BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers’ comments and the authors’ responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open’s open peer review process please email info.bmjopen@bmj.com
# BMJ Open

Radiofrequency-assisted transection of the pancreas vs stapler in distal pancreatectomy: study protocol for a multicentric randomized clinical trial (TRANSPIARE)

| Journal: | BMJ Open |
| --- | --- |
| Manuscript ID | bmjopen-2022-062873 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 24-Mar-2022 |
| Complete List of Authors: | Sánchez-Velázquez, Patricia; Hospital del Mar, Department of Surgery; Hospital del Mar Medical Research Institute Pueyo-Pérez, Eva; Hospital del Mar, Department of Surgery Álamo, JM; University Hospital Virgen del Rocío, Department of surgery Suarez Artacho, Gonzalo; University Hospital Virgen del Rocío, Department of surgery Gómez Bravo, Miguel Ángel; University Hospital Virgen del Rocío, Department of surgery Marcello, Manuel; Alcorcon Hospital Foundation, Department of surgery Vicente, Emilio; Hospital universitario Sanchinarro, Department of surgery Quijano, Yolanda; Hospital universitario Sanchinarro, Department of surgery Ferri, Valentina ; Hospital Universitario Madrid Sanchinarro, Caruso, Ricardo; Hospital universitario Sanchinarro, Department of surgery Dorcarratto, Dimitri ; hospital clínico Valencia Sabater, Luis; hospital clínico Valencia González Chávez, Pilarena; Hospital Virgen de la Candelaria, Tenerife Noguera, Jose; Hospital Juan Canalejo de La Coruña Navarro Gonzalo, Ana; Hospital Clínico Universitario Lozano Blesa Bellido-Luque, Juan; Hospital Universitario Virgen Macarena Téllez-Marques, Clara; Hospital del Mar, Department of Surgery Ielpo, Benedetto; Parc Salut Mar Hospital, Barcelona Burdio, Fernando; Hospital del Mar; Hospital del Mar Medical Research Institute), Department of Surgery |
| Keywords: | Pancreatic surgery < SURGERY, Hepatobiliary surgery < SURGERY, Clinical trials < THERAPEUTICS |
Radiofrequency-assisted transection of the pancreas vs stapler in distal pancreatectomy: study protocol for a multicentric randomized clinical trial (TRANSPIRE)

Authors: Patricia Sánchez-Velázquez*, Eva Pueyo-Pérez1,2*, JM Álamo2, Gonzalo Suárez Artacho2, Miguel Ángel Gómez Bravo2, Manuel Marcello3, Emilio Vicente4, Yolanda Quijano4, Valentina Ferri4, Ricardo Caruso4, Dimitri Dorcaratto5, Luis Sabater5, Pilarena González Chavez6, Jose Noguera7, Ana Navarro8, Juan Bellido-Luque9, Clara Téllez-Marques1, Benedetto Ielpo1, Fernando Burdío1, Transpaire Study Group

Affiliations:
1. Hepatobiliary and Pancreatic Surgery Unit. Service of General Surgery and Digestive Surgery. Hospital del Mar. Hospital del Mar Medical Research Institute (IMIM), Passeig Marítim 25-29, Barcelona, Spain.
2. Department of Surgery, University Hospital Virgen del Rocío, Sevilla
3. Department of Surgery, Fundación Alcorcón, Madrid
4. Department of Surgery, Hospital Universitario Sanchinarro, Madrid
5. Department of Surgery, Liver, Biliary and Pancreatic Unit, Hospital Clinico, University of Valencia, Biomedical Research Institute (INCLIVA)
6. Department of surgery, Hospital Virgen de la Candelaria, Canarias, Spain
7. Department of surgery, Hospital Juan Canalejo, La Coruña, Spain
8. Department of surgery, Hospital clinico de Zaragoza, Spain

* Co-first authors

Corresponding author:
Patricia Sánchez-Velázquez MD, PhD, FEBS
Hepato-Biliary and Pancreatic Surgery Unit, Service of General Surgery, Hospital del Mar.
Passeig Marítim de la Barceloneta, 25, 29
Barcelona
ZIP Code: 08003
Email: Psanchezvelazquez@psmar.cat
Abstract

Introduction: To date, no pancreatic stump closure technique has been shown to be superior to any other in distal pancreatectomy. Although several studies have shown a trend towards improved outcomes in transection by a radiofrequency device (RFT) in terms of reducing clinically relevant pancreatic fistula (CR-POPF) no randomized trial has been carried out for this purpose to date. We therefore designed an RCT, hypothesizing that this technique used in distal pancreatectomies is superior in reducing CR-POPF than mechanical closures.

Methods and analysis: TRANSPAIRE is a multicentric randomized controlled trial performed in 7 Spanish pancreatic centres. A total of 75 patients undergoing elective distal pancreatectomy for any indication will be randomly allocated to RFT or classical stapler transections (Control Group) in a ratio of 1:1. The primary outcome is the CR-POPF percentage, which is assessed by the international Study Group for Pancreatic Fistula (ISGPF) classification. The sample size is calculated with the following assumptions: 5% one-sided significance level (α), 80% power (1-β), expected POPF in the control group of 32%, expected POPF in the RFT group of 5%, and a clinically relevant difference of 27%. Secondary outcomes include postoperative outcomes (e.g., clinically relevant surgical complications graded by Clavien-Dindo classification, in-hospital mortality and oncological variables), long-term complications (e.g., endocrine and exocrine impairment), radiological assessment of the pancreatic stump in the follow-up, metabolomic profiling of peritoneal fluid after surgery, survival and quality of life. Follow-ups will be made at the Outpatient Clinic after 1, 6 and 12 postoperative months.

Ethics and dissemination: The TRANSPAIRE trial has been approved by the Ethics Committee of Hospital Universitario del Mar (2020/9390/I). Results concerning the primary endpoint will be available in 2024 and will be published at national or international meetings as well as open access, peer-reviewed journals.

Trial registration: Clinicaltrials.gov registry: NCT04402346.

Keywords: Distal pancreatectomy, Left pancreatectomy, Pancreatic tail resection, Pancreatic surgery, Radiofrequency, Radiofrequency-Assisted, Stapler
Introduction

Pancreatic surgery is currently the gold-standard option for curative treatment not only in neoplastic diseases but also in benign diseases and mucinous cystic neoplasms. Distal pancreatectomy consists of resecting the portion of the pancreas on the left aspect of the superior mesenteric vein and inevitably leads to a pancreatic stump, as no anastomosis is performed between the pancreatic remnant and the bowel. The most feared and potentially serious complication after distal pancreatectomy is a postoperative pancreatic fistula (POPF), which consists of the leakage of pancreatic juice from the main and secondary branches of the duct to the peri-pancreatic space or peritoneal cavity [1]. Although different surgical techniques have been applied to seal the pancreatic stump throughout the history of pancreatic surgery, and with the centralization of surgery and the multidisciplinary approach we have witnessed a considerable reduction in postoperative mortality and morbidity [2], the POPF rate remains however unchanged, around 30% -40% [3]. Historically, the closure of the pancreatic stump by manual suture (hand-sewn) was the standard of care [4] but with later technological developments and the implementation of the minimally invasive approach, staplers, ultrasonic scalpels, [5] biological glues [6] and even fatty tissue patches attached to the pancreatic stump [7] have been widely accepted.

Since none of the previously mentioned techniques have been able to reduce the incidence of POPF, energy-assisted and radiofrequency-assisted devices have been implemented in both experimental studies [8, 9] and clinical settings to try to reduce the POPF rate. The preliminary data from retrospective studies showed promising results, with a significant reduction of POPF of up to 10-14% [10, 11] and despite their major limitation of being retrospective uncontrolled studies with few patients, they provided an insight into the efficacy of the technique for solving a serious clinical dilemma.

In a recent retrospective propensity-score matched analysis of 89 patients we suggested that the use of the Coolingbis radiofrequency device was associated with a significant reduction of POPF rates compared to stapler closure [12]. Under these premises, in a randomized trial we aim to evaluate the effectiveness of radiofrequency transection of the pancreas in terms of duct sealing compared to the classical method of (stapler) transection to significantly reduce POPF rates in distal pancreatectomy.
Methods and analysis:

Study design:

The TRANSPAIRE trial is a multicentric randomized controlled parallel-group trial carried out in 7 Spanish pancreatic centres to compare two different methods of pancreatic transection in distal pancreatectomy (DP), i.e. radiofrequency assisted transection (RFT- study group) vs stapler (ST- control group). Inclusion of the centres started with the approval of the Institutional Review Board (IRB) in the Hospital del Mar (2020/9390/I), Barcelona. Local approval was acquired required for the individual participating centres and the study was registered at ClinicalTrials.gov (NCT04402346). The patients eligible to participate in the study will be approached by the investigators and recorded, even if they did not decide to participate. All the patients will sign a written informed consent before randomization. The protocol was designed according to SPIRIT guidelines [13]

Study population and eligibility criteria:

All consecutive patients requiring distal pancreatectomy for any cause will be considered eligible if they complied with all of the following at randomization: (Fig. 1-flowchart)

- Inclusion criteria:
  
  - Over 18 years old
  - Patients with benign or malignant solid or cystic pancreatic neoplasms.
  - Transection of the pancreas performed at least > 2cm on the left from the medial aspect of the superior mesenteric vein (assessed by computed tomography or magnetic resonance at least 2 months before the surgical intervention) to avoid potential iatrogenic lesions of the intrapancreatic common bile duct.
  - Either spleen-preserving or espleno-pancreatectomy were accepted
  - Either open or minimally invasive approach (laparoscopic or robotic) were acceptable

- Exclusion criteria:
  
  - Any other system of pancreatic transection in the control group apart from stapling was excluded
Patients were also involved in this trial, as the patients association for pancreatic cancer (Asociación española contra el cancer-AECC) also identified this research as being a priority area for clinicians.

Calculation and justification of the sample size

The sample size was calculated following Delgado M et al. [14] and hypothesizing that RFT was superior to ST. Assumptions were made considering a POPF rate of 30.6% for ST [15] and 6.6% for RFT, respectively, so that there was a clinically-relevant difference of 27%. At 5% one-sided significance level (\(\alpha\)), 80% power (1-\(\beta\)), the required sample size was 34 patients per arm, including a 10% drop-out rate after randomization (patients who underwent no surgery after randomization) led to a total number of 75 patients to be randomized.

Trial specific interventions:

- **RFT group:** the technique will be conducted with either an open or minimally invasive approach (robotic or laparoscopic). All the procedures will be performed by a pancreatic surgeon with at least 5 years of experience in the field and having completed the learning curve. All the surgeons are familiar with both techniques of stump closure after pancreatectomy. After examination of the abdominal cavity, the gastrocolic ligament will be divided to allow correct visualization of the upper border of the pancreatic gland and the course of the splenic vessels. In case of splenic preservation, these vessels must be spared. The position of the pancreas division line will be selected in the proximal normal pancreas according to the position of the lesion and intraoperatively guided by ultrasonography to ensure correct margins. In all cases pancreatic transection will be performed in the RFT group with a 10-mm diameter version of the Coolingbis device (*Apeiron Medical, Valencia, Spain*). By applying the device and moving it backwards over the surface of the parenchyma, the blunt section of the device coagulates the tissue and the blade cuts through the portion of
coagulated tissue. If transection with RFT is impossible, the surgeon will be free to cross over to perform any other transection technique. The specific techniques used will be recorded together with the consequent data analysis.

- ST group: The surgical procedure will be performed in essentially the same way as in the RF Group, except for the step of pancreatic transection, which will be carried out with a stapler. As the aim is to compare the technique itself to RF, no restrictions were set concerning the stapler load/cartridge or the use of Bioabsorbable Staple Line Reinforcement. A gradual compression will be applied for 5-10 min, the stapler will be then fired and slowly released after transection. Hand-sewn or other transection methods such as the harmonic dissector are absolute exclusion criteria.

As the TRANSPAIRE trial is pragmatic no extra effort will be focused on standardizing the patients’ postoperative care, as long as the same protocol will be applied to both RFT and ST groups in each individual centre. Participants will receive postoperative care according to the centre’s daily routine, however, all surgical techniques, materials, and medical devices used were reported in detail to detect any differences among the participants, identify potential confounders and to register any imbalance among the treatment groups.

Data capture and trial end-points:

Primary endpoint(s)

The primary endpoint of the study is clinically relevant postoperative pancreatic fistula (CR-POPF) rate according to the updated guidelines recently published by the International Group of Pancreatic Fistula study (ISGPF), defined as: 1) Extravasation of pancreatic juice with levels in the peritoneal fluid x3 times the serum level from the 3rd postoperative day, 2) Collections of undrained amylase-rich fluids/abscesses. [16]

Pancreatic amylase will be measured in the peritoneal fluid of the drain at postoperative day 3 and 5 (if drain still in place). Any type of fistula (biochemical leak or clinically relevant -B or C-) will also be assessed.
Secondary endpoint(s)

The most important secondary end-points are in-hospital mortality, postoperative complications until discharge and long-term postoperative end-points. Complications will be graded by the Clavien-Dindo classification [17], which groups the complication according to the treatment received and the CCI [18], a value which measures overall cumulative morbidity on a scale from 0 (no complications) to 100 (death) and will be applied to cover the total number of complications by severity for individual patients. Other variables include patients’ clinical demographic characteristics (i.e. sex, age, ASA classification, jaundice level), variables associated with the type of procedure (open or laparoscopic surgery, intraoperative bleeding, duration of the intervention, size of the pancreatic duct) and oncological outcomes such as quality of lymphatic resection (see Table 1).

| Table 1: Secondary end-points |
|------------------------------|
| **Endpoint** | **Definition** | **Timeline** |
| **Intraoperative** | | |
| Blood loss | Millilitres | Day of the surgery |
| Operative time | Minutes | Day of the surgery |
| Surgical approach | Open/minimal invasive | Day of the surgery |
| Spleen-preservation | Yes/no | Day of the surgery |
| **Postoperative end-points** | | |
| CR-POPF | According to ISGPF definition [21] | Within 90 days after surgery |
| DGE | According to ISGPF definition [22] | Within 90 days after surgery |
| PPH | According to ISGPF definition [23] | Within 90 days after surgery |
| QoL Questionnaires | PAN-26, EORTC-30 [24] | Until 12 months after surgery |
| Readmission rate | Any readmission in the hospital | Within 90 days after surgery |
| Reoperation rate | Any surgery after index surgery | Within 90 days after surgery |
| Overall survival | Time from surgery to last follow-up | Within 12 months after surgery |
Metabolic phenotyping will be carried out on the peritoneal fluid on the 3rd postoperative day to assess the inflammatory changes secondary to the treatment applied. The possibility of generating metabolic phenotypes from large patient samples can thus identify candidates for metabolic biomarkers, certain disease risks or the result of a certain treatment. [19] Specifically, a battery of inflammatory cytokines is measured with the Proteome Profiler Human XL Protein array, which can test a battery of up to 105 different cytokines. The remnants of biological samples not used for this determination will be destroyed.

Patients’ quality of life will be evaluated by QLQ-C30 and PAN-26 questionnaires sent to the participants at baseline, 30, 180, and 365 days after surgery.

Long-term end-points include:
- Evaluating the postoperative morbidity of patients in the follow-up in the first year (late complications, presence of endocrine and / or exocrine insufficiency) as well as overall and disease-free survival in cancer patients.
- Radiological assessment of pancreatic stump evolution in the first month and first year after surgery. Volume of the ablation lesion created in the transection margin according to digital reconstruction with CT or MRI one month and one year after surgery using a segmented injury manual with appropriate software (3d Doctor, Able Software Corp, Mass, USA) measured in cubic centimetres [20]

Patient timeline and trial visits

All patients scheduled for elective DP in all the centres will be considered to participate in the trial and assessed for eligibility. Reasons for non-inclusion and all those who refuse to take part must be reported. Patients will be enrolled by their ability to understand the extent and nature of the trial and provided written informed consent after receiving detailed information and by fulfilling all inclusion criteria. Baseline data together with the first QoL questionnaire will be recorded during the baseline visit (V1). The mentioned surgical data will be collected in Visit 2 (V2), i.e surgery day. Primary and secondary outcome parameters will be collected from Visit 3 to discharge date (Visit 4). Diagnostic and any ensuing therapeutic procedures caused by postoperative complications will be collected and reported. Table 2 summarizes the visits.
### Table 2: Trials visits and documented parameters

|   | V1 | V2 | V3 | V4 | V5 | V6 | V7 |
|---|----|----|----|----|----|----|----|
| Assessment | Pre-study Screening/ Consent/ Randomization | Surgery day | POD 3 | Discharge | 1 month | 6 months | 1 year |
| Eligible criteria | x | | | | | | |
| Informed consent | x | | | | | | |
| Demographics and baseline characteristics | x | | | | | | |
| Randomization | x | | | | | | |
| QoL assessment | x | | x | x | x | | |
| Primary outcome assessment | | x | x | | | | |
| Metabolomics analysis (peritoneal fluid) | | | | | | x | |
| Secondary outcomes (CCI, complications) | | | x | x | x | x | x |

**Randomization:**

Patients who meet the inclusion and exclusion criteria and sign the informed consent in the outpatient clinic are eligible for randomization. They will be given a code or identification number (ID) in strict sequential order. Randomization will be performed before surgery so that specific devices can be prepared for the pancreatic transection. Patients will be allocated to the RFT or ST-group in the centre by the study promoter on an online computer-controlled Permuted-Block Randomization Module (Castor EDC, CIWIT B.V., Amsterdam, the Netherlands) in a 1:1 ratio without reposition and block sizes vary between 2 and 4 patients. Randomization will be stratified by centre.

**Blinding:**
The study will be single-blind since the surgeon will know and must apply the technique to be used. The patient will be not informed of the instruments and technical details to be used in his case since they are common techniques.

**Data management, statistical analyses and quality assurance:**

*Data Management*

All the variables collected in the study will be stored in the electronic data collection form (eCRF) to be automatically transferred to a database by the study coordinators, as described in the eCRF. Each researcher and study monitor will have digital access to the eCRF and database to include new patients and review any data during the follow-up. Any addition or correction in the remote data entry system will be automatically protocolled in an audit file. At least one backup copy of the database will be made monthly. Both the eCRF and a copy of the prospective database will be kept up to 5 years after completion of the study and will be treated with the same degree of confidentiality as the rest of the patients’ clinical history data.

*Data Analyses*

The main analysis will be performed following the principle of intention to treat. Both groups will be compared initially according to the POPF percentage and number of SAEs, as in relation to secondary variables already described according to a conventional univariate analysis. To adjust confounding variables, a multivariate analysis will be considered for the CR-POPF study. Time to event endpoints, such as survival, will be calculated by Kaplan-Meier estimations. A Cox regression analysis will be performed to investigate postoperative survival predictors. All parameters with a p-value < 0.1 in a univariable analysis will be included in the multivariable Cox regression analysis. A specific subanalysis will be considered in the following variables: surgical approach, histological types of tumours treated, pancreas stiffness and size of the pancreatic duct. Regression lines will be created between Di (length total pancreas) and Df (distance from the VMS to the transection zone of the pancreas) to assess differences in resection margins between groups and length of pancreatic remnant.
An interim-analysis will be performed on the primary endpoint when 50% of the patients have been randomised and completed the 6-month follow-up by an independent statistician blinded for the treatment allocation.

**Serious Adverse Effect (SAE):**

An SAE is an adverse effect and should meet one or more of the following requirements: 1) It leads to the patient’s death; 2) There is an imminent risk of death; 3) The patient requires hospitalization or prolongation of hospitalization; 4) It involves a disability or a significant persistent sequel; 5) It is a major medical life-threatening event or may require medical intervention to prevent any of the above-mentioned effects.

Any SAE will be noted on the patient’s eCRF including start time, action taken and whether it constitutes an SAE. The committee will evaluate the SAEs and will continue with the project if more than 10% of the patients treated in the first phase are SAE.

**Quality assurance**

Independent qualified IMIM (Hospital del Mar Medical Research Institute) monitors will provide risk-based clinical monitoring according to the standard operating procedures. Before initiation of the trial, interactive training will be conducted and an electronic test database will be created for familiarization with the system and entering test data. All investigators will grant the monitors access to trial-specific patient data and agree to being visited before, during and after completion of the study to ensure that the study is conducted, recorded and reported on according to the study protocol, Good Clinical Practice (GCP) requirements and all the applicable laws and regulations (e.g. data protection). The monitoring strategy will consist of a combination of centralized and on-site monitoring. Monitoring visits will be scheduled according to the number of visits ready for verification. On-site monitoring will focus on patient-informed consent and safety, inclusion and exclusion criteria, surgical procedures, randomization and correct recording and documentation of primary and secondary endpoints by source data verification. Data will be entered into an electronic eCRF, and visits will be marked as "complete data" after monitoring. The data’s completeness, validity and plausibility will be checked when entering data (edit checks) and by using validating programs that generate queries. The completed eCRF must be reviewed and signed by the investigator named in the trial protocol or a designated sub-investigator. The investigator or the designated
representative will be obliged to complete the eCRF as soon as possible after information is
collected and to clarify or explain any queries.

Duration and schedule:

The duration of the trial for each patient is 12 months. The overall trial is expected to take 3
years to complete, including study preparation and analysis. The first patient was recruited in
February 2021 at the Hospital Universitario del Mar.

Ethics

The approach can be either minimally invasive or open and the surgical procedure will be
described and standardized. There will be no special handling of patients outside normal
medical practice.

This project will be carried out in accordance with national and international guidelines, the
basic principles of protection of human rights and dignity as stated in the Declaration of
Helsinki (64th General Assembly, Fortaleza, Brazil, October 2013), and according to the
regulations in Law 14/2007 on Biomedical Research (LIB) will be followed in the studies with
biological samples.

The CEIM-PSMAR must previously approve the study, the data sheet information to the
patient and informed consent. It is essential to obtain the signature of the informed consent,
which must be signed by both the researcher and the participant, who will receive a copy.
Since in neither group is the surgical procedure modified by the clinical trial, the usual
informed consent will be used in each centre for performing the surgical procedure. However,
once signed, the patient will be asked for his participation in the study and be informed of the
possibility of being part of one or other group by means of the specific informed consent of the
study in question. Each centre will be responsible for obtaining the approval of its Institutional
Ethics Committee (CEIC). Civil liability insurance will be available.

The confidentiality of the data will be guaranteed in accordance with current regulations. All
the Information obtained will be treated confidentially in compliance with Organic Law
3/2018, of December 5, “Protection of Personal Data and guarantee of digital rights” in
compliance with EU Regulation 2016/679 of the European Parliament and Council of April 27
2016 on Data Protection (RGPD).
Contributorship statement:
Contributors PSV, EP, CT, BI, FB developed the trial concept and wrote the protocol and the manuscript of the protocol publication. DD, EDV, MM, MGB, GSA, PGC helped to develop the trial concept and the implementation of the technique itself. JMA, GS, YQ, VF, RC, LS revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript for publication and agreed to be accountable for all aspects of the work.

Competing interests:
The authors have no conflict of interests to disclose in relation to this study.

Funding:
This work was completely funded by a medical research grant from the Instituto de Salud Carlos III (ISCIII) PI20/00008

BIBLIOGRAPHY:
[1] Peng YP, Zhu X Le, Yin L Di, Zhu Y, Wei JS, Wu JL, Miao Y. 2017. Risk factors of Postoperative pancreatic fistula in patients after distal pancreatectomy: A systematic review and metaanalysis. Sci Rep 7(1):1–8.

[2] Sánchez-Velázquez P, Muller X, Malleo G, Park JS, Hwang HK, Napoli N, Javed AA, Inoue Y, Beghdadi N, Kalisvaart M, Vigia E, Walsh CD, Lovasik B, Busquets J, Scandavini C, Robin F, Yoshitomi H, Mackay TM, Busch OR, Hartog H, Heinrich S, Gleisner A, Perinel J, Passeri M, Luís N, Raptis DA, Tschuor C, Oberkofler CE, DeOliveira ML, Petrowsky H, Martinie J, Asbun H, Adham M, Schulick R, Lang H, Koerkamp BG, Besselink MG, Han HS, Miyazaki M, Ferrone CR, Fernández-Del Castillo C, Lillemoe KD, Sulpice L, Boudjema K, Del Chiario M, Fabregat J, Kooby DA, Allen P, Lavu H, Yeo CJ, Barroso E, Roberts K, Muiesan P, Sauvanet A, Saiura A, Wolfgang CL, Cameron JL, Boggi U, Yoon DS, Bassi C, Puhan MA, Clavien PA. 2019. Benchmarks in Pancreatic Surgery: A Novel Tool for Unbiased Outcome Comparisons. Ann Surg 270(2):211–218.

[3] Diener MK, Seiler CM, Rossion I, Kleeff J, Glanemann M, Butturini G, Tomazic A, Bruns CJ, Busch ORC, Farkas S, Belyaev O, Neoptolemos JP, Halloran C, Keck T, Niedergethmann M, Gellert K, Witzigmann H, Kollmar O, Langer P, Steger U, Neudecker J, Berrevoet F, Ganzera S, Heiss MM, Luntz SP, Bruckner T, Kieser M, Büchler MW. 2011. Efficacy of stapler versus hand-sewn closure after distal pancreatectomy (DISPACT): a
randomised, controlled multicentre trial. Lancet 377(9776):1514–22.

[4] Diener MK, Seiler CM, Rossion I, Kleeff J, Glanemann M, Butturini G, Tomazic A, Bruns CJ, Busch ORC, Farkas S, Belyaev O, Neoptolemos JP, Halloran C, Keck T, Niedergethmann M, Gellert K, Witzigmann H, Kollmar O, Langer P, Steger U, Neudecker J, Berrevoet F, Ganzer S, Heiss MM, Luntz SP, Bruckner T, Kieser M, Büchler MW. 2011. Efficacy of stapler versus hand-sewn closure after distal pancreatectomy (DISPACT): A randomised, controlled multicentre trial. Lancet 377(9776):1514–1522.

[5] Landoni L, De Pastena M, Fontana M, Malleo G, Esposito A, Casetti L, Marchegiani G, Tuveri M, Paiella S, Pea A, Ramera M, Borin A, Giardino A, Frigerio I, Girelli R, Bassi C, Butturini G, Salvia R. 2021. A randomized controlled trial of stapled versus ultrasonic transection in distal pancreatectomy. Surg Endosc. doi: 10.1007/s00464-021-08724-3.

[6] Suc B, Msika S, Fingerhut A, Fourtanier G, Hay JM, Holmières F, Sastre B, Fagniez PL. 2003. Temporary fibrin glue occlusion of the main pancreatic duct in the prevention of intra-abdominal complications after pancreatic resection: Prospective randomized trial. Ann Surg 237(1):57–65.

[7] Montorsi M, Zerbi A, Bassi C, Capussotti L, Coppola R, Sacchi M. 2012. Efficacy of an absorbable fibrin sealant patch (TachoSil) after distal pancreatectomy: a multicenter, randomized, controlled trial. Ann Surg 256(5):853–860.

[8] Dorcaratto D, Burdío F, Fondevila D, Andaluz A, Quesada R, Poves I, Caceres M, Mayol X, Berjano E, Grande L. 2013. Radiofrequency is a secure and effective method for pancreatic transection in laparoscopic distal pancreatectomy: Results of a randomized, controlled trial in an experimental model. Surg Endosc 27(10):3710–3719.

[9] Dorcaratto D, Burdío F, Fondevila D, Andaluz A, Poves I, Martinez MA, Quesada R, Berjano E, Grande L. 2012. Laparoscopic distal pancreatectomy: feasibility study of radiofrequency-assisted transection in a porcine model. J Laparoendosc Adv Surg Tech A 22(3):242–8.

[10] Fronza JS, Bentrem DJ, Baker MS, Talamonti MS, Ujiki MB. 2010. Laparoscopic distal pancreatectomy using radiofrequency energy. Am J Surg 199(3):401–404.

[11] Blansfield JA, Rapp MM, Chokshi RJ, Woll NL, Hunsinger MA, Sheldon DG, Shabahang MM. 2011. Novel Method of Stump Closure for Distal Pancreatectomy with a 75 % Reduction in Pancreatic Fistula Rate. doi: 10.1007/s11605-011-1794-1.

[12] Pueyo Périz EM, Téllez Marqués C, Martinez Solà A, Radosevic A, Morató O, De Vicente E, Grande L, Ielpo B, Burdío F, Sánchez Velázquez P. 2021. Towards zero postoperative pancreatic fistula after distal pancreatectomy: a propensity score matching analysis of pancreatic stump closure with radiofrequency vs stapler. Hpb 23:S844–S845.

[13] Chan AW, Tetzlaff JM, Götzsche PC, Altman DG, Mann H, Berlin JA, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleza-Jeric K, Laupacis A, Moher D. 2013. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 346:1–42.

[14] Delgado M, Domenech J. 2015. Fundamentos de diseño y estadística, diseño de estudios, 16ª. .

[15] De Rooij T, Van Hilst J, Van Santvoort H, Boerma D, Van Den Boezem P, Daams F, Van Dam R, Dejong C, Van Duyun E, Dijkgraaf M, Van Eijck C, Festsen S, Gerhards M, Groot Koerkamp B, De Hingh I, Kazernier G, Klaase J, De Kleine R, Van Laarhoven C, Luyer M, Patijn G, Steenvoorde P, Suker M, Abu Hilal M, Busch O, Besselink M. 2019. Minimally Invasive Versus Open Distal Pancreatectomy (LEOPARD): A Multicenter Patient-blinded
Randomized Controlled Trial. Ann Surg 269(1):2–9.

[16] Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, Allen P, Andersson R, Asbun HJ, Besselink MG, Conlon K, Del Chiaro M, Falconi M, Fernandez-Cruz L, Fernandez-del Castillo C, Fingerhut A, Friess H, Gouma DJ, Hackert T, Izbicki J, Lillemoe KD, Neoptolemos JP, Olah A, Schulick R, Shrikhande S V., Takada T, Takaori K, Traverso W, Vollmer CR, Wolfgang CL, Yeo CJ, Salvia R, Buchler M. 2017. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surg (United States) 161(3):584–591.

[17] Dindo D, Demartines N, Clavien P-A. 2004. Classification of Surgical Complications. Ann Surg 240(2):205–213.

[18] Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien P-A. 2013. The Comprehensive Complication Index A Novel Continuous Scale to Measure Surgical Morbidity. Ann Surg 258:1–7.

[19] Jiang Z, Wen C, Wang C, Zhao Z, Bo L, Wan X, Deng X. 2019. Plasma metabolomics of early parenteral nutrition followed with enteral nutrition in pancreatic surgery patients. Sci Rep 9(1):18846.

[20] Topp SA, McClurken M, Lipson D, Upadhya GA, Ritter JH, Linehan D, Strasberg SM. 2004. Saline-Linked Surface Radiofrequency Ablation: Factors Affecting Steam Popping and Depth of Injury in the Pig Liver. Ann Surg 239(4):518–527.

[21] Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, Allen P, Andersson R, Asbun HJ, Besselink MG, Conlon K, Del Chiaro M, Falconi M, Fernandez-Cruz L, Fernandez-del Castillo C, Fingerhut A, Friess H, Gouma DJ, Hackert T, Izbicki J, Lillemoe KD, Neoptolemos JP, Olah A, Schulick R, Shrikhande S V., Takada T, Takaori K, Traverso W, Vollmer CR, Wolfgang CL, Yeo CJ, Salvia R, Buchler M. 2017. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surg (United States) 161(3):584–591.

[22] Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW, Yeo CJ, Büchler MW. 2007. Delayed gastric emptying (DGE) after pancreatic surgery: A suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. doi: 10.1016/j.surg.2007.05.005.

[23] Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Yeo CJ, Büchler MW. 2007. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 142(1):20–25.

[24] Quality of Life. Quality of life group website, 2020.
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

**Fig. 1: Flow-Chart**

- **Visite 1: preoperative assessment**
  - Patients assessed for eligibility
  - Eligible patients
  - Informed consent
  - Randomization 1:1

- **Visite 2: surgery day**
  - Control group: stapler
  - Study group: RF

- **Visite 3: Assessment primary end-point**
  - Postoperative day 3
  - Postoperative day 3

- **Visite 4: Discharge**
  - Assessment of secondary end-points
    - Pathology outcomes
    - Functional recovery

- **Visite 5, 6, 7: Postoperative Follow-up**
  - QoL questionnaires: PAN 26, EORTC-C30
  - Readmission rate and SAEs
  - Postoperative Imaging
  - Overall survival

**Exclusion criteria:**
- Pancreas transection <2 cm from SMV
- ASA > III
- Age < 18 years
# Radiofrequency-assisted transection of the pancreas vs stapler in distal pancreatectomy: study protocol for a multicentric randomized clinical trial (TRANSPAIRE)

| Journal: | BMJ Open |
| --- | --- |
| Manuscript ID | bmjopen-2022-062873.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 10-Aug-2022 |
| Complete List of Authors: | Sánchez-Velázquez, Patricia; Hospital del Mar, Department of Surgery; Hospital del Mar Medical Research Institute Pueyo-Pérez, Eva; Hospital del Mar, Department of Surgery Álamo, JM; University Hospital Virgen del Rocío, Department of surgery Suarez Artacho, Gonzalo; University Hospital Virgen del Rocío, Department of surgery Gómez Bravo, Miguel Ángel; University Hospital Virgen del Rocío, Department of surgery Marcello, Manuel; Alcorcon Hospital Foundation, Department of surgery Vicente, Emilio; Hospital universitario Sanchinarro, Department of surgery Quijano, Yolanda; Hospital universitario Sanchinarro, Department of surgery Ferri, Valentina ; Hospital Universitario Madrid Sanchinarro, Caruso, Riccardo ; Hospital Universitario Madrid Sanchinarro, Department of Surgery Dorcaratto, Dimitri ; hospital clínico Valencia Sabater, Luis; hospital clínico Valencia González Chávez, Pilar; Hospital Virgen de la Candelaria, Tenerife Noguer, Jose; Hospital Juan Canalejo de La Coruña Navarro Gonzalo, Ana; Hospital Clínico Universitario Lozano Blesa Bellido-Luque, Juan; Hospital Universitario Virgen Macarena Téllez-Marques, Clara; Hospital del Mar, Department of Surgery Ielpo, Benedetto; Parc Salut Mar Hospital, Barcelona Burdio, Fernando; Hospital del Mar; Hospital del Mar Medical Research Institute, Department of Surgery |
| Primary Subject Heading: | Surgery |
| Secondary Subject Heading: | Surgery |
| Keywords: | Pancreatic surgery < SURGERY, Hepatobiliary surgery < SURGERY, Clinical trials < THERAPEUTICS |
Radiofrequency-assisted transection of the pancreas vs stapler in distal pancreatectomy: study protocol for a multicentric randomized clinical trial (TRANSPIRE)

Authors: Patricia Sánchez-Velázquez1*, Eva Pueyo-Périz12*, JM Álamo2, Gonzalo Suárez Artacho2, Miguel Ángel Gómez Bravo2, Manuel Marcello3, Emilio Vicente4, Yolanda Quijano4, Valentina Ferri6, Riccardo Caruso6, Dimitri Dorcaratto5, Luis Sabater5, Pilarena González Chávez6, Jose Noguera7, Ana Navarro8, Juan Bellido-Luque9, Clara Téllez-Marques1, Benedetto Ielpo1, Fernando Burdio1, Transpaire Study Group

Affiliations:
1. Hepatobiliary and Pancreatic Surgery Unit. Service of General Surgery and Digestive Surgery. Hospital del Mar. Hospital del Mar Medical Research Institute (IMIM), Passeig Maritim 25-29, Barcelona, Spain.
2. Department of Surgery, University Hospital Virgen del Rocío, Sevilla
3. Department of Surgery, Fundación Alcorcón, Madrid
4. Department of Surgery, Hospital Universitario Sanchinarro, Madrid
5. Department of Surgery, Liver, Biliary and Pancreatic Unit, Hospital Clinico, University of Valencia, Biomedical Research Institute (INCLIVA)
6. Department of surgery, Hospital Virgen de la Candelaria, Canarias, Spain
7. Department of surgery, Hospital Juan Canalejo, La Coruña, Spain
8. Department of surgery, Hospital clinico de Zaragoza, Spain

* Co-first authors

Funding: Project "PI20/00008 ", funded by Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union.

Corresponding author:
Patricia Sánchez-Velázquez MD, PhD, FEBS
Hepato-Biliary and Pancreatic Surgery Unit, Service of General Surgery, Hospital del Mar.
Passeig Marítim de la Barceloneta, 25, 29
Barcelona
ZIP Code: 08003
Email: Psanchezvelazquez@psmar.cat

Conflict of interest: The authors have no conflict of interests to disclose in relation to this study.
Abstract

Background: To date, no pancreatic stump closure technique has been shown to be superior to any other in distal pancreatectomy. Although several studies have shown a trend towards improved outcomes in transection by a radiofrequency device (RFT) in terms of reducing clinically relevant pancreatic fistula (CR-POPF) no randomized trial has been carried out for this purpose to date. We therefore designed an RCT, hypothesizing that this technique used in distal pancreatectomies is superior in reducing CR-POPF than mechanical closures.

Methods/design: TRANSPAIRE is a multicentric randomized controlled trial performed in 7 Spanish pancreatic centres. A total of 112 patients undergoing elective distal pancreatectomy for any indication will be randomly allocated to RFT or classical stapler transections (Control Group) in a ratio of 1:1. The primary outcome is the CR-POPF percentage, which is assessed by the international Study Group for Pancreatic Fistula (ISGPF) classification. The sample size is calculated with the following assumptions: 5% one-sided significance level (α), 80% power (1-β), expected POPF in the control group of 32%, expected POPF in the RFT group of 10%, and a clinically relevant difference of 22%. Secondary outcomes include postoperative outcomes (e.g., clinically relevant surgical complications graded by Clavien-Dindo classification, in-hospital mortality and oncological variables), long-term complications (e.g., endocrine and exocrine impairment), radiological assessment of the pancreatic stump in the follow-up, metabolomic profiling of peritoneal fluid after surgery, survival and quality of life. Follow-ups will be made at the Outpatient Clinic after 1, 6 and 12 postoperative months

Discussion: The TRANSPAIRE trial is designed to investigate the superiority of RFT versus stapler in the CR-POPF incidence in distal pancreatectomy in a multicentric setting.

Trial registration: Clinicaltrials.gov registry: NCT04402346.

Keywords: Distal pancreatectomy, Left pancreatectomy, Pancreatic tail resection, Pancreatic surgery, Radiofrequency, Radiofrequency-Assisted, Stapler
**Strengths and limitations of this study**

- For the first time, a randomized clinical trial addresses specifically the unresolved problem of the pancreatic transection after distal pancreatectomy assessing the efficacy of Radiofrequency in this setting.

- Despite the novelty of the technique, TRANSPIRE trial is a multicentric study, which has been implemented in several different specialized pancreatic centers.

- The trial also evaluates the metabolic phenotype in peritoneal liquid from the patients in each arm in order to identify inflammatory changes secondary to the treatment applied.

- One limitation would be that tumors close to the pancreatic neck should be excluded and therefore reducing the generalizability of the results.
Introduction

Pancreatic surgery is currently the gold-standard option for curative treatment not only in neoplastic diseases but also in benign diseases and mucinous cystic neoplasms. Distal pancreatectomy consists of resecting the portion of the pancreas on the left aspect of the superior mesenteric vein and inevitably leads to a pancreatic stump, as no anastomosis is performed between the pancreatic remnant and the bowel. The most feared and potentially serious complication after distal pancreatectomy is a postoperative pancreatic fistula (POPF), which consists of the leakage of pancreatic juice from the main and secondary branches of the duct to the peri-pancreatic space or peritoneal cavity [1]. Although different surgical techniques have been applied to seal the pancreatic stump throughout the history of pancreatic surgery, and with the centralization of surgery and the multidisciplinary approach we have witnessed a considerable reduction in postoperative mortality and morbidity [2], the POPF rate remains however unchanged, around 30%-40% [3]. Historically, the closure of the pancreatic stump by manual suture (hand-sewn) was the standard of care [3] but with later technological developments and the implementation of the minimally invasive approach, staplers, ultrasonic scalpels, [4] biological glues [5] and even fatty tissue patches attached to the pancreatic stump [6] have been widely accepted.

Since none of the previously mentioned techniques have been able to reduce the incidence of POPF, energy-assisted and radiofrequency-assisted devices have been implemented in both experimental studies [7, 8] and clinical settings to try to reduce the POPF rate. The preliminary data from retrospective studies showed promising results, with a significant reduction of POPF of up to 10-14% [9, 10] and despite their major limitation of being retrospective uncontrolled studies with few patients, they provided an insight into the efficacy of the technique for solving a serious clinical dilemma.

In a recent retrospective propensity-score matched analysis of 89 patients we suggested that the use of the Coolingbis radiofrequency device was associated with a significant reduction of POPF rates compared to stapler closure [11]. Under these premises, in a randomized trial we aim to evaluate the effectiveness of radiofrequency transection of the pancreas in terms of duct sealing compared to the classical method of (stapler) transection to significantly reduce POPF rates in distal pancreatectomy.
Methods and analysis:

Study design:

The TRANSPAIRE trial is a multicentric randomized controlled parallel-group trial carried out in 7 Spanish pancreatic centres to compare two different methods of pancreatic transection in distal pancreatectomy (DP), i.e. radiofrequency assisted transection (RFT- study group) vs stapler (ST- control group). Inclusion of the centres started with the approval of the Institutional Review Board (IRB) in the Hospital del Mar (2020/9390/I), Barcelona. Local approval was required for the individual participating centres and the study was registered at ClinicalTrials.gov (NCT04402346). The patients eligible to participate in the study will be approached by the investigators and recorded, even if they did not decide to participate. All the patients will sign a written informed consent before randomization. The protocol was designed according to SPIRIT guidelines [12]

Study population and eligibility criteria:

All consecutive patients requiring distal pancreatectomy for any cause will be considered eligible if they complied with all of the following at randomization: (Fig. 1-flowchart)

- Inclusion criteria:
  - Over 18 years old
  - Patients with benign or malignant solid or cystic pancreatic neoplasms.
  - Transection of the pancreas performed at least > 2cm on the left from the medial aspect of the superior mesenteric vein (assessed by computed tomography or magnetic resonance at least 2 months before the surgical intervention) to avoid potential iatrogenic lesions of the intrapancreatic common bile duct.
  - Either spleen-preserving or espleno-pancreatectomy were accepted
  - Either open or minimally invasive approach (laparoscopic or robotic) were acceptable

- Exclusion criteria:
  - Any other system of pancreatic transection in the control group apart from stapling was excluded
• American Society of Anesthesiology physical status > 3
• Inability to sign the informed consent and under 18 years old
• Pregnancy
• Emergent surgery (i.e. post-traumatic)

**Patient and Public Involvement**

Patients were not directly involved in the design and conduct of this research. However, patients were asked in setting the outcome measures for the quality of life questionnaires and help to decide about the most appropriate ones. Once the trial has been published, results will be communicated to keep people informed throughout the project, reporting negative and positive results.

**Calculation and justification of the sample size**

The sample size was calculated following Delgado M et al. [13] and hypothesizing that RFT was superior to ST. Assumptions were made considering a POPF rate of 32% for ST [14] and 10% for RFT, respectively, so that there was a clinically-relevant difference of 22%. At 5% one-sided significance level (α), 80% power (1-β), the required sample size was 56 patients per arm, including a 10% drop-out rate after randomization (patients who underwent no surgery after randomization) led to a total number of 112 patients to be randomized.

**Trial specific interventions:**

- **RFT group:** The technique will be conducted with either an open or minimally invasive approach (robotic or laparoscopic). All procedures will be performed by a pancreatic surgeon with at least 5 years of experience in the field and having completed the learning curve with the performance of more than 10 pancreatic transections using the radiofrequency device.

All the surgeons are familiar with both techniques of stump closure after pancreatectomy. After examination of the abdominal cavity, the gastrocolic ligament will be divided to allow correct visualization of the upper border of the pancreatic gland and the course of the splenic vessels. In case of splenic preservation, these vessels must be spared. The position of the pancreas division line will be selected in the proximal normal pancreas according to the position of the lesion and intraoperatively guided by ultrasonography to ensure correct
margins. In all cases pancreatic transection will be performed in the RFT group with a 10-mm diameter version of the *Coolingbis device* (Vec Medical, Valencia, Spain). By applying the device and moving it backwards over the surface of the parenchyma, the blunt section of the device coagulates the tissue and the blade cuts through the portion of coagulated tissue. If transection with RFT is impossible, the surgeon will be free to cross over to perform any other transection technique. The specific techniques used will be recorded together with the consequent data analysis.

- ST group: The surgical procedure will be performed in essentially the same way as in the RF Group, except for the step of pancreatic transection, which will be carried out with a stapler. As the aim is to compare the technique itself to RF, no restrictions were set concerning the stapler load/cartridge or the use of Bioabsorbable Staple Line Reinforcement. A gradual compression will be applied for 5-10 min, the stapler will be then fired and slowly released after transection. Hand-sewn or other transection methods such as the harmonic dissector are absolute exclusion criteria.

As the TRANSPAIRE trial is pragmatic no extra effort will be focused on standardizing the patients’ postoperative care, as long as the same protocol will be applied to both RFT and ST groups in each individual centre. Participants will receive postoperative care according to the centre’s daily routine, however, all surgical techniques, materials, and medical devices used were reported in detail to detect any differences among the participants, identify potential confounders and to register any imbalance among the treatment groups.

**Data capture and trial end-points:**

**Primary endpoint (s)**

The primary endpoint of the study is clinically relevant postoperative pancreatic fistula (CR-POPF) rate according to the updated guidelines recently published by the International Group of Pancreatic Fistula study (ISGPF). i.e.: a drainage output of any measurable volume of fluid with an amylase level > 3 times the institutional upper limit of normal serum amylase activity, associated with a clinically relevant development/condition directly related to the postoperative pancreatic fistula.[15]

Pancreatic amylase will be measured in the peritoneal fluid of the drain at postoperative day 3 and 5 (if drain still in place). Any type of fistula (biochemical leak or clinically relevant -B or C-) will be assessed.
Secondary endpoint(s)

The most important secondary end-points are in-hospital mortality, postoperative complications until discharge and long-term postoperative end-points (see Table 1).

| Endpoint         | Definition                              | Timeline                        |
|------------------|-----------------------------------------|---------------------------------|
| **Intraoperative** |                                         |                                 |
| Blood loss       | Millilitres                             | Day of the surgery              |
| Operative time   | Minutes                                 | Day of the surgery              |
| Surgical approach| Open/minimal invasive                   | Day of the surgery              |
| Spleen-preservation | Yes/no                                | Day of the surgery              |
| **Postoperative end-points** |                                 |                                 |
| CR-POPF          | According to ISGPF definition [15]      | Within 90 days after surgery    |
| DGE              | According to ISGPF definition [16]      | Within 90 days after surgery    |
| PPH              | According to ISGPF definition [17]      | Within 90 days after surgery    |
| QoL Questionnaires | PAN-26, EORTC-30 [18]                  | Until 12 months after surgery   |
| Readmission rate | Any readmission in the hospital         | Within 90 days after surgery    |
| Reoperation rate | Any surgery after index surgery         | Within 90 days after surgery    |
| Overall survival | Time from surgery to last follow-up     | Within 12 months after surgery  |

Complications will be graded by the Clavien-Dindo classification [19], which groups the complication according to the treatment received and the CCI [20], a value which measures overall cumulative morbidity on a scale from 0 (no complications) to 100 (death) and will be applied to cover the total number of complications by severity for individual patients. Other variables include patients’ clinical demographic characteristics (i.e. sex, age, ASA classification, jaundice level), variables associated with the type of procedure (open or laparoscopic surgery, intraoperative bleeding, duration of the intervention, size of the pancreatic duct) and
oncological outcomes such as quality of lymphatic resection. Pathological assessment of the specimen will be performed as standard in both groups.

Metabolic phenotyping will be carried out on the peritoneal fluid on the 3rd postoperative day to assess the inflammatory changes secondary to the treatment applied. The possibility of generating metabolic phenotypes from large patient samples can thus identify candidates for metabolic biomarkers, certain disease risks or the result of a certain treatment. [21] Specifically, a battery of inflammatory cytokines is measured with the Proteome Profiler Human XL Protein array, which can test a battery of up to 105 different cytokines. The remnants of biological samples not used for this determination will be destroyed.

Patients’ quality of life will be evaluated by QLQ-C30 and PAN-26 questionnaires sent to the participants at baseline, 30, 180, and 365 days after surgery.

Long-term end-points include:
- Evaluating the postoperative morbidity of patients in the follow-up in the first year (late complications, presence of endocrine and / or exocrine insufficiency) as well as overall and disease-free survival in cancer patients.
- Radiological assessment of pancreatic stump evolution in the first month and first year after surgery. Volume of the ablation lesion created in the transection margin according to digital reconstruction with CT or MRI one month and one year after surgery using a segmented injury manual with appropriate software (3d Doctor, Able Software Corp, Mass, USA) measured in cubic centimetres [22]

Patient timeline and trial visits

All patients scheduled for elective DP in all the centres will be considered to participate in the trial and assessed for eligibility. Reasons for non-inclusion and all those who refuse to take part must be reported. Patients will be enrolled by their ability to understand the extent and nature of the trial and provided written informed consent after receiving detailed information and by fulfilling all inclusion criteria. Baseline data together with the first QoL questionnaire will be recorded during the baseline visit (V1). The mentioned surgical data will be collected in Visit 2 (V2), i.e surgery day. Primary and secondary outcome parameters will be collected from Visit 3 to discharge date (Visit 4). Diagnostic and any ensuing therapeutic procedures caused by postoperative complications will be collected and reported. Table 2 summarizes the visits.
Table 2: Trials visits and documented parameters

|            | V1                  | V2                  | V3                  | V4                  | V5                  | V6                  | V7                  |
|------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Assessment | Pre-study Screening/| Consent/ Randomization | Surgery day         | POD 3               | Discharge           | 1 month             | 6 months            | 1 year              |
| Eligible criteria | x                  |                     |                     |                     |                     |                     |                     |                     |
| Informed consent | x                  |                     |                     |                     |                     |                     |                     |                     |
| Demographics and baseline characteristics | x                  |                     |                     |                     |                     |                     |                     |                     |
| Randomization | x                  |                     |                     |                     |                     |                     |                     |                     |
| QoL assessment | x                  |                     | x                   | x                   | x                   | x                   | x                   |
| Primary outcome assessment | x                  |                     | x                   | x                   |                     |                     |                     |                     |
| Metabolomics analysis (peritoneal fluid) | x                  |                     |                     |                     |                     |                     |                     |                     |
| Secondary outcomes (CCI, complications) | x                  |                     | x                   | x                   | x                   | x                   | x                   |

**Randomization:**

Patients who meet the inclusion and exclusion criteria and sign the informed consent in the outpatient clinic are eligible for randomization. They will be given a code or identification number (ID) in strict sequential order. Randomization will be performed before surgery so that specific devices can be prepared for the pancreatic transection. Patients will be allocated to the RFT or ST-group in the centre by the study promoter on an online computer-controlled Permuted-Block Randomization Module (Castor EDC, CIWIT B.V., Amsterdam, the Netherlands) in a 1:1 ratio without reposition and block sizes vary between 2 and 4 patients. Randomization will be stratified by centre.
Blinding:
The study will be single-blind since the surgeon will know and must apply the technique to be used. The patient will be not informed of the instruments and technical details to be used in his case since they are common techniques.

Data management, statistical analyses and quality assurance:

Data Management
All the variables collected in the study will be stored in the electronic data collection form (eCRF) to be automatically transferred to a database by the study coordinators, as described in the eCRF. Each researcher and study monitor will have digital access to the eCRF and database to include new patients and review any data during the follow-up. Any addition or correction in the remote data entry system will be automatically protocolled in an audit file. At least one backup copy of the database will be made monthly. Both the eCRF and a copy of the prospective database will be kept up to 5 years after completion of the study and will be treated with the same degree of confidentiality as the rest of the patients’ clinical history data.

Data Analyses
The main analysis will be performed following the principle of intention to treat. Both groups will be compared initially according to the POPF percentage and number of SAEs, as in relation to secondary variables already described according to a conventional univariate analysis. To adjust confounding variables, a multivariate analysis will be considered for the CR-POPF study. Time to event endpoints, such as survival, will be calculated by Kaplan-Meier estimations. A Cox regression analysis will be performed to investigate postoperative survival predictors. All parameters with a p-value <0.1 in a univariable analysis will be included in the multivariable Cox regression analysis. A specific subanalysis will be considered in the following variables: surgical approach, histological types of tumours treated, pancreas stiffness and size of the pancreatic duct. Regression lines will be created between Di (length total pancreas) and Df (distance from the VMS to the transection zone of the pancreas) to assess differences in resection margins between groups and length of pancreatic remnant.
An interim-analysis will be performed on the primary endpoint when 50% of the patients have been randomised and completed the 6-month follow-up by an independent statistician blinded for the treatment allocation.

**Serious Adverse Effect (SAE):**

An SAE is an adverse effect and should meet one or more of the following requirements: 1) It leads to the patient’s death; 2) There is an imminent risk of death; 3) The patient requires hospitalization or prolongation of hospitalization; 4) It involves a disability or a significant persistent sequel; 5) It is a major medical life-threatening event or may require medical intervention to prevent any of the above-mentioned effects.

Any SAE will be noted on the patient’s eCRF including start time, action taken and whether it constitutes an SAE. The committee will evaluate the SAEs and will continue with the project if more than 10% of the patients treated in the first phase are SAE.

**Quality assurance**

Independent qualified IMIM (Hospital del Mar Medical Research Institute) monitors will provide risk-based clinical monitoring according to the standard operating procedures. Before initiation of the trial, interactive training will be conducted and an electronic test database will be created for familiarization with the system and entering test data. All investigators will grant the monitors access to trial-specific patient data and agree to being visited before, during and after completion of the study to ensure that the study is conducted, recorded and reported on according to the study protocol, Good Clinical Practice (GCP) requirements and all the applicable laws and regulations (e.g. data protection). The monitoring strategy will consist of a combination of centralized and on-site monitoring. Monitoring visits will be scheduled according to the number of visits ready for verification. On-site monitoring will focus on patient-informed consent and safety, inclusion and exclusion criteria, surgical procedures, randomization and correct recording and documentation of primary and secondary endpoints by source data verification. Data will be entered into an electronic eCRF, and visits will be marked as "complete data" after monitoring. The data’s completeness, validity and plausibility will be checked when entering data (edit checks) and by using validating programs that generate queries. The completed eCRF must be reviewed and signed by the investigator named in the trial protocol or a designated sub-investigator. The investigator or the designated
representative will be obliged to complete the eCRF as soon as possible after information is collected and to clarify or explain any queries.

**Duration and schedule:**

The duration of the trial for each patient is 12 months. The overall trial is expected to take 3 years to complete, including study preparation and analysis. The first patient was recruited in February 2021 at the Hospital Universitario del Mar.

**Ethics and dissemination**

The approach can be either minimally invasive or open and the surgical procedure will be described and standardized. There will be no special handling of patients outside normal medical practice.

This project will be carried out in accordance with national and international guidelines, the basic principles of protection of human rights and dignity as stated in the Declaration of Helsinki (64th General Assembly, Fortaleza, Brazil, October 2013), and according to the regulations in Law 14/2007 on Biomedical Research (LIB) will be followed in the studies with biological samples.

The CEIM-PSMAR must previously approve the study, the data sheet information to the patient and informed consent. It is essential to obtain the signature of the informed consent, which must be signed by both the researcher and the participant, who will receive a copy. Since in neither group is the surgical procedure modified by the clinical trial, the usual informed consent will be used in each centre for performing the surgical procedure. However, once signed, the patient will be asked for his participation in the study and be informed of the possibility of being part of one or other group by means of the specific informed consent of the study in question. The study promoter will be responsible of obtaining the approval of each Institutional Ethics Committee (CEIC) involved in the study, which will be checked by the independent monitors. Civil liability insurance will be available.

The confidentiality of the data will be guaranteed in accordance with current regulations. All the Information obtained will be treated confidentially in compliance with Organic Law 3/2018, of December 5, “Protection of Personal Data and guarantee of digital rights” in compliance with EU Regulation 2016/679 of the European Parliament and Council of April 27 2016 on Data Protection (RGPD).
Contributorship statement:

EPP and PSV are surgeons have equally contributed in the conception and design, acquisition and interpretation of data and participation in drafting the article. DD and LS have taken part in drafting the article and interpretation data together. EV, VF, RC and YQ have taken place in interpretation of the results and the preparation of the discussion by critically reviewing it as they have great expertise on the topic and the technique. MGB, GSA and JMA has have very much contributed in the design of the study, in interpretation of the results and critical review and give the final approval of the version to be published. MM, ANG, JBL, PGC and JN, also surgeons who have active included patients in the study and have reviewed the literature and then critically reviewed the final manuscript. BI, FB, CTM and PSV have contributed in conception and design, acquisition, interpretation and analysis of data and participation in drafting the article, and give the final approval of the version to be published.

Acknowledgements: We would like to thank the patient advisors for their work and involvement in this study.

Competing interests: Authors disclose no conflict of interests.

Funding: Project "PI20/00008 ", funded by Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union.
BIBLIOGRAPHY:

[1] Peng YP, Zhu X Le, Yin L Di, Zhu Y, Wei JS, Wu JL, Miao Y. 2017. Risk factors of Postoperative pancreatic fistula in patients after distal pancreatectomy: A systematic review and metaanalysis. Sci Rep 7(1):1–8.

[2] Sánchez-Velázquez P, Muller X, Malleo G, Park JS, Hwang HK, Napoli N, Javed AA, Inoue Y, Begehadi N, Kalisvaart M, Vigia E, Walsh CD, Lovasik B, Busquets J, Scandavini C, Robin F, Yoshihomi H, Mackay TM, Busch OR, Hartog H, Heinrich S, Gleisner A, Perinel J, Passeri M, Lluis N, Raptis DA, Tschuor C, Oberkofler CE, DeOliveira ML, Petsowsky H, Martinie J, Ashun H, Adham M, Schlicker R, Lang H, Koerkamp BG, Besselink MG, Han HS, Miyazaki M, Ferrone CR, Fernández-Del Castillo C, Lillemoe KD, Sulpice L, Boudjema K, Del Chiaro M, Fabregat J, Kooby DA, Allen P, Lavu H, Yeo CJ, Barroso E, Roberts K, Muiesan P, Sauvanet A, Saiura A, Wolfgang CL, Cameron JL, Boggi U, Yoon DS, Bassi C, Puhan MA, Clavien PA. 2019. Benchmarks in Pancreatic Surgery: A Novel Tool for Unbiased Outcome Comparisons. Ann Surg 270(2):211–218.

[3] Diener MK, Seiler CM, Rossion I, Kleeff J, Glanemann M, Butturini G, Tomazic A, Bruns CJ, Busch ORC, Farkas S, Belyaev O, Neoptolemos JP, Halloran C, Keck T, Niedergethmann M, Gellert K, Witzigmann H, Kollmar O, Langer P, Steger U, Neudecker J, Berrevoet F, Ganzera S, Heiss MM, Mintz SP, Bruckner T, Kieser M, Büchler MW. 2011. Efficacy of stapler versus hand-sewn closure after distal pancreatectomy (DISPACT): a randomised, controlled multicentre trial. Lancet 377(9776):1514–22.

[4] Landoni L, De Pastena M, Fontana M, Malleo G, Esposito A, Casetti L, Marchegiani G, Tuveri M, Pialetta S, Pea A, Ramera M, Borin A, Giardino A, Frigerio I, Gorelli R, Bassi C, Butturini G, Salvia R. 2021. A randomized controlled trial of stapled versus ultrasonic transection in distal pancreatectomy. Surg Endosc. doi: 10.1007/s00464-021-08724-3.

[5] Suc B, Miska S, Fingerhut A, Fourtanier G, Hay JM, Holmières F, Sastre B, Fagniez PL. 2003. Temporary fibrin glue occlusion of the main pancreatic duct in the prevention of intra-abdominal complications after pancreatic resection: Prospective randomized trial. Ann Surg 237(1):57–65.

[6] Montorsi M, Zerbi A, Bassi C, Capussotti L, Coppola R, Sacchi M. 2012. Efficacy of an absorbable fibrin sealant patch (TachoSil) after distal pancreatectomy: a multicenter, randomized, controlled trial. Ann Surg 256(5):853–860.

[7] Dorcaratto D, Burdio F, Fondevila D, Andaluz A, Quesada R, Poves I, Caceres M, Mayol X, Berjano E, Grande L. 2013. Radiofrequency is a secure and effective method for pancreatic transection in laparoscopic distal pancreatectomy: Results of a randomized, controlled trial in an experimental model. Surg Endosc 27(10):3710–3719.

[8] Dorcaratto D, Burdio F, Fondevila D, Andaluz A, Poves I, Martinez MA, Quesada R, Berjano E, Grande L. 2012. Laparoscopic distal pancreatectomy: feasibility study of radiofrequency-assisted transection in a porcine model. J Laparoendosc Adv Surg Tech A 22(3):242–8.

[9] Fronza JS, Bentrem DJ, Baker MS, Talamonti MS, Ujiki MB. 2010. Laparoscopic distal pancreatectomy using radiofrequency energy. Am J Surg 199(3):401–404.

[10] Blansfield JA, Rapp MM, Chokshi R, Woll NL, Hunsinger MA, Shelden DG, Shabahang MM. 2011. Novel Method of Stump Closure for Distal Pancreatectomy with a 75% Reduction in Pancreatic Fistula Rate. doi: 10.1007/s11605-011-1794-1.
[11] Pueyo Périz EP, Marquès CT, Radošević A, Morató O, Visa L. 2022. Radiofrequency-assisted transection of the pancreas vs stapler in distal pancreatectomy: a propensity score matched cohort analysis. Sci Rep 1–8.

[12] Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krolewski J, Laupacis A, Moher D. 2013. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 346:1–42.

[13] Delgado M, Domenech J. 2015. Fundamentos de diseño y estadística, diseño de estudios, 16ª.

[14] De Rooij T, Van Hilst J, Van Santvoort H, Boerma D, Van Den Boezem P, Daams F, Van Dam R, Dejong C, Van Duyn E, Dijkstra M, Van Eijk C, Festen S, Gerhards M, Groot Koerkamp B, de Hingh I, Kazemier G, Klaase J, De Kleine R, Van Laarhoven C, Luyer M, Patijn G, Steenvoorde P, Suker M, Abu Hilal M, Busch O, Besselink M. 2019. Minimally Invasive Versus Open Distal Pancreatectomy (LEOPARD): A Multicenter Patient-blinded Randomized Controlled Trial. Ann Surg 269(1):2–9.

[15] Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, Allen P, Andersson R, Asbun HJ, Besselink MG, Conlon K, Del Chiaro M, Falconi M, Fernandez-Cruz L, Fernandez-del Castillo C, Fingerhut A, Friess H, Gouma DJ, Hackert T, Ibicki J, Lillemoe KD, Neoptolemos JP, Olah A, Schulick R, Shrikhande S V., Takada T, Takaori K, Traverso W, Vollmer CR, Wolfgang CL, Yeo CJ, Salvia R, Buchler M. 2017. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surg (United States) 161(3):584–591.

[16] Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Ibicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW, Yeo CJ, Büchler MW. 2007. Delayed gastric emptying (DGE) after pancreatic surgery: A suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. doi: 10.1016/j.surg.2007.05.005.

[17] Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Ibicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Yeo CJ, Büchler MW. 2007. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 142(1):20–25.

[18] Quality of Life. Quality of life group website, 2020.

[19] Dindo D, Demartines N, Clavien P-A. 2004. Classification of Surgical Complications. Ann Surg 240(2):205–213.

[20] Slankamenac K, Graf R, Barkun J, Puhar MA, Clavien P-A. 2013. The Comprehensive Complication Index A Novel Continuous Scale to Measure Surgical Morbidity. Ann Surg 258:1–7.

[21] Jiang Z, Wen C, Wang C, Zhao Z, Bo L, Wan X, Deng X. 2019. Plasma metabolomics of early parenteral nutrition followed with enteral nutrition in pancreatic surgery patients. Sci Rep 9(1):18846.

[22] Topp SA, McClurken M, Lipson D, Upadhya GA, Ritter JH, Linehan D, Strasberg SM. 2004. Saline-Linked Surface Radiofrequency Ablation: Factors Affecting Steam Popping and Depth of Injury in the Pig Liver. Ann Surg 239(4):518–527.

Figure Legend: Flow-chart followed by patients once they meet inclusion criteria and can be randomized.
Fig. 1: Flow-Chart

Patients assessed for eligibility

Visite 1: preoperative assessment

Exclusion criteria:
- Pancreas transection <2cm from SMV
- ASA >III
- Age <18 years

Eligible patients
Informed consent

Randomization 1:1

Visite 2: surgery day

Control group: stapler

Study group: RF

Visite 3: Assessment primary end-point

Postoperative day 3

Postoperative day 3

Assessment of secondary end-points
Pathology outcomes
Functional recovery

Visite 4: Discharge

Visite 5, 6, 7: Postoperative Follow-up

QoL questionnaires: PAN 26, EORTC-C30
Readmission rate and SAEs
Postoperative Imaging
Overall survival
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item          | Item No | Description                                                                                                                                 |
|-----------------------|---------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Administrative information |        |                                                                                                                                           |
| Title                 | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (Lines 4-6; Page 1)              |
| Trial registration    | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry (Lines 64; Page 2)                                       |
|                       | 2b      | All items from the World Health Organization Trial Registration Data Set (NA)                                                               |
| Protocol version      | 3       | Date and version identifier (NA)                                                                                                           |
| Funding               | 4       | Sources and types of financial, material, and other support (Lines 28,29; Page 1)                                                            |
| Roles and responsibilities | 5a    | Names, affiliations, and roles of protocol contributors (Lines 8-25; Page 1)                                                              |
|                       | 5b      | Name and contact information for the trial sponsor (Line 31-37; Page 1)                                                                     |
|                       | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (NA) |
|                       | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (NA) |
| Introduction          |         |                                                                                                                                           |
| Background and rationale | 6a  | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (Line 95-125; Page 4) |
|                       | 6b      | Explanation for choice of comparators (NA)                                                                                                 |
| Section            | Page |
|--------------------|------|
| Objectives         | 7    |
| Specific objectives or hypotheses (7 Pages 7-8) |
| Trial design       | 8    |
| Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (Lines 132-141; Page 5) |
| Methods: Participants, interventions, and outcomes |
| Study setting      | 9    |
| Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (Lines 132-145; Page 5) |
| Eligibility criteria | 10  |
| Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (Lines 144-162; Page 5-6) |
| Interventions      | 11a  |
| Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (Lines 172-217; Page 6) |
| 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (NA) |
| 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (NA) |
| 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial (Lines 212-217; Page 6) |
| Outcomes           | 12   |
| Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (Lines 220-278; page 7-8) |
| Participant timeline | 13  |
| Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (Lines 280-289; page 8-9) |
| Sample size        | 14   |
| Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (Lines 164-170; Page 6) |
Recruitment

Strategies for achieving adequate participant enrolment to reach target sample size (NA)

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation

Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (Lines 291-299; Page 9)

Allocation concealment mechanism

Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned (Lines 291-299; Page 9)

Implementation

Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (Lines 291-299; Page 9)

Blinding (masking)

Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (Lines 301-304; Pages 9)

If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial (NA)

Methods: Data collection, management, and analysis

Data collection methods

Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (Lines 308-316; Page 9-10)

Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols (Lines 308-316; Page 9-10)

Data management

Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (Lines 308-316; Page 9-10)
| Section                          | Method(s)       | Description                                                                                                                                                                                                 |
|---------------------------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Statistical methods             | 20a             | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (Lines 318-330; Pages 10) |
|                                 | 20b             | Methods for any additional analyses (e.g., subgroup and adjusted analyses) (Lines 299-301; Page 10)                                                                                                             |
|                                 | 20c             | Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation) (NA) |
| Methods: Monitoring             |                 |                                                                                                                                                                                                             |
| Data monitoring                 | 21a             | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (Lines 345-364; Page 10-11) |
|                                 | 21b             | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (Lines 331-333; Page 10) |
| Harms                           | 22              | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (Lines 335-343; Page 10) |
| Auditing                        | 23              | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (Lines 345-364; Page 10-11) |
| Ethics and dissemination        |                 |                                                                                                                                                                                                             |
| Research ethics approval        | 24              | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (Lines 382-386; Page 12)                                                                                                    |
| Protocol amendments            | 25              | Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (N.A) |
| Consent or assent               | 26a             | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (Lines 383-384; Page 12)                                                                 |
|                                 | 26b             | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (N.A)                                                                  |
| Title                                      | Number | Description                                                                                                                                 |
|--------------------------------------------|--------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Confidentiality                            | 27     | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (Lines 392-396; Page 12) |
| Declaration of interests                    | 28     | Financial and other competing interests for principal investigators for the overall trial and each study site (Lines 28-29 and 39-40; Page 1)       |
| Access to data                              | 29     | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (Lines 317-321 Page 10) |
| Ancillary and post-trial care               | 30     | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation (Lines 391; Page 12) |
| Dissemination policy                        | 31a    | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (NA) |
|                                              | 31b    | Authorship eligibility guidelines and any intended use of professional writers (NA)                                                  |
|                                              | 31c    | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (NA)                          |
| Appendices                                  |        |                                                                                                                                              |
| Informed consent materials                  | 32     | Model consent form and other related documentation given to participants and authorised surrogates                                        |
| Biological specimens                        | 33     | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (NA) |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.*
Radiofrequency-assisted transection of the pancreas vs stapler in distal pancreatectomy: study protocol for a multicentric randomized clinical trial (TRANSPIARE)

| Journal: | BMJ Open |
|----------|-----------|
| Manuscript ID | bmjopen-2022-062873.R2 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 29-Aug-2022 |
| Complete List of Authors: | Sánchez-Velázquez, Patricia; Hospital del Mar, Department of Surgery; Hospital del Mar Medical Research Institute Pueyo-Périz, Eva; Hospital del Mar Medical Research Institute), Department of Surgery Alamo, JM; University Hospital Virgen del Rocío, Department of surgery Suárez Artacho, Gonzalo; University Hospital Virgen del Rocío, Department of surgery Gómez Bravo, Miguel Ángel; University Hospital Virgen del Rocío, Department of surgery Marcello, Manuel; Alcorcon Hospital Foundation, Department of surgery Vicente, Emilio; Hospital universitario Sanchinarro, Department of surgery Quijano, Yolanda; Hospital universitario Sanchinarro, Department of surgery Ferri, Valentina; Hospital Universitario Madrid Sanchinarro, Department of Surgery Caruso, Riccardo; Hospital Universitario Madrid Sanchinarro, Department of Surgery Dorcaratto, Dimitri; hospital clínico Valencia Sabater, Luis; hospital clínico Valencia González Chávez, Pilarena; Hospital Virgen de la Candelaria, Tenerife Noguera, Jose; Hospital Juan Canalejo de La Coruña Navarro Gonzalo, Ana; Hospital Clínico Universitario Lozano Blesa Bellido-Luque, Juan; Hospital Universitario Virgen Macarena Téllez-Marques, Clara; Hospital del Mar, Department of Surgery Ielpo, Benedetto; Parc Salut Mar Hospital, Barcelona Burdio, Fernando; Hospital del Mar; Hospital del Mar Medical Research Institute), Department of Surgery |
| Primary Subject Heading: | Surgery |
| Secondary Subject Heading: | Surgery |
| Keywords: | Pancreatic surgery < SURGERY, Hepatobiliary surgery < SURGERY, Clinical trials < THERAPEUTICS |
Radiofrequency-assisted transection of the pancreas vs stapler in distal pancreatectomy: study protocol for a multicentric randomized clinical trial (TRANSPIARE)

Authors: Patricia Sánchez-Velázquez1*, Eva Pueyo-Périz1,2*, JM Álamo2, Gonzalo Suárez Artacho2, Miguel Ángel Gómez Bravo2, Manuel Marcello3, Emilio Vicente4, Yolanda Quijano4, Valentina Ferri4, Riccardo Caruso4, Dimitri Dorcaratto5, Luis Sabater5, Pilarena González Chávez6, Jose Noguera6, Ana Navarro6, Juan Bellido-Luque9, Clara Téllez-Marques2, Benedetto Ielpo1, Fernando Burdio4, Transpaire Study Group

Affiliations:
1. Hepatobiliary and Pancreatic Surgery Unit. Service of General Surgery and Digestive Surgery. Hospital del Mar. Hospital del Mar Medical Research Institute (IMIM), Passeig Maritim 25-29, Barcelona, Spain.
2. Department of Surgery, University Hospital Virgen del Rocío, Sevilla
3. Department of Surgery, Fundación Alcorcón, Madrid
4. Department of Surgery, Hospital Universitario Sanchinarro, Madrid
5. Department of Surgery, Liver, Biliary and Pancreatic Unit, Hospital Clínico, University of Valencia, Biomedical Research Institute (INCLIVA)
6. Department of surgery, Hospital Virgen de la Candelaria, Canarias, Spain
7. Department of surgery, Hospital Juan Canalejo, La Coruña, Spain
8. Department of surgery, Hospital clínico de Zaragoza, Spain

* Co-first authors

Funding: Project "PI20/00008 ", funded by Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union.

Corresponding author:
Patricia Sánchez-Velázquez MD, PhD, FEBS
Hepato-Biliary and Pancreatic Surgery Unit, Service of General Surgery, Hospital del Mar.
Passeig Marítim de la Barceloneta, 25, 29
Barcelona
ZIP Code: 08003
Email: Psanchezvelazquez@psmar.cat

Conflict of interest: The authors have no conflict of interests to disclose in relation to this study.
Abstract

Background: To date, no pancreatic stump closure technique has been shown to be superior to any other in distal pancreatectomy. Although several studies have shown a trend towards improved outcomes in transection by a radiofrequency device (RFT) in terms of reducing clinically relevant pancreatic fistula (CR-POPF) no randomized trial has been carried out for this purpose to date. We therefore designed an RCT, hypothesizing that this technique used in distal pancreatectomies is superior in reducing CR-POPF than mechanical closures.

Methods/design: TRANSPAIRE is a multicentric randomized controlled trial performed in 7 Spanish pancreatic centres. A total of 112 patients undergoing elective distal pancreatectomy for any indication will be randomly allocated to RFT or classical stapler transections (Control Group) in a ratio of 1:1. The primary outcome is the CR-POPF percentage, which is assessed by the international Study Group for Pancreatic Fistula (ISGPF) classification. The sample size is calculated with the following assumptions: 5% one-sided significance level (α), 80% power (1-β), expected POPF in the control group of 32%, expected POPF in the RFT group of 10%, and a clinically relevant difference of 22%. Secondary outcomes include postoperative outcomes, long-term complications, radiological assessment of the pancreatic stump in the follow-up, metabolomic profiling of peritoneal fluid after surgery, survival and quality of life. Follow-ups will be made at the Outpatient Clinic after 1, 6 and 12 postoperative months.

Ethics and dissemination: Transaire has been approved by the Ethics Committee of the CEM-PSMAR. This project is being carried out in accordance with national and international guidelines, the basic principles of protection of human rights and dignity established in the Declaration of Helsinki (64th General Assembly, Fortaleza, Brazil, October 2013), and in accordance with the regulations in In studies with biological samples, Law 14/2007 on Biomedical Research (LIB) will be followed.

Trial registration: Clinicaltrials.gov registry: NCT04402346.

Keywords: Distal pancreatectomy, Left pancreatectomy, Pancreatic tail resection, Pancreatic surgery, Radiofrequency, Radiofrequency-Assisted, Stapler
Strengths and limitations of this study

- For the first time, a randomized clinical trial addresses specifically the unresolved problem of the pancreatic transection after distal pancreatectomy assessing the efficacy of Radiofrequency in this setting.
- Despite the novelty of the technique, TRANSPIRE trial is a multicentric study, which has been implemented in several different specialized pancreatic centers.
- The trial also evaluates the metabolic phenotype in peritoneal liquid from the patients in each arm in order to identify inflammatory changes secondary to the treatment applied.
- One limitation would be that tumors close to the pancreatic neck should be excluded and therefore reducing the generalizability of the results.
Introduction

Pancreatic surgery is currently the gold-standard option for curative treatment not only in neoplastic diseases but also in benign diseases and mucinous cystic neoplasms. Distal pancreatectomy consists of resecting the portion of the pancreas on the left aspect of the superior mesenteric vein and inevitably leads to a pancreatic stump, as no anastomosis is performed between the pancreatic remnant and the bowel. The most feared and potentially serious complication after distal pancreatectomy is a postoperative pancreatic fistula (POPF), which consists of the leakage of pancreatic juice from the main and secondary branches of the duct to the peri-pancreatic space or peritoneal cavity [1]. Although different surgical techniques have been applied to seal the pancreatic stump throughout the history of pancreatic surgery, and with the centralization of surgery and the multidisciplinary approach we have witnessed a considerable reduction in postoperative mortality and morbidity [2], the POPF rate remains however unchanged, around 30% -40% [3]. Historically, the closure of the pancreatic stump by manual suture (hand-sewn) was the standard of care [3] but with later technological developments and the implementation of the minimally invasive approach, staplers, ultrasonic scalpels, [4] biological glues [5] and even fatty tissue patches attached to the pancreatic stump [6] have been widely accepted.

Since none of the previously mentioned techniques have been able to reduce the incidence of POPF, energy-assisted and radiofrequency-assisted devices have been implemented in both experimental studies [7, 8] and clinical settings to try to reduce the POPF rate. The preliminary data from retrospective studies showed promising results, with a significant reduction of POPF of up to 10-14% [9, 10] and despite their major limitation of being retrospective uncontrolled studies with few patients, they provided an insight into the efficacy of the technique for solving a serious clinical dilemma.

In a recent retrospective propensity-score matched analysis of 89 patients we suggested that the use of the Coolingbis radiofrequency device was associated with a significant reduction of POPF rates compared to stapler closure [11]. Under these premises, in a randomized trial we aim to evaluate the effectiveness of radiofrequency transection of the pancreas in terms of duct sealing compared to the classical method of (stapler) transection to significantly reduce POPF rates in distal pancreatectomy.
Methods and analysis:

Study design:

The TRANSPAIRE trial is a multicentric randomized controlled parallel-group trial carried out in 7 Spanish pancreatic centres to compare two different methods of pancreatic transection in distal pancreatectomy (DP), i.e. radiofrequency assisted transection (RFT- study group) vs stapler (ST- control group). Local approval was required for the individual participating centres and the study was registered at ClinicalTrials.gov (NCT04402346). The patients eligible to participate in the study will be approached by the investigators and recorded, even if they did not decide to participate. All the patients will sign a written informed consent before randomization. [12]

Study population and eligibility criteria:

All consecutive patients requiring distal pancreatectomy for any cause will be considered eligible if they complied with all of the following at randomization: (Fig. 1-flowchart)

- Inclusion criteria:
  
  - Over 18 years old
  - Patients with benign or malignant solid or cystic pancreatic neoplasms.
  - Transection of the pancreas performed at least > 2cm on the left from the medial aspect of the superior mesenteric vein (assessed by computed tomography or magnetic resonance at least 2 months before the surgical intervention) to avoid potential iatrogenic lesions of the intrapancreatic common bile duct.
  - Either spleen-preserving or espleno-pancreatectomy were accepted
  - Either open or minimally invasive approach (laparoscopic or robotic) were acceptable

- Exclusion criteria:
  
  - Any other system of pancreatic transection in the control group apart from stapling was excluded
  - American Society of Anesthesiology physical status > 3
  - Inability to sign the informed consent and under 18 years old
  - Pregnancy
- Emergent surgery (i.e. post-traumatic)

**Patient and Public Involvement**

Patients were not directly involved in the design and conduct of this research. However, patients were asked in setting the outcome measures for the quality of life questionnaires and help to decide about the most appropriate ones. Once the trial has been published, results will be communicated to keep people informed throughout the project, reporting negative and positive results.

**Calculation and justification of the sample size**

The sample size was calculated following Delgado M et al. [13] and hypothesizing that RFT was superior to ST. Assumptions were made considering a POPF rate of 32% for ST [14] and 10% for RFT, respectively, so that there was a clinically-relevant difference of 22%. At 5% one-sided significance level ($\alpha$), 80% power (1-$\beta$), the required sample size was 56 patients per arm, including a 10% drop-out rate after randomization (patients who underwent no surgery after randomization) led to a total number of 112 patients to be randomized.

**Trial specific interventions:**

- **RFT group:** The technique will be conducted with either an open or minimally invasive approach (robotic or laparoscopic). All procedures will be performed by a pancreatic surgeon with at least 5 years of experience in the field and having completed the learning curve with the performance of more than 10 pancreatic transections using the radiofrequency device. All the surgeons are familiar with both techniques of stump closure after pancreatectomy. After examination of the abdominal cavity, the gastrocolic ligament will be divided to allow correct visualization of the upper border of the pancreatic gland and the course of the splenic vessels. In case of splenic preservation, these vessels must be spared. The position of the pancreas division line will be selected in the proximal normal pancreas according to the position of the lesion and intraoperatively guided by ultrasonography to ensure correct margins. In all cases pancreatic transection will be performed in the RFT group with a 10-mm diameter version of the **Coolingbis device** *(Vec Medical, Valencia, Spain).* By applying the device and moving it backwards over the surface of the parenchyma, the blunt section of the device coagulates the tissue and the blade cuts through the portion of coagulated tissue. If transection with RFT is impossible, the surgeon will be free to cross over to perform any other
transection technique. The specific techniques used will be recorded together with the consequent data analysis.

- ST group: The surgical procedure will be performed in essentially the same way as in the RF Group, except for the step of pancreatic transection, which will be carried out with a stapler. As the aim is to compare the technique itself to RF, no restrictions were set concerning the stapler load/cartridge or the use of Bioabsorbable Staple Line Reinforcement. A gradual compression will be applied for 5-10 min, the stapler will be then fired and slowly released after transection. Hand-sewn or other transection methods such as the harmonic dissector are absolute exclusion criteria.

As the TRANSPAIRE trial is pragmatic no extra effort will be focused on standardizing the patients’ postoperative care, as long as the same protocol will be applied to both RFT and ST groups in each individual centre. Participants will receive postoperative care according to the centre’s daily routine, however, all surgical techniques, materials, and medical devices used were reported in detail to detect any differences among the participants, identify potential confounders and to register any imbalance among the treatment groups.

Data capture and trial end-points:

Primary endpoint (s)

The primary endpoint of the study is clinically relevant postoperative pancreatic fistula (CR-POPF) rate according to the updated guidelines recently published by the International Group of Pancreatic Fistula study (ISGPF). i.e.: a drainage output of any measurable volume of fluid with an amylase level > 3 times the institutional upper limit of normal serum amylase activity, associated with a clinically relevant development/condition directly related to the postoperative pancreatic fistula.[15]

Pancreatic amylase will be measured in the peritoneal fluid of the drain at postoperative day 3 and 5 (if drain still in place). Any type of fistula (biochemical leak or clinically relevant -B or C-) will be assessed.

Secondary endpoint (s)

The most important secondary end-points are in-hospital mortality, postoperative complications until discharge and long-term postoperative end-points (see Table 1).
Table 1: Secondary end-points

| Endpoint               | Definition                     | Timeline                   |
|------------------------|-------------------------------|----------------------------|
| **Intraoperative**     |                               |                            |
| Blood loss             | Millilitres                   | Day of the surgery         |
| Operative time         | Minutes                       | Day of the surgery         |
| Surgical approach      | Open/minimal invasive         | Day of the surgery         |
| Spleen-preservation    | Yes/no                        | Day of the surgery         |
| **Postoperative end-points** |                           |                            |
| CR-POPF                | According to ISGPF definition [15] | Within 90 days after surgery |
| DGE                    | According to ISGPF definition [16] | Within 90 days after surgery |
| PPH                    | According to ISGPF definition [17] | Within 90 days after surgery |
| QoL Questionnaires     | PAN-26, EORTC-30 [18]         | Until 12 months after surgery |
| Readmission rate       | Any readmission in the hospital | Within 90 days after surgery |
| Reoperation rate       | Any surgery after index surgery | Within 90 days after surgery |
| Overall survival       | Time from surgery to last follow-up | Within 12 months after surgery |

Complications will be graded by the Clavien-Dindo classification [19], which groups the complication according to the treatment received and the CCI [20], a value which measures overall cumulative morbidity on a scale from 0 (no complications) to 100 (death) and will be applied to cover the total number of complications by severity for individual patients. Other variables include patients’ clinical demographic characteristics (i.e. sex, age, ASA classification, jaundice level), variables associated with the type of procedure (open or laparoscopic surgery, intraoperative bleeding, duration of the intervention, size of the pancreatic duct) and...
oncological outcomes such as quality of lymphatic resection. Pathological assessment of the specimen will be performed as standard in both groups.

Metabolic phenotyping will be carried out on the peritoneal fluid on the 3rd postoperative day to assess the inflammatory changes secondary to the treatment applied. The possibility of generating metabolic phenotypes from large patient samples can thus identify candidates for metabolic biomarkers, certain disease risks or the result of a certain treatment. [21] Specifically, a battery of inflammatory cytokines is measured with the Proteome Profiler Human XL Protein array, which can test a battery of up to 105 different cytokines. The remnants of biological samples not used for this determination will be destroyed.

Patients’ quality of life will be evaluated by QLQ-C30 and PAN-26 questionnaires sent to the participants at baseline, 30, 180, and 365 days after surgery.

Long-term end-points include:

- Evaluating the postoperative morbidity of patients in the follow-up in the first year (late complications, presence of endocrine and / or exocrine insufficiency) as well as overall and disease-free survival in cancer patients.
- Radiological assessment of pancreatic stump evolution in the first month and first year after surgery. Volume of the ablation lesion created in the transection margin according to digital reconstruction with CT or MRI one month and one year after surgery using a segmented injury manual with appropriate software (3d Doctor, Able Software Corp, Mass, USA) measured in cubic centimetres [22]

Patient timeline and trial visits

All patients scheduled for elective DP in all the centres will be considered to participate in the trial and assessed for eligibility. Reasons for non-inclusion and all those who refuse to take part must be reported. Patients will be enrolled by their ability to understand the extent and nature of the trial and provided written informed consent after receiving detailed information and by fulfilling all inclusion criteria. Baseline data together with the first QoL questionnaire will be recorded during the baseline visit (V1). The mentioned surgical data will be collected in Visit 2 (V2), i.e surgery day. Primary and secondary outcome parameters will be collected from Visit 3 to discharge date (Visit 4). Diagnostic and any ensuing therapeutic procedures caused by postoperative complications will be collected and reported. Table 2 summarizes the visits.
Table 2: Trials visits and documented parameters

|             | V1                | V2                | V3                | V4                | V5                | V6                | V7                |
|-------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Assessment  | Pre-study         | Screening/Consent/| Randomization     | Surgery           | POD 3             | Discharge         | 1 month           | 6 months          | 1 year            |
|             | Screening/       | Consent/Randomizati|                  | day               | POD 3             | 1 month           | 6 months          | 1 year            |
| Eligible criteria | x                      |                    |                   |                   |                   |                   |                   |
| Informed consent | x                      |                    |                   |                   |                   |                   |                   |
| Demographics and baseline characteristics | x                      |                    |                   |                   |                   |                   |                   |
| Randomization | x                      |                    |                   |                   |                   |                   |                   |
| QoL assessment | x                      |                    |                   |                   |                   |                   |                   |
| Primary outcome assessment |                       |                    |                   | x                 | x                 |                   |                   |
| Metabolomics analysis (peritoneal fluid) |                       |                    |                   | x                 |                   |                   |                   |
| Secondary outcomes (CCI, complications) |                       |                    | x                 |                   |                   |                   |                   |

Randomization:

Patients who meet the inclusion and exclusion criteria and sign the informed consent in the outpatient clinic are eligible for randomization. They will be given a code or identification number (ID) in strict sequential order. Randomization will be performed before surgery so that specific devices can be prepared for the pancreatic transection. Patients will be allocated to the RFT or ST-group in the centre by the study promoter on an online computer-controlled Permuted-Block Randomization Module (Castor EDC, CIWIT B.V., Amsterdam, the Netherlands).
in a 1:1 ratio without reposition and block sizes vary between 2 and 4 patients. Randomization will be stratified by centre.

Blinding:
The study will be single-blind since blinding the surgeon is not possible. Therefore, the surgeon will know and must apply the technique to be used. However, the patient will not be informed of the instruments and technical details to be used in their case, since they are common techniques. Blinding will be reported according to the standards of surgical trial methodology. Patients are blinded to the intervention for as long as possible. Therefore, the outcome assessment will be as free from detection bias as possible. No attempt will be made to blind trial statisticians; however, they will not have access to unblinded data during the study and will perform analyses according to a predefined statistical analysis plan.

Data management, statistical analyses and quality assurance:

Data Management
All the variables collected in the study will be stored in the electronic data collection form (eCRF) to be automatically transferred to a database by the study coordinators, as described in the eCRF. Each researcher and study monitor will have digital access to the eCRF and database to include new patients and review any data during the follow-up. Any addition or correction in the remote data entry system will be automatically protocollled in an audit file. At least one backup copy of the database will be made monthly. Both the eCRF and a copy of the prospective database will be kept up to 5 years after completion of the study and will be treated with the same degree of confidentiality as the rest of the patients’ clinical history data.

Data Analyses
The main analysis will be performed following the principle of intention to treat. Both groups will be compared initially according to the POPF percentage and number of SAEs, as in relation to secondary variables already described according to a conventional univariate analysis. To adjust confounding variables, a multivariate analysis will be considered for the CR-POPF study. Time to event endpoints, such as survival, will be calculated by Kaplan-Meier estimations. A Cox regression analysis will be performed to investigate postoperative survival predictors. All parameters with a p-value <0.1 in a univariable analysis will be included in the multivariable Cox regression analysis. A specific subanalysis will be considered in the following variables:
surgical approach, histological types of tumours treated, pancreas stiffness and size of the pancreatic duct. Regression lines will be created between Di (length total pancreas) and Df (distance from the VMS to the transection zone of the pancreas) to assess differences in resection margins between groups and length of pancreatic remnant.

An interim-analysis will be performed on the primary endpoint when 50% of the patients have been randomised and completed the 6-month follow-up by an independent statistician blinded for the treatment allocation.

**Serious Adverse Effect (SAE):**

An SAE is an adverse effect and should meet one or more of the following requirements: 1) It leads to the patient’s death; 2) There is an imminent risk of death; 3) The patient requires hospitalization or prolongation of hospitalization; 4) It involves a disability or a significant persistent sequel; 5) It is a major medical life-threatening event or may require medical intervention to prevent any of the above-mentioned effects.

Any SAE will be noted on the patient’s eCRF including start time, action taken and whether it constitutes an SAE. The committee will evaluate the SAEs and will continue with the project if more than 10% of the patients treated in the first phase are SAE.

**Quality assurance**

Independent qualified IMIM (Hospital del Mar Medical Research Institute) monitors will provide risk-based clinical monitoring according to the standard operating procedures. Before initiation of the trial, interactive training will be conducted and an electronic test database will be created for familiarization with the system and entering test data. All investigators will grant the monitors access to trial-specific patient data and agree to being visited before, during and after completion of the study to ensure that the study is conducted, recorded and reported on according to the study protocol. The monitoring strategy will consist of a combination of centralized and on-site monitoring. Monitoring visits will be scheduled according to the number of visits ready for verification. On-site monitoring will focus on patient-informed consent and safety, inclusion and exclusion criteria, surgical procedures, randomization and correct recording and documentation of primary and secondary endpoints by source data verification. Data will be entered into an electronic eCRF, and visits will be marked as "complete data" after monitoring. The data's completeness, validity and plausibility will be checked when entering data (edit checks) and by using validating programs that generate queries. The completed eCRF must be reviewed and signed by the investigator.
named in the trial protocol or a designated sub-investigator. The investigator or the designated representative will be obliged to complete the eCRF as soon as possible after information is collected and to clarify or explain any queries.

**Duration and schedule:**

The duration of the trial for each patient is 12 months. The overall trial is expected to take 3 years to complete, including study preparation and analysis. The first patient was recruited in February 2021 at the Hospital Universitario del Mar.

**Ethics and dissemination:**

The approach can be minimally invasive or open, and the surgical procedure will be described and standardized. There will be no special handling of patients outside of normal medical practice.

This project will be carried out in accordance with national and international guidelines, the basic principles of protection of human rights and dignity established in the Declaration of Helsinki (64th General Assembly, Fortaleza, Brazil, October 2013), and in accordance with the regulations in In studies with biological samples, Law 14/2007 on Biomedical Research (LIB) will be followed.

The CEIM-PSMAR has previously approved the study, the patient information sheet and the informed consent. It is essential to obtain the signature of the informed consent, which must be signed by both the researcher and the participant, who will receive a copy. The study promoter is responsible for obtaining the approval of each Institutional Ethics Committee (CEIC) involved in the study. Given that in neither of the two groups is the surgical procedure modified by the clinical trial, the usual informed consent will be used in each center to perform the surgical procedure. However, once signed, the patient will be asked to participate in the study and will be informed of the possibility of being part of one or another group through the specific informed consent of the study in question. The PI is responsible for informing the Ethics Committee of any amendment to the protocol in accordance with local requirements.

Civil liability insurance will be available.

The study protocol has been approved by the Institutional Review Board (IRB) of the Hospital del Mar (2020/9390/I) and that a list of IRB approvals from the other participating centres can be found in the supplementary information file.

The confidentiality of the data is guaranteed in accordance with current regulations. All information obtained is treated confidentially in compliance with Organic Law 3/2018, of...
December 5, "Protection of Personal Data and guarantee of digital rights" in compliance with Regulation EU 2016/679 of the European Parliament and of the Council of April 27, 2016 of Data Protection (RGPD).

**Contributorship statement:**

EPP and PSV are surgeons have equally contributed in the conception and design, acquisition and interpretation of data and participation in drafting the article. DD and LS have taken part in drafting the article and interpretation data together. EV, VF, RC and YQ have taken place in interpretation of the results and the preparation of the discussion by critically reviewing it as they have great expertise on the topic and the technique. MGB, GSA and JMA has have very much contributed in the design of the study, in interpretation of the results and critical review and give the final approval of the version to be published. MM, ANG, JBL, PGC and JN, also surgeons who have active included patients in the study and have reviewed the literature and then critically reviewed the final manuscript. BI, FB, CTM and PSV have contributed in conception and design, acquisition, interpretation and analysis of data and participation in drafting the article, and give the final approval of the version to be published.

**Acknowledgements:** We would like to thank the patient advisors for their work and involvement in this study.

**Competing interests:** Authors disclose no conflict of interests.

**Funding:** Project "PI20/00008 ", funded by Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union.
BIBLIOGRAPHY:

[1] Peng YP, Zhu X Le, Yin L Di, Zhu Y, Wei JS, Wu JL, Miao Y. 2017. Risk factors of Postoperative pancreatic fistula in patients after distal pancreatectomy: A systematic review and metaanalysis. Sci Rep 7(1):1–8.

[2] Sánchez-Velázquez P, Muller X, Malleo G, Park JS, Hwang HK, Napoli N, Javed AA, Inoue Y, Beghdadi N, Kalisvaart M, Vigia E, Walsh CD, Lovasik B, Busquets J, Scandavini C, Robin F, Yoshitomi H, Mackay TM, Busch OR, Hartog H, Heinrich S, Gleisner A, Perinel J, Passeri M, Lluis N, Raptis DA, Tschuor C, Oberkofler CE, DeOliveira ML, Petrovsy H, Martinie J, Asbun H, Adatham M, Schulick R, Lang H, Koerkamp BG, Besselin MG, Han HS, Miyazaki M, Ferrone CR, Fernández-Del Castillo C, Lillemoe KD, Sulpice L, Boudjema K, Del Chiaro M, Fabregat J, Kooby DA, Allen P, Lavu H, Yeo CJ, Barroso E, Roberts K, Muiesan P, Sauvanet A, Safira A, Wolfgang CL, Cameron JL, Boggi U, Yoon DS, Bassi C, Puhan MA, Clavien PA. 2019. Benchmarks in Pancreatic Surgery: A Novel Tool for Unbiased Outcome Comparisons. Ann Surg 270(2):211–218.

[3] Diener MK, Seiler CM, Rossion I, Kleeff J, Glanemann M, Butturini G, Tomazic A, Bruns CJ, Busch ORC, Farkas S, Belyaev O, Neoptolemos JP, Halloran C, Keck T, Niedergethmann M, Gellert K, Witzigmann H, Kollmar O, Langer P, Steger U, Neudecker J, Berrevoet F, Ganzera S, Heiss MM, Luntz SP, Bruckner T, Kieser M, Büchler MW. 2011. Efficacy of stapler versus hand-sewn closure after distal pancreatectomy (DISPACT): a randomised, controlled multicentre trial. Lancet 377(9776):1514–22.

[4] Landoni L, De Pastena M, Fontana M, Elitlua A, Casetti L, Marchegiani G, Tuveri M, Pailla S, Bea A, Ramera M, Borin A, Giardino A, Frigerio I, Girelli R, Bassi C, Butturini G, Salvia R. 2021. A randomized controlled trial of stapled versus ultrasonic transection in distal pancreatectomy. Surg Endosc. doi: 10.1007/s00464-021-08724-3.

[5] Suc B, Miska S, Fingerhut A, Fourtanier G, Hay JM, Holmières F, Sastre B, Fagniez PL. 2003. Temporary fibrin glue occlusion of the main pancreatic duct in the prevention of intra-abdominal complications after pancreatic resection: Prospective randomized trial. Ann Surg 237(1):57–65.

[6] Montorsi M, Zerbi A, Bassi C, Capussotti L, Coppola R, Sacchi M. 2012. Efficacy of an absorbable fibrin sealant patch (TachoSil) after distal pancreatectomy: a multicenter, randomized, controlled trial. Ann Surg 256(5):853–860.

[7] Dorcaratto D, Burdio F, Fondevila D, Andaluz A, Quesada R, Poves I, Caceres M, Mayol X, Berjano E, Grande L. 2013. Radiofrequency is a secure and effective method for pancreatic transection in laparoscopic distal pancreatectomy: Results of a randomized, controlled trial in an experimental model. Surg Endosc 27(10):3710–3719.

[8] Dorcaratto D, Burdio F, Fondevila D, Andaluz A, Poves I, Martinez MA, Quesada R, Berjano E, Grande L. 2012. Laparoscopic distal pancreatectomy: feasibility study of radiofrequency-assisted transection in a porcine model. J Laparoendosc Adv Surg Tech A 22(3):242–8.

[9] Fronza JS, Bentrem DJ, Baker MS, Talamonti MS, Ujiki MB. 2010. Laparoscopic distal pancreatectomy using radiofrequency energy. Am J Surg 199(3):401–404.

[10] Blansfield JA, Rapp MM, Chokshi RJ, Woll NL, Hunsinger MA, Sheldon DG, Shabahang MM. 2011. Novel Method of Stump Closure for Distal Pancreatectomy with a 75% Reduction in Pancreatic Fistula Rate. doi: 10.1007/s11605-011-1794-1.

[11] Pueyo Pérez EP, Marquès CT, Radošević A, Morató O, Visa L. 2022. Radiofrequency-assisted transection of the pancreas vs stapler in distal pancreatectomy: a propensity score matched cohort analysis. Sci Rep 1:1–8.

[12] Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, Dickersin K, Hróbjartsson A, Schulz SF, Parulekar WR, Krleza-Jeric K, Laupacis A, Moher D. 2013. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 346:1–42.
Delgado M, Domenech J. 2015. Fundamentos de diseño y estadística, diseño de estudios, 16th.

De Rooij T, Van Hilst J, Van Santvoort H, Boerma D, Van Den Boezem P, Daams F, Van Dam R, Dejong C, Van Duyf E, Dijkstra M, Van Eijck C, Festen S, Gerhards M, Groot Koerkamp B, De Hingh I, Kazemier G, Klaase J, De Kleine R, Van Laarhoven C, Luyer M, Patijn G, Steenvoorde P, Suker M, Abu Hilal M, Busch O, Besselink M. 2019. Minimally Invasive Versus Open Distal Pancreatectomy (LEOPARD): A Multicenter Patient-blinded Randomized Controlled Trial. Ann Surg 269(1):2–9.

Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, Allen P, Andersson R, Asbun HJ, Besselink MG, Conlon K, Del Chiaro M, Falconi M, Fernandez-Cruz L, Fernandez-del Castillo C, Fingerhut A, Friess H, Gouma DJ, Hackert T, Izbicki J, Lillemoe KD, Neoptolemos JP, Olah A, Schulick R, Shrikhande S V., Takada T, Takaori K, Traverso W, Vollmer CR, Wolfgang CL, Yeo CJ, Salvia R, Buchler M. 2017. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surg (United States) 161(3):584–591.

Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW, Yeo CJ, Büchler MW. 2007. Delayed gastric emptying (DGE) after pancreatic surgery: A suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. doi: 10.1016/j.surg.2007.05.005.

Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Yeo CJ, Büchler MW. 2007. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 142(1):20–25.

Quality of Life. Quality of life group website, 2020.

Dindo D, Demartines N, Clavien P-A. 2004. Classification of Surgical Complications. Ann Surg 240(2):205–213.

Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien P-A. 2013. The Comprehensive Complication Index A Novel Continuous Scale to Measure Surgical Morbidity. Ann Surg 258:1–7.

Jiang Z, Wen C, Wang C, Zhao Z, Bo L, Wan X, Deng X. 2019. Plasma metabolomics of early parenteral nutrition followed with enteral nutrition in pancreatic surgery patients. Sci Rep 9(1):18846.

Topp SA, McClurken M, Lipson D, Upadhyya GA, Ritter JH, Linehan D, Strasberg SM. 2004. Saline-Linked Surface Radiofrequency Ablation: Factors Affecting Steam Popping and Depth of Injury in the Pig Liver. Ann Surg 239(4):518–527.

Figure Legend: Flow-chart followed by patients once they meet inclusion criteria and can be randomized.
Fig. 1: Flow-Chart

Visit 1: preoperative assessment

Exclusion criteria:
- Pancreas transection <2cm from SMV
- ASA >III
- Age <18 years

Patients assessed for eligibility

Visit 2: surgery day

Eligible patients
Informed consent

Randomization 1:1

Visit 3: Assessment primary end-point

Control group: stapler

Postoperative day 3

Study group: RF

Postoperative day 3

Visit 4: Discharge

Assessment of secondary end-points
Pathology outcomes
Functional recovery

Visit 5, 6, 7: Postoperative Follow-up

QoL questionnaires: PAN 26, EORTC-C30
Readmission rate and SAEs
Postoperative Imaging
Overall survival
**Institutional Review Board (IRB) list**

| Hospital                                                                 | CEIm (comité ético investigación clínica). Approved version of the protocol                      |
|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Hospital del Mar                                                        | CEIm – PSMAR (2020/9390/I)                                                                     |
| CEI de los hospitales universitarios Virgen Macarena-Virgen del Rocío  | CEIm-PEIBA * PSMAR (2020/9390/I)                                                                |
| Hospital Clínico Universitario de Valencia                             | CEIm – INCLIVA (2021/097)                                                                     |
| Hospital Universitario HM Sanchinarro                                   | CEIm – INCLIVA (2021/097)                                                                     |
| Hospital Universitario Fundación Alcorcón                               | CEIm HUFA – * PSMAR (2020/9390/I)                                                              |
| Hospital Universitario Nuestra Señora de Candelaria                    | CEIm Complejo Hospitalario Universitario de Canarias (2021-194-1)                             |
| Hospital Clínico Universitario Lozano Blesa                            | CEICA –CEICaragon * PSMAR (2020/9390/I)                                                         |
| Complejo Hospitalario Universitario A Coruña                            | CEIC-Galicia * PSMAR (2020/9390/I)                                                             |

* Local CEIm assessment is not necessary if the approval of the CEImPSMar as promoter is granted; only ratification in accordance to national guidelines.
Radiofrequency-assisted transection of the pancreas vs staple in distal pancreatectomy: study protocol for a multicentric randomized clinical trial (TRANSPIARE)

| Journal:        | BMJ Open |
|-----------------|----------|
| Manuscript ID   | bmjopen-2022-062873.R3 |
| Article Type:   | Protocol |
| Date Submitted by the Author: | 27-Sep-2022 |
| Complete List of Authors: | Sánchez-Velázquez, Patricia; Hospital del Mar, Department of Surgery; Hospital del Mar Medical Research Institute Pueyo-Pérez, Eva; Hospital del Mar Medical Research Institute, Department of Surgery Alamo, JM; University Hospital Virgen del Rocío, Department of surgery Suarez Artacho, Gonzalo; University Hospital Virgen del Rocío, Department of surgery Gómez Bravo, Miguel Ángel; University Hospital Virgen del Rocío, Department of surgery Marcello, Manuel; Alcorcon Hospital Foundation, Department of surgery Vicente, Emilio; Hospital universitario Sanchinarro, Department of surgery Quijano, Yolanda; Hospital universitario Sanchinarro, Department of surgery Ferri, Valentina; Hospital Universitario Madrid Sanchinarro, Caruso, Riccardo; Hospital Universitario Madrid Sanchinarro, Department of Surgery Dorcaratto, Dimitri; hospital clínico Valencia Sabater, Luis; hospital clínico Valencia González Chávez, Pilara; Hospital Virgen de la Candelaria, Tenerife Noguera, Jose; Hospital Juan Canalejo de La Coruña Navarro Gonzalez, Ana; Hospital Clínico Universitario Lozano Blesa Bellido-Luque, Juan; Hospital Universitario Virgen Macarena Téllez-Marques, Clara; Hospital del Mar, Department of Surgery Ielpo, Benedetto; Parc Salut Mar Hospital, Barcelona Burdio, Fernando; Hospital del Mar; Hospital del Mar Medical Research Institute, Department of Surgery |
| Primary Subject Heading: | Surgery |
| Secondary Subject Heading: | Surgery |
| Keywords: | Pancreatic surgery < SURGERY, Hepatobiliary surgery < SURGERY, Clinical trials < THERAPEUTICS |

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
Radiofrequency-assisted transection of the pancreas vs stapler in distal pancreatectomy: study protocol for a multicentric randomized clinical trial (TRANSPIARE)

Authors: Patricia Sánchez-Velázquez1*, Eva Pueyo-Périz1,2*, JM Álamo2, Gonzalo Suárez Artacho2, Miguel Ángel Gómez Bravo2, Manuel Marcello3, Emilio Vicente4, Yolanda Quijano4, Valentina Ferri4, Riccardo Caruso4, Dimitri Dorcaratto5, Luis Sabater5, Pilarena González Chávez5, Jose Noguera5, Ana Navarro5, Juan Bellido-Luque5, Clara Téllez-Marques5, Benedetto Ielpo1, Fernando Burdio4, Transpaire Study Group

Affiliations:
1. Hepatobiliary and Pancreatic Surgery Unit. Service of General Surgery and Digestive Surgery. Hospital del Mar. Hospital del Mar Medical Research Institute (IMIM), Passeig Maritim 25-29, Barcelona, Spain.
2. Department of Surgery, University Hospital Virgen del Rocío, Sevilla
3. Department of Surgery, Fundación Alcorcón, Madrid
4. Department of Surgery, Hospital Universitario Sanchinarro, Madrid
5. Department of Surgery, Liver, Biliary and Pancreatic Unit, Hospital Clínico, University of Valencia, Biomedical Research Institute (INCLIVA)
6. Department of surgery, Hospital Virgen de la Candelaria, Canarias, Spain
7. Department of surgery, Hospital Juan Canalejo, La Coruña, Spain
8. Department of surgery, Hospital clinic de Zaragoza, Spain

* Co-first authors
Funding: Project "PI20/00008 ", funded by Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union.

Corresponding author:
Patricia Sánchez-Velázquez MD, PhD, FEBS
Hepato-Biliary and Pancreatic Surgery Unit, Service of General Surgery, Hospital del Mar.
Passeig Marítim de la Barceloneta, 25, 29
Barcelona
ZIP Code: 08003
Email: Psanchezvelazquez@psmar.cat

Conflict of interest: The authors have no conflict of interests to disclose in relation to this study.
Abstract

Background: To date, no pancreatic stump closure technique has been shown to be superior to any other in distal pancreatectomy. Although several studies have shown a trend towards better results in transection using a radiofrequency device (RFT), no randomized trial for this purpose has been performed to date. Therefore, we designed a randomized clinical trial (RCT), with the hypothesis that this technique used in distal pancreatectomies is superior in reducing clinically relevant pancreatic fistula (CR-POPF) than mechanical closures.

Methods/design: TRANSPAIRE is a multicenter randomized controlled trial conducted in 7 Spanish pancreatic centers that includes 112 patients undergoing elective distal pancreatectomy for any indication who will be randomly assigned to RFT or classic stapler transections (control group) in a ratio of 1:1. The primary outcome is the CR-POPF percentage. Sample size is calculated with the following assumptions: 5% one-sided significance level (α), 80% power (1-β), expected POPF in control group 32%, expected POPF in RFT group of 10%, and a clinically relevant difference of 22%. Secondary outcomes include postoperative results, complications, radiological evaluation of the pancreatic stump, metabolomic profile of postoperative peritoneal fluid, survival, and quality of life. Follow-ups will be carried out in the External Consultation at 1, 6 and 12 months postoperatively.

Ethics and dissemination: Transpaire has been approved by the CEIM-PSMAR Ethics Committee. This project is being carried out in accordance with national and international guidelines, the basic principles of protection of human rights and dignity established in the Declaration of Helsinki (64th General Assembly, Fortaleza, Brazil, October 2013), and in accordance with regulations in studies with biological samples, Law 14/2007 on Biomedical Research (LIB) will be followed. We have defined a dissemination strategy, whose main objective is the participation of stakeholders and the transfer of knowledge to support the exploitation of activities.

Trial registration: Clinicaltrials.gov registry: NCT04402346.

Keywords: Distal pancreatectomy, Left pancreatectomy, Pancreatic tail resection, Pancreatic surgery, Radiofrequency, Radiofrequency-Assisted, Stapler
**Strengths and limitations of this study**

- For the first time, a randomized clinical trial addresses specifically the unresolved problem of the pancreatic transection after distal pancreatectomy assessing the efficacy of Radiofrequency in this setting.

- Despite the novelty of the technique, TRANSPAIRE trial is a multicentric study, which has been implemented in several different specialized pancreatic centers.

- The trial also evaluates the metabolic phenotype in peritoneal liquid from the patients in each arm in order to identify inflammatory changes secondary to the treatment applied.

- One limitation would be that tumors close to the pancreatic neck should be excluded and therefore reducing the generalizability of the results.
Introduction

Pancreatic surgery is currently the gold-standard option for curative treatment not only in neoplastic diseases but also in benign diseases and mucinous cystic neoplasms. Distal pancreatectomy consists of resecting the portion of the pancreas on the left aspect of the superior mesenteric vein and inevitably leads to a pancreatic stump, as no anastomosis is performed between the pancreatic remnant and the bowel. The most feared and potentially serious complication after distal pancreatectomy is a postoperative pancreatic fistula (POPF), which consists of the leakage of pancreatic juice from the main and secondary branches of the duct to the peri-pancreatic space or peritoneal cavity [1]. Although different surgical techniques have been applied to seal the pancreatic stump throughout the history of pancreatic surgery, and with the centralization of surgery and the multidisciplinary approach we have witnessed a considerable reduction in postoperative mortality and morbidity [2], the POPF rate remains however unchanged, around 30% -40% [3]. Historically, the closure of the pancreatic stump by manual suture (hand-sewn) was the standard of care [3] but with later technological developments and the implementation of the minimally invasive approach, staplers, ultrasonic scalpels, [4] biological glues [5] and even fatty tissue patches attached to the pancreatic stump [6] have been widely accepted.

Since none of the previously mentioned techniques have been able to reduce the incidence of POPF, energy-assisted and radiofrequency-assisted devices have been implemented in both experimental studies [7, 8] and clinical settings to try to reduce the POPF rate. The preliminary data from retrospective studies showed promising results, with a significant reduction of POPF of up to 10-14% [9, 10] and despite their major limitation of being retrospective uncontrolled studies with few patients, they provided an insight into the efficacy of the technique for solving a serious clinical dilemma.

In a recent retrospective propensity-score matched analysis of 89 patients we suggested that the use of the Coolingbis radiofrequency device was associated with a significant reduction of POPF rates compared to stapler closure [11]. Under these premises, in a randomized trial we aim to evaluate the effectiveness of radiofrequency transection of the pancreas in terms of duct sealing compared to the classical method of (stapler) transection to significantly reduce POPF rates in distal pancreatectomy.
Methods and analysis:

Study design:

The TRANSPAIRE trial is a multicentric randomized controlled parallel-group trial carried out in 7 Spanish pancreatic centres to compare two different methods of pancreatic transection in distal pancreatectomy (DP), i.e. radiofrequency assisted transection (RFT- study group) vs stapler (ST- control group). Local approval was required for the individual participating centres and the study was registered at ClinicalTrials.gov (NCT04402346). The patients eligible to participate in the study will be approached by the investigators and recorded, even if they did not decide to participate. All the patients will sign a written informed consent before randomization. [12]

Study population and eligibility criteria:

All consecutive patients requiring distal pancreatectomy for any cause will be considered eligible if they complied with all of the following at randomization: (Fig. 1-flowchart)

- Inclusion criteria:
  - Over 18 years old
  - Patients with benign or malignant solid or cystic pancreatic neoplasms.
  - Transection of the pancreas performed at least > 2cm on the left from the medial aspect of the superior mesenteric vein (assessed by computed tomography or magnetic resonance at least 2 months before the surgical intervention) to avoid potential iatrogenic lesions of the intrapancreatic common bile duct.
  - Either spleen-preserving or espleno-pancreatectomy were accepted
  - Either open or minimally invasive approach (laparoscopic or robotic) were acceptable

- Exclusion criteria:
  - Any other system of pancreatic transection in the control group apart from stapling was excluded
  - American Society of Anesthesiology physical status > 3
  - Inability to sign the informed consent and under 18 years old
  - Pregnancy
• Emergent surgery (i.e. post-traumatic)

Patient and Public Involvement

Patients were not directly involved in the design and conduct of this research. However, patients were asked in setting the outcome measures for the quality of life questionnaires and help to decide about the most appropriate ones. Once the trial has been published, results will be communicated to keep people informed throughout the project, reporting negative and positive results.

Calculation and justification of the sample size

The sample size was calculated following Delgado M et al. [13] and hypothesizing that RFT was superior to ST. Assumptions were made considering a POPF rate of 32% for ST [14] and 10% for RFT, respectively, so that there was a clinically-relevant difference of 22%. At 5% one-sided significance level (α), 80% power (1-β), the required sample size was 56 patients per arm, including a 10% drop-out rate after randomization (patients who underwent no surgery after randomization) led to a total number of 112 patients to be randomized.

Trial specific interventions:

- RFT group: The technique will be conducted with either an open or minimally invasive approach (robotic or laparoscopic). All procedures will be performed by a pancreatic surgeon with at least 5 years of experience in the field and having completed the learning curve with the performance of more than 10 pancreatic transections using the radiofrequency device.

All the surgeons are familiar with both techniques of stump closure after pancreatectomy. After examination of the abdominal cavity, the gastrocolic ligament will be divided to allow correct visualization of the upper border of the pancreatic gland and the course of the splenic vessels. In case of splenic preservation, these vessels must be spared. The position of the pancreas division line will be selected in the proximal normal pancreas according to the position of the lesion and intraoperatively guided by ultrasonography to ensure correct margins. In all cases pancreatic transection will be performed in the RFT group with a 10-mm diameter version of the Coolingbis device (Vec Medical, Valencia, Spain). By applying the device and moving it backwards over the surface of the parenchyma, the blunt section of the device coagulates the tissue and the blade cuts through the portion of coagulated tissue. If transection with RFT is impossible,
the surgeon will be free to cross over to perform any other transection technique. The specific
techniques used will be recorded together with the consequent data analysis.
- ST group: The surgical procedure will be performed in essentially the same way as in the RF
Group, except for the step of pancreatic transection, which will be carried out with a stapler. As
the aim is to compare the technique itself to RF, no restrictions were set concerning the stapler
load/cartridge or the use of Bioabsorbable Staple Line Reinforcement. A gradual compression
will be applied for 5-10 min, the stapler will be then fired and slowly released after transection.
Hand-sewn or other transection methods such as the harmonic dissector are absolute exclusion
criteria.

As the TRANSPAIRE trial is pragmatic no extra effort will be focused on standardizing the
patients’ postoperative care, as long as the same protocol will be applied to both RFT and ST
groups in each individual centre. Participants will receive postoperative care according to the
centre’s daily routine, however, all surgical techniques, materials, and medical devices used
were reported in detail to detect any differences among the participants, identify potential
confounders and to register any imbalance among the treatment groups.

Data capture and trial end-points:

Primary endpoint (s)

The primary endpoint of the study is clinically relevant postoperative pancreatic fistula (CR-
POPF) rate according to the updated guidelines recently published by the International Group
of Pancreatic Fistula study (ISGPF). i.e.: a drainage output of any measurable volume of fluid
with an amylase level > 3 times the institutional upper limit of normal serum amylase activity,
associated with a clinically relevant development/condition directly related to the postoperative
pancreatic fistula.[15]
Pancreatic amylase will be measured in the peritoneal fluid of the drain at postoperative day 3
and 5 (if drain still in place). Any type of fistula (biochemical leak or clinically relevant -B or C-)
will be assessed.

Secondary endpoint (s)

The most important secondary end-points are in-hospital mortality, postoperative
complications until discharge and long-term postoperative end-points (see Table 1).
### Table 1: Secondary end-points

| Endpoint               | Definition                      | Timeline                          |
|------------------------|---------------------------------|-----------------------------------|
| **Intraoperative**     |                                 |                                   |
| Blood loss             | Millilitres                     | Day of the surgery                |
| Operative time         | Minutes                         | Day of the surgery                |
| Surgical approach      | Open/minimal invasive           | Day of the surgery                |
| Spleen-preservation    | Yes/no                          | Day of the surgery                |
| **Postoperative end-points** |                            |                                   |
| CR-POPF                | According to ISGPF definition [15]| Within 90 days after surgery      |
| DGE                    | According to ISGPF definition [16]| Within 90 days after surgery      |
| PPH                    | According to ISGPF definition [17]| Within 90 days after surgery      |
| QoL Questionnaires     | PAN-26, EORTC-30 [18]           | Until 12 months after surgery     |
| Readmission rate       | Any readmission in the hospital  | Within 90 days after surgery      |
| Reoperation rate       | Any surgery after index surgery | Within 90 days after surgery      |
| Overall survival       | Time from surgery to last follow-up | Within 12 months after surgery |

Complications will be graded by the Clavien-Dindo classification [19], which groups the complication according to the treatment received and the CCI [20], a value which measures overall cumulative morbidity on a scale from 0 (no complications) to 100 (death) and will be applied to cover the total number of complications by severity for individual patients. Other variables include patients’ clinical demographic characteristics (i.e. sex, age, ASA classification, jaundice level), variables associated with the type of procedure (open or laparoscopic surgery, intraoperative bleeding, duration of the intervention, size of the pancreatic duct) and
oncological outcomes such as quality of lymphatic resection. Pathological assessment of the specimen will be performed as standard in both groups. Metabolic phenotyping will be carried out on the peritoneal fluid on the 3rd postoperative day to assess the inflammatory changes secondary to the treatment applied. The possibility of generating metabolic phenotypes from large patient samples can thus identify candidates for metabolic biomarkers, certain disease risks or the result of a certain treatment. [21] Specifically, a battery of inflammatory cytokines is measured with the Proteome Profiler Human XL Protein array, which can test a battery of up to 105 different cytokines. The remnants of biological samples not used for this determination will be destroyed.

Patients’ quality of life will be evaluated by QLQ-C30 and PAN-26 questionnaires sent to the participants at baseline, 30, 180, and 365 days after surgery.

Long-term end-points include:
- Evaluating the postoperative morbidity of patients in the follow-up in the first year (late complications, presence of endocrine and / or exocrine insufficiency) as well as overall and disease-free survival in cancer patients.
- Radiological assessment of pancreatic stump evolution in the first month and first year after surgery. Volume of the ablation lesion created in the transection margin according to digital reconstruction with CT or MRI one month and one year after surgery using a segmented injury manual with appropriate software (3d Doctor, Able Software Corp, Mass, USA) measured in cubic centimetres [22]

Patient timeline and trial visits

All patients scheduled for elective DP in all the centres will be considered to participate in the trial and assessed for eligibility. Reasons for non-inclusion and all those who refuse to take part must be reported. Patients will be enrolled by their ability to understand the extent and nature of the trial and provided written informed consent after receiving detailed information and by fulfilling all inclusion criteria. Baseline data together with the first QoL questionnaire will be recorded during the baseline visit (V1). The mentioned surgical data will be collected in Visit 2 (V2), i.e surgery day. Primary and secondary outcome parameters will be collected from Visit 3 to discharge date (Visit 4). Diagnostic and any ensuing therapeutic procedures caused by postoperative complications will be collected and reported. Table 2 summarizes the visits.
### Table 2: Trials visits and documented parameters

| V1     | V2     | V3     | V4     | V5     | V6     | V7     |
|--------|--------|--------|--------|--------|--------|--------|
| Assessment | Pre-study Screening/Consent/Randomization | Surgery day | POD 3 | Discharge | 1 month | 6 months | 1 year |
| Eligible criteria | x | | | | | | |
| Informed consent | x | | | | | | |
| Demographics and baseline characteristics | x | | | | | | |
| Randomization | x | | | | | | |
| QoL assessment | x | | x | x | x | | |
| Primary outcome assessment | | x | x | | | | |
| Metabolomics analysis (peritoneal fluid) | | x | | | | | |
| Secondary outcomes (CCI, complications) | | x | x | x | x | | |

**Randomization:**

Patients who meet the inclusion and exclusion criteria and sign the informed consent in the outpatient clinic are eligible for randomization. They will be given a code or identification number (ID) in strict sequential order. Randomization will be performed before surgery so that specific devices can be prepared for the pancreatic transection. Patients will be allocated to the RFT or ST-group in the centre by the study promoter on an online computer-controlled Permuted-Block Randomization Module (Castor EDC, CIWIT B.V., Amsterdam, the Netherlands).
in a 1:1 ratio without reposition and block sizes vary between 2 and 4 patients. Randomization will be stratified by centre.

Blinding:
The study will be single-blind since blinding the surgeon is not possible. Therefore, the surgeon will know and must apply the technique to be used. However, the patient will not be informed of the instruments and technical details to be used in their case, since they are common techniques. Blinding will be reported according to the standards of surgical trial methodology.

Patients are blinded to the intervention for as long as possible. Therefore, the outcome assessment will be as free from detection bias as possible. No attempt will be made to blind trial statisticians; however, they will not have access to unblinded data during the study and will perform analyses according to a predefined statistical analysis plan.

**Data management, statistical analyses and quality assurance:**

**Data Management**

All the variables collected in the study will be stored in the electronic data collection form (eCRF) to be automatically transferred to a database by the study coordinators, as described in the eCRF. Each researcher and study monitor will have digital access to the eCRF and database to include new patients and review any data during the follow-up. Any addition or correction in the remote data entry system will be automatically protocolled in an audit file. At least one backup copy of the database will be made monthly. Both the eCRF and a copy of the prospective database will be kept up to 5 years after completion of the study and will be treated with the same degree of confidentiality as the rest of the patients’ clinical history data.

**Data Analyses**

The main analysis will be performed following the principle of intention to treat. Both groups will be compared initially according to the POPF percentage and number of SAEs, as in relation to secondary variables already described according to a conventional univariate analysis. To adjust confounding variables, a multivariate analysis will be considered for the CR-POPF study.

Time to event endpoints, such as survival, will be calculated by Kaplan-Meier estimations. A Cox regression analysis will be performed to investigate postoperative survival predictors. All parameters with a p-value <0.1 in a univariable analysis will be included in the multivariable Cox regression analysis. A specific subanalysis will be considered in the following variables: surgical
approach, histological types of tumours treated, pancreas stiffness and size of the pancreatic duct. Regression lines will be created between $D_i$ (length total pancreas) and $D_f$ (distance from the VMS to the transection zone of the pancreas) to assess differences in resection margins between groups and length of pancreatic remnant.

An interim-analysis will be performed on the primary endpoint when 50% of the patients have been randomised and completed the 6-month follow-up by an independent statistician blinded for the treatment allocation.

**Serious Adverse Effect (SAE):**

An SAE is an adverse effect and should meet one or more of the following requirements: 1) It leads to the patient’s death; 2) There is an imminent risk of death; 3) The patient requires hospitalization or prolongation of hospitalization; 4) It involves a disability or a significant persistent sequel; 5) It is a major medical life-threatening event or may require medical intervention to prevent any of the above-mentioned effects.

Any SAE will be noted on the patient’s eCRF including start time, action taken and whether it constitutes an SAE. The committee will evaluate the SAEs and will continue with the project if more than 10% of the patients treated in the first phase are SAE.

**Quality assurance**

Independent qualified IMIM (Hospital del Mar Medical Research Institute) monitors will provide risk-based clinical monitoring according to the standard operating procedures. Before initiation of the trial, interactive training will be conducted and an electronic test database will be created for familiarization with the system and entering test data. All investigators will grant the monitors access to trial-specific patient data and agree to being visited before, during and after completion of the study to ensure that the study is conducted, recorded and reported on according to the study protocol. The monitoring strategy will consist of a combination of centralized and on-site monitoring. Monitoring visits will be scheduled according to the number of visits ready for verification. On-site monitoring will focus on patient-informed consent and safety, inclusion and exclusion criteria, surgical procedures, randomization and correct recording and documentation of primary and secondary endpoints by source data verification.

Data will be entered into an electronic eCRF, and visits will be marked as "complete data" after monitoring. The data's completeness, validity and plausibility will be checked when entering data (edit checks) and by using validating programs that generate queries. The completed eCRF must be reviewed and signed by the investigator named in the trial protocol or a designated
sub-investigator. The investigator or the designated representative will be obliged to complete the eCRF as soon as possible after information is collected and to clarify or explain any queries.

Duration and schedule:
The duration of the trial for each patient is 12 months. The overall trial is expected to take 3 years to complete, including study preparation and analysis. The first patient was recruited in February 2021 at the Hospital Universitario del Mar.

Ethics and dissemination:
The approach can be minimally invasive or open, and the surgical procedure will be described and standardized. There will be no special handling of patients outside of normal medical practice.
This project will be carried out in accordance with national and international guidelines, the basic principles of protection of human rights and dignity established in the Declaration of Helsinki (64th General Assembly, Fortaleza, Brazil, October 2013), and in accordance with the regulations in In studies with biological samples, Law 14/2007 on Biomedical Research (LIB) will be followed.
The CEIM-PSMAR has previously approved the study, the patient information sheet and the informed consent. It is essential to obtain the signature of the informed consent, which must be signed by both the researcher and the participant, who will receive a copy. The study promoter is responsible for obtaining the approval of each Institutional Ethics Committee (CEIC) involved in the study. Given that in neither of the two groups is the surgical procedure modified by the clinical trial, the usual informed consent will be used in each center to perform the surgical procedure. However, once signed, the patient will be asked to participate in the study and will be informed of the possibility of being part of one or another group through the specific informed consent of the study in question. The PI is responsible for informing the Ethics Committee of any amendment to the protocol in accordance with local requirements.
Civil liability insurance will be available.
The study protocol has been approved by the Institutional Review Board (IRB) of the Hospital del Mar (2020/9390/I) and that a list of IRB approvals from the other participating centres can be found in the supplementary information file.
The confidentiality of the data is guaranteed in accordance with current regulations. All information obtained is treated confidentially in compliance with Organic Law 3/2018, of December 5, "Protection of Personal Data and guarantee of digital rights" in compliance with
Regulation EU 2016/679 of the European Parliament and of the Council of April 27, 2016 of Data Protection (RGPD).

We have defined a dissemination strategy, whose the main objective is the engagement of the stakeholders and the transfer of knowledge to support the exploitation of the activities. Our first target audiences will be health organisations and the medical research community. Beyond this, we will target the medical device industry and other social stakeholders such as a policy makers and/or key opinion leaders. In this context, we will develop a dissemination strategy that will be crucial to provide the broadest distribution of our clinical results.

Contributorship statement:

EPP and PSV are surgeons have equally contributed in the conception and design, acquisition and interpretation of data and participation in drafting the article. DD and LS have taken part in drafting the article and interpretation data together. EV, VF, RC and YQ have taken place in interpretation of the results and the preparation of the discussion by critically reviewing it as they have great expertise on the topic and the technique. MGB, GSA and JMA has have very much contributed in the design of the study, in interpretation of the results and critical review and give the final approval of the version to be published. MM, ANG, JBL, PGC and JN, also surgeons who have active included patients in the study and have reviewed the literature and then critically reviewed the final manuscript. BI, FB, CTM and PSV have contributed in conception and design, acquisition, interpretation and analysis of data and participation in drafting the article, and give the final approval of the version to be published.

Acknowledgements: We would like to thank the patient advisors for their work and involvement in this study.

Competing interests: Authors disclose no conflict of interests.

Funding: Project "PI20/00008", funded by Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union.

BIBLIOGRAPHY:

[1] Peng YP, Zhu X Le, Yin L Di, Zhu Y, Wei JS, Wu JL, Miao Y. 2017. Risk factors of
Postoperative pancreatic fistula in patients after distal pancreatectomy: A systematic review and metaanalysis. Sci Rep 7(1):1–8.

[2] Sánchez-Velázquez P, Muller X, Malleo G, Park JS, Hwang HK, Napoli N, Javed AA, Inoue Y, Beghdadi N, Kalisvaart M, Vigia E, Walsh CD, Lovasik B, Busquets J, Scandavini C, Robin F, Yoshitomi H, Mackay TM, Busch OR, Hartog H, Heinrich S, Gleisner A, Perinel J, Passeri M, Luís N, Raptis DA, Tschuor C, Oberkofler CE, DeOliveira ML, Petskysh H, Martinie J, Asbun H, Adham M, Schulicch R, Lang H, Koerkamp BG, Besselink MG, Han HS, Miyazaki M, Ferrone CR, Fernández-Del Castillo C, Lillemoe KD, Sulpice L, Boudjemja K, Del Chiaro M, Fabregat J, Kooby DA, Allen P, Lavu H, Yeo CJ, Barroso E, Roberts K, Muiesan P, Sauvanet A, Saitu A, Wolfgang CL, Cameron JL, Boggi U, Yoon DS, Bassi C, Puhan MA, Clavien PA. 2019. Benchmarks in Pancreatic Surgery: A Novel Tool for Unbiased Outcome Comparisons. Ann Surg 270(2):211–218.

[3] Diener MK, Seiler CM, Rossion I, Kleeff J, Glanemann M, Butturini G, Tomazic A, Bruns CJ, Busch OR, Farkas S, Belyaev O, Neoptolemos JP, Halloran C, Keck T, Niedergethmann M, Gellert K, Witzigmann H, Kollmar O, Langer P, Steger U, Neudecker J, Berrevoet F, Ganzera S, Heiss MM, Luntz SP, Bruckner T, Kieser M, Bülcher MW. 2011. Efficacy of stapler versus hand-sewn closure after distal pancreatectomy (DISPACT): a randomised, controlled multicentre trial. Lancet 377(9776):1514–22.

[4] Landoni L, De Pastena M, Fontana M, Malleo G, Esposito A, Casetti L, Marchegiani G, Tuveri M, Paiella S, Pfeifer A, Ramera M, Borin A, Giardino A, Frigerio I, Girelli R, Bassi C, Butturini G, Savina R. 2021. A randomized controlled trial of stapled versus ultrasonic transection in distal pancreatectomy. Surg Endosc. doi: 10.1007/s00464-021-08724-3.

[5] Suc B, Msika S, Fingerhut A, Fourtandier G, Hay JM, Holmíeres F, Sastre B, Fagniez PL. 2003. Temporary fibrin glue occlusion of the main pancreatic duct in the prevention of intra-abdominal complications after pancreatic resection: Prospective randomized trial. Ann Surg 237(1):57–65.

[6] Montorsi M, Zerbi A, Bassi C, Capussotti L, Coppola R, Sacchi M. 2012. Efficacy of an absorbable fibrin sealant patch (TachoSil) after distal pancreatectomy: a multicenter, randomized, controlled trial. Ann Surg 256(5):853–860.

[7] Dorcaratto D, Burdío F, Fondevila D, Andaluz A, Poves I, Caceres M, Mayol X, Berjano E, Grande L. 2013. Radiofrequency is a secure and effective method for pancreatic transection in laparoscopic distal pancreatectomy: Results of a randomized, controlled trial in an experimental model. Surg Endosc 27(10):3710–3719.

[8] Dorcaratto D, Burdío F, Fondevila D, Andaluz A, Poves I, Martinez MA, Quesada R, Berjano E, Grande L. 2012. Laparoscopic distal pancreatectomy: feasibility study of radiofrequency-assisted transection in a porcine model. J Laparoendosc Adv Surg Tech A 22(3):242–8.

[9] Fronza JS, Bentrem DJ, Baker MS, Talamonti MS, Ujiki MB. 2010. Laparoscopic distal pancreatectomy using radiofrequency energy. Am J Surg 199(3):401–404.

[10] Blansfield JA, Rapp MM, Chokshi RJ, Woll NL, Hunsinger MA, Sheldon DG, Shabahang MM. 2011. Novel Method of Stump Closure for Distal Pancreatectomy with a 75 % Reduction in Pancreatic Fistula Rate. doi: 10.1007/s11605-011-1794-1.

[11] Pueyo Pérez EP, Marquès CT, Radosavljevic A, Morató O, Visa L. 2022. Radiofrequency-assisted transection of the pancreatecs vs stapler in distal pancreatectomy: a propensity score matched cohort analysis. Sci Rep 1:1–8.

[12] Chan AW, Tetzlaff JM, Götzsche PC, Altman DG, Mann H, Berlin JA, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krieva-Jeric K, Laupacis A, Moher D. 2013. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 346:1–42.

[13] Delgado M, Domenech J. 2015. Fundamentos de diseño y estadística, diseño de estudios, 16a. ed.

[14] De Rooij T, Van Hilst J, Van Santvoort H, Boerma D, Van Den Boezem P, Daams F, Van Dam R, Dejong C, Van Duyn E, Dijkstra M, Van Eijck C, Festen S, Gerhards M, Groot
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Koerkamp B, De Hingh I, Kazemier G, Klaase J, De Kleine R, Van Laarhoven C, Luyer M, Patijn G, Steenvoorde P, Suker M, Abu Hilal M, Busch O, Besselink M. 2019. Minimally Invasive Versus Open Distal Pancreatectomy (LEOPARD): A Multicenter Patient-blinded Randomized Controlled Trial. Ann Surg 269(1):2–9.

Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, Allen P, Andersson R, Asbun HJ, Besselink MG, Conlon K, Del Chiaro M, Falconi M, Fernandez-Cruz L, Fernandez-del Castillo C, Fingerhut A, Friess H, Gouma DJ, Hackert T, Izbicki J, Lillemoe KD, Neoptolemos JP, Olah A, Schulick R, Shrikhande S V., Takada T, Takaori K, Traverso W, Vollmer CR, Wolfgang CL, Yeo CJ, Salvia R, Buchler M. 2017. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surg (United States) 161(3):584–591.

Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW, Yeo CJ, Büchler MW. 2007. Delayed gastric emptying (DGE) after pancreatic surgery: A suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. doi: 10.1016/j.surg.2007.05.005.

Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Yeo CJ, Büchler MW. 2007. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 142(1):20–25.

Quality of Life. Quality of life group website, 2020.

Dindo D, Demartines N, Clavien P-A. 2004. Classification of Surgical Complications. Ann Surg 240(2):205–213.

Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien P-A. 2013. The Comprehensive Complication Index A Novel Continuous Scale to Measure Surgical Morbidity. Ann Surg 258:1–7.

Jiang Z, Wen C, Wang C, Zhao Z, Bo L, Wan X, Deng X. 2019. Plasma metabolomics of early parenteral nutrition followed with enteral nutrition in pancreatic surgery patients. Sci Rep 9(1):18846.

Topp SA, McClurken M, Lipson D, Upadhyea GA, Ritter JH, Linehan D, Strasberg SM. 2004. Saline-LinkeD Surface Radiofrequency Ablation: Factors Affecting Steam Popping and Depth of Injury in the Pig Liver. Ann Surg 239(4):518–527.

Figure Legend: Flow-chart followed by patients once they meet inclusion criteria and can be randomized.
Fig. 1: Flow-Chart

Exclusion criteria:
- Pancreas transection
- <2cm from SMV
- ASA >III
- Age <18 years

Visite 1: preoperative assessment
- Patients assessed for eligibility
- Eligible patients
- Informed consent
- Randomization 1:1

Control group: stapler
- Study group: RF

Visite 2: surgery day
- Postoperative day 3

Visite 3: Assessment primary end-point
- Postoperative day 3

Visite 4: Discharge
- Assessment of secondary end-points
- Pathology outcomes
- Functional recovery

Visite 5, 6, 7: Postoperative Follow-up
- QoL questionnaires: PAN 26, EORTC-C30
- Readmission rate and SAEs
- Postoperative Imaging
- Overall survival
### Institutional Review Board (IRB) list

| Hospital                                                          | CEIm (comité ético investigación clínica). Approved version of the protocol |
|-------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Hospital del Mar                                                  | CEIm – PSMAR (2020/9390/I)                                                    |
| CEI de los hospitales universitarios Virgen Macarena-Virgen del Rocío | CEIm-PEIBA * PSMAR (2020/9390/I)                                              |
| Hospital Clínico Universitario de Valencia                       | CEIm – INCLIVA (2021/097)                                                    |
| Hospital Universitario HM Sanchinarro                            | CEIm HM Hospitales (21.03.1799-GHM)                                           |
| Hospital Universitario Fundación Alcorcón                        | CEIm HUFA- * PSMAR (2020/9390/I)                                              |
| Hospital Universitario Nuestra Señora de Candelaria              | CEIm Complejo Hospitalario Universitario de Canarias (2021-194-1)             |
| Hospital Clínico Universitario Lozano Blesa                      | CEICA –CEICaragon * PSMAR (2020/9390/I)                                       |
| Complejo Hospitalario Universitario A Coruña                     | CEIC-Galicia * PSMAR (2020/9390/I)                                            |

* Local CEIm assessment is not necessary if the approval of the CEImPSMar as promoter is granted; only ratification in accordance to national guidelines.