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Radiofrequency-assisted transection of the pancreas versus stapler in distal pancreatectomy: study protocol for a multicentric randomised clinical trial (TRANSPAIRE)

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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 better results in transection using a radiofrequency device (radiofrequency-assisted transection (RFT)), no randomised trial for this purpose has been performed to date. Therefore, we designed a randomised clinical trial, with the hypothesis that this technique used in distal pancreatectomies is superior in reducing clinically relevant postoperative pancreatic fistula (CR-POPF) than mechanical closures.

Methods and analysis TRANSPAIRE is a multicentre randomised controlled trial conducted in seven Spanish pancreatic centres 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 of 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 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.

Registration details ClinicalTrials.gov Registry (NCT04402346).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ For the first time, a randomised 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 specialised pancreatic centres.
⇒ 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 tumours close to the pancreatic neck should be excluded and therefore reducing the generalisability 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 peripancreatic 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 centralisation 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 with stapler closure.[11] Under these premises, in a randomised trial, we aim to evaluate the effectiveness of radiofrequency-assisted transection (RFT) of the pancreas in terms of duct sealing compared with the classic method of (stapler) transection (ST) to significantly reduce POPF rates in distal pancreatectomy.

METHODS AND ANALYSIS

Study design

The TRANSPAIRE trial is a multicentric randomised controlled parallel-group trial carried out in seven Spanish pancreatic centres to compare two different methods of pancreatic transection in distal pancreatectomy (DP), that is, RFT (study group) versus 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 form before randomisation.[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 randomisation (figure 1—flow chart):

Inclusion criteria

- Over 18 years old.
- Patients with benign or malignant solid or cystic pancreatic neoplasms.
- Transection of the pancreas performed at least >2 cm on the left from the medial aspect of the superior mesenteric vein (assessed by CT 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 is accepted.
- Either open or minimally invasive approach (laparoscopic or robotic) is acceptable.

Exclusion criteria

- Any other system of pancreatic transection in the control group apart from stapling will be excluded.
- American Society of Anesthesiologists (ASA) physical status >3.
- Inability to sign the informed consent and under 18 years old.
- Pregnancy.
- Emergent surgery (ie, post-traumatic).

Patient and public involvement

Patients were not directly involved in the design and conduct of this research. However, patients will be 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 and Domenech[13] and hypothesising 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 randomisation (patients who underwent no surgery after randomisation) led to a total number of 112 patients to be randomised.

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

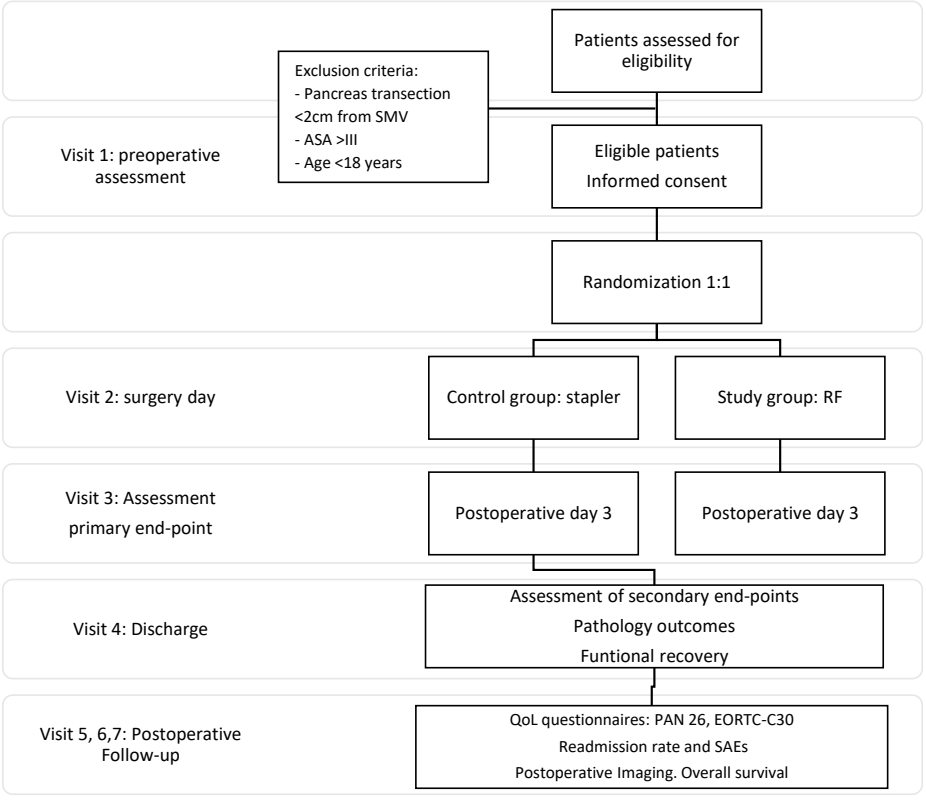

Figure 1 Flow chart followed by patients once they meet inclusion criteria and can be randomised. ASA, American Society of Anesthesiologists; QoL, quality of life; RF radiofrequency; SAEs, serious adverse effects. SMV: superior mesenteric vein; PAN-26/ EORTC-C30: EORT Quality of life Questionnarie - Pancreatic Cancer Module

the abdominal cavity, the gastrocolic ligament will be divided to allow correct visualisation 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 RFT 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 with RFT, 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 standardising 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 endpoints

Primary endpoint(s)

The primary endpoint of the study is clinically relevant POPF (CR-POPF) rate according to the updated guidelines recently published by the International Study Group of Pancreatic Fistula, that is, 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 POPF.[15]

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

Table 1 Secondary endpoints

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 endpoints		
CR-POPF	According to ISGPF definition[15]	Within 90 days after surgery
DGE	According to ISGPF definition[20]	Within 90 days after surgery
PPH	According to ISGPF definition[21]	Within 90 days after surgery
QoL questionnaires	PAN-26, EORTC-30 (PAN-26/ EORTC-C30: European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire -Core Questionnaire (C30) - Pancreatic Cancer Module)[22]	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

CR-POPF, clinically relevant postoperative pancreatic fistula; DGE, delayed gastric emptying; ISGPF, Internation Study Group Pancreatic Fistula; ISGPF, International Study Group of Pancreatic Fistula; PPH, postpancreatectomy haemorrhage; QoL, quality of life.

Secondary endpoint(s)

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

Complications will be graded by the Clavien-Dindo classification,[16] which groups the complication according to the treatment received and the Comprehensive Complication Index,[17] 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 (ie, 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 third 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.[18] 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 (European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Core Questionnaire) and PAN-26 (EORT Quality of life Questionnarie - Pancreatic Cancer) questionnaires sent to the participants at baseline, 30, 180, and 365 days after surgery.

Long-term endpoints

- 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 patients with cancer.
- 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 1 month and 1 year after surgery using a segmented injury manual with appropriate software (3D Doctor, Able Software Corp, Massachusetts, USA) measured in cubic centimetres.[19]

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 quality of life questionnaire will be recorded during the baseline visit. The mentioned surgical data will be collected in visit 2, that is, surgery day. Primary and secondary outcome parameters will be collected from visit 3 to discharge date (visit 4). Diagnostic and any

Table 2 Trial visits and documented parameters

Assessment	V1 Prestudy screening/consent/ randomisation	V2 Surgery day	V3 POD 3	V4 Discharge	V5 1 month	V6 6 months	V7 1 year
Eligible criteria	x						
Informed consent	x						
Demographics and baseline characteristics	x						
Randomisation	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

CCI, Comprehensive Complication Index; POD, postoperative day; QoL, quality of life; V, visit.

ensuing therapeutic procedures caused by postoperative complications will be collected and reported. Table 2 summarises the visits.

Randomisation

Patients who meet the inclusion and exclusion criteria and sign the informed consent in the outpatient clinic are eligible for randomisation. They will be given a code or identification number in strict sequential order. Randomisation 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, Amsterdam, the Netherlands) in a 1:1 ratio without reposition and block sizes vary between two and four patients. Randomisation 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 case report 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 serious adverse effects (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 $p<0.1$ 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 superior mesenteric vein (SMV) 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

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 hospitalisation or prolongation of hospitalisation; (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 have SAEs.

Quality assurance

Independent-qualified 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 familiarisation 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 according to the study protocol. The monitoring strategy will consist of a combination of centralised 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, randomisation and correct recording and documentation of primary and secondary endpoints by source data verification. Data will be entered into an 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 programmes that generate queries. The completed eCRF must be reviewed and signed by the investigator named in the trial protocol or a designated subinvestigator. 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 standardised. 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 studies with biological samples, Law 14/2007 on Biomedical Research 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 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 centre 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 principal investigator 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 online supplemental 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 5 December, 'Protection of Personal Data and guarantee of digital rights' in compliance with Regulation European Union 2016/679 of the European Parliament and of the Council of 27 April 2016 of Data Protection.

We have defined a dissemination strategy, whose 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 policymakers 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.

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Contributors EP-P and PS-V are surgeons who have equally contributed in the conception and design, acquisition and interpretation of data and participation in drafting the article. DD and LS have both taken part in drafting the article and interpretation of data. EV, VF, RC and YQ have interpreted the results and prepared the discussion by critically reviewing it as they have great expertise on the topic and the technique. MAGB, GS-A and JMA have very much contributed to the design of the study, to interpretation of the results and critical review, and give the final approval of the version to be published. MM, ANG, JB-L, PGC and JN, also surgeons, have actively included patients in the study and have reviewed the literature and then critically reviewed the final manuscript. BI, FB, CT-M and PS-V have contributed to 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.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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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.