POPF in the two groups: 23% for the control group, and 7% for the Hemopatch group.

With these assumptions, it will take 57 patients to detect, with an 80% probability and a level of significance of 5%, a decrease of the POPF rate of 23% in the control group to 7% in the experimental group (Hemopatch). Considering an expected proportion of losses of 10%, the sample size will be 64 patients.

8.2. Randomization and groups.

All patient data are anonymous. Each patient who meets the selection criteria and has signed the informed consent will be entered into a database and identified by a number (from 1 to 64). The list of patient identification numbers will be in the hands of the principal investigator. After carrying out the surgery, the patient number is entered into an online computerized randomization tool ("Randomizer for clinical trials"), <https://www.meduniwien.ac.at/randomizer>. It is a tool of the University of Vienna in Austria, where the study is registered, which allows, once the patient number is entered, the randomization of the same, obtaining one of the two methods to compare, as explained in Section 7.4. (32 patients in each study group):

- Basic treatment: duct-to-mucosa pancreaticojejunostomy WITHOUT Hemopatch reinforcement.
- The same, but reinforced WITH Hemopatch.

Once the treatment to be performed is obtained, surgery will be carried out according to the treatment obtained in the randomization.

8.3. Efficacy assessments (that is, data that must be collected).

- Daily drainage debit.
- Concentration of amylase and lipase from the drainage fluid (days 3, 5 and 7 postoperatively) and every 2 days in case of permanent fistula.
- Number of postoperative days with drainage (minimum 7 days). If the amylase / lipase content of the drainage on the 7th postoperative day is within normal limits, it may be withdrawn.
- Body temperature, VAS pain score, leukocyte count and CRP.
- Duration of the stay in the ICU.
- Duration of the total hospital stay.
- Reinterventions, including percutaneous drainage of collections.
- Re-entry.
- Degree of complications according to the Clavien-Dindo classification, including both complications derived from surgery (delay of gastric emptying, bleeding, biliary fistula, wound infection, intra-abdominal

abscess, etc.) and general (atelectasis, pneumonia, urine infection, thromboembolism, etc.)

8.4. Patient data sheet.

It contains patient information including personal history (ie, smoking, diabetes, BMI), preoperative and postoperative data, intraoperative incidents, special treatment details, complications and adverse events such as new onset diabetes, pneumonia or heart problems.

All the data are collected in a central database.

All study personnel must sign a confidentiality agreement that covers all aspects of the study and its data. The study directors will take particular responsibility for the security of the data, the documents of origin and the information about the patients.

The coordinator of the main study is also responsible for continuing education in Good Clinical Practices (GCP) in accordance with the Declaration of Helsinki.

8.5. Statistical methods and data analysis.

For the evaluation of the primary objective, patients will be dichotomized by the presence or absence of the sealant reinforcement. In addition, patients will be classified by the type of pancreatic fistula defined according to the ISGPF. Next, a contingency table will be created to calculate the positive predictive value, specificity, sensitivity and the c-index. The association between sealant reinforcement and pancreatic fistula rate will be expressed as an odds ratio calculated by logistic regression models with the appropriate covariates. The strength of association between the categorical variables will be tested with a chi-square test with the Yate correction.

Secondary objectives will be analyzed descriptively by tabulation. Chi-square tests will be used to test associations between categorical variables, while Student's t-test or Mann-Whitney U-test will be used to compare normal or non-normal data, respectively. Time-dependent variables will be tested by Kaplan-Meier analysis and Cox regression. The statistical analysis will be carried out with R.

9. PATIENT SAFETY.

A monitoring team will receive all patient data electronically including expected and unexpected events and side effects for all patients in the study. All patient data are analyzed to detect any unusual pattern. There will be permanent contact with the main coordinator of the study and will meet face to face three times a year to evaluate the course of the study based on the data collected.

10. IMPACT ON CLINICAL PRACTICE.

Hemopatch is expected to reduce the risk of postoperative type B and C pancreatic fistula from 30% to 15%, so that the number of patients currently requiring readmission with possible surgeries and interventional radiological procedures is halved. This implies not only clinical but also economic advantages, since a pancreatic fistula can double the cost of hospital treatment.

11. ETHICS AND LEGAL REQUIREMENTS.

This study is carried out in full compliance with the principles of the "Declaration of Helsinki" (amended at the 56th General Assembly of the AMM, Tokyo, Japan, 2008). Following good clinical practices should guarantee the scientific conduct of the clinical trial and the credibility of the results. This study is approved by the Clinical Research Ethics Committee of Aragon (CEICA).

12. REGISTRATION.

Once approved, this study will be registered in the EU Clinical Trials Register or ClinicalTrials.gov.

13. PUBLICATION.

Once the study is completed and the statistical study has been carried out, a publication will be made and sent to a high-impact surgical journal in English.

14. REFERENCES.

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