Comparative Randomized Multicenter Study Of Plastic Vs. Self-expanding Metal Stents In The Endoscopic Ultrasound-guided Drainage Of Walled-off Pancreatic Necrosis

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Abstract

Background: It seems that the appearance of lumen-apposing metal stents (LAMS), are displacing the role of plastic stents in the therapy of pancreatic fluid collection as walled-off necrosis (WON). To date there is no quality of evidence to recommend LAMS as the standard treatment in management of WON. The theoretical benefit of LAMS over PLASTIC stents, need to be proved.

Methods/design: This is a multicenter prospective study, superiority, randomized controlled clinical trial by parallel groups, without masking. One hundred fourteen patients with WON will be Endoscopic ultrasound (EUS)-guided transmural drained in 9 tertiary hospitals in Spain and will be randomized to the LAMS or PLASTIC stent group. The primary endpoint is to assess the short-term (4 weeks) clinical success determined by the reduction of the collection (to <50% or < 5cm in size), along with clinical improvement. Secondary endpoints: the long-term (4 months) clinical success (total resolution or 5cm); the procedure’s duration, the level of difficulty, safety and recurrences.

Discussion: The PROMETHEUS trial has been designed to response if LAMS are superior over PLASTIC stents in the EUS-guided transmural drainage of WON.

Trial registration: ClinicalTrials.gov, NCT03100578. Registered on April 4, 2017.

https://clinicaltrials.gov/ct2/home

Background

The Atlanta classification of pancreatic fluid collection establishes that WON (walled-off necrosis) consists of a variable amount of necrotic tissue within reactive tissue wall. These derive from the encapsulation of acute necrotic collections. Imaging tests reveal a well-defined wall surrounding the collection, the formation of which typically occurs at about four weeks’ time from the origin of the acute or chronic pancreatitis. The presence of more necrosis worsens the prognosis; mortality in patients with necrotizing pancreatitis is as high as 15%, and it can reach 30% in patients with infected necrosis [1, 2]. In case of symptomatic WON, the drainage is considered, and in the last 2 decades the minimally invasive approaches (surgical or endoscopic) has increased acceptance in the management of necrotic collections over open surgical necrosectomy, with less adverse event (AE) and long-term morbidity. Recent trials have evidenced that endoscopic approaches can offer better clinical
outcomes, with and improvement of quality of life and less costs [3-6].

In the last decade, endoscopic techniques as the use of endoscopic ultrasound-guided transmural drainage, have been increasingly used as a first-line option for the treatment of symptomatic WON [5,7]. To date, plastic stent (as double plastic stents) has been used as the mainstay of endoscopic therapy for WON, until the introduction of a new dedicated stent, (lumen-apposing metal stents, LAMS) [8-10]. There is the hypothesis or suggestion that large diameter of LAMS improves the drainage of WON respect the plastic stents (7-10 Fr) and it will carry a less-time consuming interventions, with a smaller number of endoscopic procedures to achieve a final success. Regarding the safety, theoretically the risk of leakage, perforation or migration would be reduced using the specific stent design of LAMS. On the other hand, LAMS are more expensive, and its safety is controversial, with a significantly higher rate of adverse events as bleeding compared with plastic stents [11-14].

Although some endoscopic international consensus, systematic reviews or meta-analysis has recommended LAMS as the standard care for WON drainage, there is no high quality of evidence (retrospective, registry-based or non-comparative) that LAMS are superior to PLASTIC stents in the management of WON by EUS-guided transmural drainage, and few studies are comparing LAMS and plastic stents [15-20]. For all these reasons, a multicenter prospective, parallel group, randomized controlled clinical trial was designed to assess if LAMS are superior to plastic stents in the endoscopic treatment of WON.

Methods/design

The PROMETHEUS trial is a multicenter prospective, superiority, randomized controlled clinical trial with two parallel groups, without masking and with 1:1 allocation ratio. One hundred fourteen patients with WON will be scheduled for an Endoscopic ultrasound (EUS)-guided transmural drainage in 9 tertiary Spanish hospitals and will be randomized to the LAMS or PLASTIC stent group. All these centers are members of the Spanish Society of digestive Endoscopy (SEED), who acts as the promoter of this trial.

Central ethical approval of the study protocol has been confirmed from the Comité Ético de
Investigación Clínica (CEIC) del Hospital Universitari de Bellvitge-IDIBELL (ref approval no. 140/15) and we will not begin recruiting at other centers in the trial until local ethical approval has been obtained. A checklist with the recommendations for interventional trials (SPIRIT) is attached as an additional file (see appendix 1).

**Study population**

This clinical trial will be performed at the Endoscopy Unit of Digestive Diseases department, from 9 tertiary and university centers in Spain, Europe. In order to participate in this study, the patient must be a candidate for guided transmural drainage with EUS of WON-type pancreatic collection as a local complication in acute pancreatitis. The investigator at each center will be contacted to evaluate the inclusion of the patient in the study. The patient will be correctly informed by personnel knowledgeable about the specifics of the study, who may help to resolve any questions that may arise. The informed consent form will be signed in the presence of participating personnel knowledgeable about the study. Any patient has the right to opt out of the study at any time. Randomization will be applied using a dedicated web.

The inclusion and exclusion criteria are listed in Table 2.

**Recruitment**

Principal investigators from each center will have the role of exposing strategies to promote an adequate enrolment and to ensure the target sample size.

**Randomization and masking**

Patients will be enrolled in this trial by gastroenterologists, surgeons and endoscopists that will evaluate the cases in the inpatient awards or in a consultation area. The participant will be randomized with a random number table generated by an online platform.

A code list will be generated by randomization with a 1: 1 randomization ratio, by blocks, stratified by centers and by the ASA score. Each individual will be assigned a randomization code along with the treatment that corresponds. Once the patient meets the criteria of eligibility has informed consent, will proceed to the allocation of each participant centrally, ensuring the allocation concealment, and based on the randomization list. To prevent different subject recruitment rates at the various
hospitals from interfering in the development of the study, the entire population will be randomized in blocks of four between the two treatment possibilities.

**Procedural Technique**

**Qualification of centers**

The participation of a minimum of 9 hospitals with an inclusion of about 13–15 patients per year per hospital is required. The investigators at the participating centers all will have: experience in endoscopic intervention and therapeutics; previous experience in EUS-guided transmural drainage with metal and plastic stents (>25 overall) and a casuistic minimum of 10 procedures per year; and appropriate material at their disposal for carrying out transmural drainage with both types of stent.

**General description of the technique**

Each selected case will ensure a conclusive diagnostic revision with WON. In case of doubt, EUS-guided fine needle aspiration will be considered prior to drainage to rule out cystic tumor.

Prophylactic antibiotic prophylaxis will be administered in accordance with protocol of each center. In case of INR>1.5, it will be corrected in accordance with protocol of each center until INR<1.5.

Procedures will be performed under deep sedation in accordance with the directives of each center. In case of collection >10 cm (>700mL), tracheal intubation by anesthesiologist is recommended. CO₂ insufflation is recommended, especially of endoscopic necrosectomy. The WON will be localized by using a linear echoendoscope, selecting the appropriate and optimal region for carrying out the EUS-guided puncture. The collection will be punctured with a 19G needle (plastic or LAMS group) or directly with an electrocauterizing device (freehand technique, only in the LAMS group). The guidewire will be advanced and coiled into the WON cavity. Then, the transmural ostomy will be carried out in accordance with the normal procedure of the experienced endoscopist. The use of fluoroscope will be decided upon on the basis of technical considerations and the opinion of the endoscopic interventionist. The use (or not) of fluoroscope will be noted in the case report form (CRF). The scale of the ostomy will be determined by the size of the collection (see table 3).

After the interventional procedure, all inpatients cases will be returned to the hospital ward and will discharged after clinical improvement. Outpatients will spend a minimal of 24 hours observation and
will be discharged the next day unless no symptoms improvement or appearance of adverse events.

**Plastic stent group**

Double pigtail plastic stents (5-10 cm length, diameter 7-8.5-10Fr, Advanix, Boston Scientific) will be used. A minimum of one 10Fr pigtail plastic stent will be placed. After initial EUS-guided access, the ostomy will be dilated first, using a cystotome, and secondly with a balloon dilation. The plastic stent will be inserted and delivered following the routinary technique of each interventional endoscopist. Number of plastic stent and size of the balloon used to dilate the ostomy will depend of the WON size and content (see table 3). The time to plastic stent withdrawal will be considered until total resolution by imaging. If pancreatic duct involvement, non-withdrawal of stent will be considered.

**Metal group**

The metal stents used in this study will be LAMS (10, 15 or 20-mm in diameter, and 10-mm in length, HotAXIOS stent with electrocautery-enhanced delivery system, Boston Sc). This stent is a self-expanding metal totally covered with luminal apposition. After the EUS-guided access into the WON using first a 19G or directly with the electrocautery tip, the delivery system will advanced into the cavity and the distal flange will be deployed under EUS guidance. Otherwise, the proximal flange will be release under EUS or endoscopic guidance. The time to stent withdrawal, will depend until total resolution by imaging, however there will be the intention to remove a LAMS no later than 4-6 weeks.

**Additional interventions:**

Necrosectomy will be considered in WON with predominantly of solid debris, using the technique at the discretion of the endoscopist. In cases that require sessions of endoscopic necrosectomy, the different technical variants described in the literature will be used (irrigation technique with normal saline; mechanical technique using the common devices as snares, Dormia basket or retrieval nets for extraction of necrotic debris; or combined with nasocystic catheters). The periodicity will be every 2-5 days depending on the decision of the expert endoscopist and the clinical evolution of the patient.

**Additional comments:**

In the event of technical failure in the placement of the stent (plastic or LAMS) for any reason, alternative treatment will be decided upon in accordance with the directives of the endoscopic
interventionist, with the aim of offering the patient the best possible solution.

The first controls will be on the first day following and at four weeks (see table 4). If there is no short-term clinical success, the most beneficial therapeutic approach for the patient will be adopted in accordance with the criteria of the patient’s medical team (Example: use of technical variants at initial drainage such as placement of coaxial plastic pigtail within the LAMS, replacement or change the stent type, use of nasocystic drainage or other known variants).

Every intervention, diagnostic procedure, and additional therapeutic contribution will be noted in the CRF.

In the case of collections of significant size (ie. 14cm) with clinical-radiological success but without disappearance of the collection (ie. CTMD reduction from 14 cm to 6cm), and does not allow the removal of the stent, a new CTMD will be performed at 4 weeks (8w) to assess removal of the stent. Therefore, the removal of a stent is contemplated when there is disappearance of the collection or a decrease <5cm.

Patients will remain in the hospital for a minimum of 24 hours for clinical observation, under medical supervision.

Clinical evaluation and follow-up

Data collection

The collecting of clinical information on the patients will begin at the outset (baseline) and will continue with follow-up as established and defined in the study. AEs will be noted from the beginning of the test until the conclusion of follow-up by means of scheduled controls.

Calendar

The following time-points and data items will constitute the data collection from the beginning through successive controls: The collecting of data for purposes of documentation will be carried out using a CRF, which will serve as an easily accessed source of information. After collection, the data will be introduced into an electronic database by the participating investigator of each center.

Follow-up

Patients will be assessed (visit, telephone call) on days 1 and 7, at 4, 8, and 16 weeks, and at 6, 8,
and 12 months by personnel participating in the study, with the aim of obtaining information regarding signs and symptoms pointing to possible stent obstruction or migration, recurrence, or other AEs.

Any instances of death during the follow-up will be investigated to rule out possible relation to the endoscopic procedure. Such occurrences will also be recorded in the CRF.

If there is clinical suspicion of obstruction or migration of the stent, an upper endoscopy will be carried out. Based on the findings of this procedure, the problem will be resolved in accordance with the directives of the intervening endoscopist. Any additional procedure or endoscopic intervention will be duly documented.

Complications will be handled and treated in accordance with the directives of the patient’s medical team. All additional tests and interventions will be duly documented.

Definitions

The term of WON is according to the literature (latest revision of Atlanta, Banks PA et al. Gut 2013) [1]. At least two imaging tests will be required (CTMD, MRI, EUS) prior to the transmural drainage, the results of which must be in agreement on the classification of the collection as WON.

Technical success is defined as the correct release of the stent at both ends, with observed drainage of the liquid.

Clinical success is defined as the significant reduction of the collection along with clinical resolution.

Recurrence, defined as asymptomatic pancreatic collection diagnosed with imaging test during the follow-up of prior procedure with initial clinical success.

AEs are defined as undesirable situations suffered by patients during the study, whether related or not to the EUS-guided transmural drainage with a stent (plastic or metal). All AEs referred by patients or observed by the medical team will be duly documented. All serious AEs will be detailed, and the study promoter/principal investigator will be notified within seven days. In the event of a death, notification will be made within 24 hours. AEs will be recorded in both the clinical history of the patient and the CRF, with appropriate medical terminology. Whenever possible the diagnosis rather than the symptoms will be recorded. These guidelines are to be followed from the time of the signing
of informed consent until 30 days after the final visit in the study calendar. AEs will be classified as mild, moderate, serious, or fatal, in accordance with the nomenclature for AEs in endoscopy (ASGE Workshops 2010, Cotton GIE 2010; 71:446-54). The determination as to whether an AE is related to the EUS-guided transmural drainage with stent (plastic or metal) will be made by the patient’s medical team, the local investigator, and the principal investigator of the study.

In appendix 2 is included information about AEs definitions and MEDDEV guidelines. ‘Research product security surveillance’ section, according to the definitions set out in the MEDDEV 2.7 / 3 guidelines (rev 3, May 2015) “Guidelines on medical devices: Clinical investigations: Serious Adverse event reporting under Directives 90/385 / EECC and 93/42 / EEC” (appendix 2).

**Outcomes**

The primary outcome is the short-term (4 weeks) clinical success (metal vs. plastic) determined by the reduction of the collection (to <50% or < 5cm in size), along with clinical improvement.

The secondary outcomes are: the long-term (4 months) clinical success (metal vs. plastic) determined by total resolution or 5cm, along with clinical improvement. Technical: to assess the duration of the procedure and the level of difficulty. Safety: to assess AE (early and late). Hospital length of stay. Recurrences. Financial: evaluate the relative costs of the two strategies.

**Sample size calculation**

The sample size calculation is based on the primary hypothesis of detecting differences statistically significant in the percentage of clinical success among groups LAMS and plastic stents at four weeks after the intervention. Published data suggest that the clinical success rate at 4 weeks in the LAMS group is expected to be 0.75 and in the plastic stent group it is expected to be 0.5. Fifty-seven patients will be recruited in each group to reject the null hypothesis that the proportion of clinical success in the LAMS group is equal to that of the plastic group with an 80% power. The type I error associated with this test will be 5%. To evaluate the hypothesis, the Chi-square test or Fisher’s exact test will be used depending on of the application criteria. For the calculation, a planned interim analysis for half of the recruitment using O’Brien-Fleming’s type I error expense function and a global loss rate of 5%. http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html
Statistical analysis

All study variables will be presented by stent’s groups and in total, using descriptive statistics consistent with the nature of the variable. The continuous variables will be described indicating the number of non-missing observations, the mean, the standard deviation, the minimum, the first quartile, the median, the third quartile and the maximum. Categorical variables will be described indicating the number of non-missing observations and the percentages of the different categories by column.

Main analysis: main outcome is the percentage of patients radiological (morphological) success between transmural drainage of the collection, measured at four weeks of intervention. The null hypothesis suggests that there are no differences between proportions of the intervention group and the control group.

The level of statistical significance has been set at 5%. To test the hypothesis, use the Chi-square test or Fisher’s exact test depending on the application criteria. To quantify the magnitude of the difference, the relative risk of success will be estimated, in the metal stent group with respect to the plastic stent group and its confidence interval will be calculated at 95%

Secondary variable analyses: To study which factors are associated with clinical-radiological success to in the short term, a multivariate logistic regression will be carried out. They will be taken as variables of adjust age, sex and as factors predict the location of the disease, treatments received, size and characteristics of the collection, previous ASA, etc. On the other hand, the appearance of clinical recurrence will be analysed by means of an analysis of Kaplan-Meier survival. The factors associated with clinical recurrence will be explored through a multivariate Cox proportional risk model and will also be taken adjustment variables

Subgroup analysis: The main analysis will also be carried out in the following subgroups:

ASA patients I-II vs III-IV.

Data Management: Throughout the study the promoters will monitor the quality of the trial with special attention to protocol deviations and the quality of the data entered in the database. At the end of the trial, a meeting will be held where the data management report. This report will describe
the different deviations on the protocol identified in each of the patients. These deviations will be classified as major or minor, and those patients with major deviations will be excluded from the protocol analysis. After the meeting, the database will be considered suitable for analysis, and the database will be closed.

Statistical analysis plan: The statistical analysis plan will be finalized before the close of the database. This plan will include all the analysis described and others mainly on the sensitivity of the results and the management of the missing data. In the case that in the plan of statistical analysis there would be some deviation over the analysis of the main variable, an addendum to the protocol will be made. No changes will be made to the analysis plan original once opened the blind and closed the database.

Cost analysis

The procedure for determining the cost of the diagnostic test is made up of several steps: calculation of the unit cost; accounting for all the costs associated with the test, both direct and indirect.

Calculation process: observation of the performance; accounting for all the factors involved in the procedure (units, time, number of professionals involved).

Criteria to be considered: human resources; disposable material; generic fungible supplies; pharmacy; laundry; equipment; repairs/maintenance of equipment and facilities; energy; cleaning; waste handling; rental; telephone (calls to contact subjects in follow-up); structure costs; hospital admissions

Other considerations

Rescue: depending on the initial endoscopic treatment carried out, a rescue cross-over rescue treatment can be considered when the initial protocol treatment fails. For the plastic treatment group metal stent (LAMS); for the metal treatment group plastic stent. Another accepted rescue technique (only in cases of initial treatment failure) in the branch of metal stent: insertion of coaxial plastic pigtail within a LAMS.

In all these cases, the follow-up of the patients will be maintained until the end of the study according to protocol. Alternatively, if a cross treatment or technical variant is not possible, percutaneous surgical or radiological treatment will be offered.
Withdrawal: AE or other clinical condition of the patient that, at the clinical discretion, the withdrawal of the patient in the study is considered appropriate; pregnancy; or expressed wishes of the patient. Withdrawal from treatment will not mean suspension of the study, given that follow-up will be maintained until the end of the study in accordance with the protocol.

Need for surgical intervention for under study: in these cases, patient follow-up will be ended.

Ethical aspects and confidentiality

The protocol will be approved by the CEIC of each participating hospital as well as that of the coordinating center (HUB). The study researchers will carry out their tasks in compliance with ethical principles of the clinical research established in the Declaration of Helsinki, and with the norms of Good Clinical Practices. It is planned to hire a policy to cover the concepts and compensations according to current legislation (RD 1591/2009) that regulates investigations clinics with sanitary products. Before starting the clinical trial, it is planned to request authorization to the Spanish Agency for Medicines and Health Products (AEMPS) and the CEICs. Before the inclusion of the patient in the trial, a written informed consent will be requested. In relation to the study data will follow the provisions of Organic Law 15/1999 of December 13 on “Protection of Personal Data”.

Publication of results

There is a commitment to publish the results of this study in high impact international journals, should the results be of enough scientific interest. However, no patient names will appear in any article, and no one, with the exception of the researchers in this study and the members of the hospital ethical committees, will have access to the data, in accordance with the Law on the Protection of Data of a Personal Nature.

Discussion

Although open surgical necrosectomy has been the traditional treatment of choice in patients with infected or symptomatic pancreatic necrosis, other minimally invasive techniques have been developed in the last years (endoscopic necrosectomy, guided radiological percutaneous drainage, and retroperitoneal treatment) for treating collections, so as to improve on the high morbidity and mortality rates of traditional surgical treatment [3, 21–23].
At present, endoscopic transmural drainage plus endoscopic necrosectomy are a viable technique that are reasonably safe and effective when carried out in centers that have experience in doing so. Although, these minimally invasive endoscopic treatments, it is not entirely free of complications and the most common of these are bleeding, perforation, post-procedural infection, and stent migration [7, 24]. Additionally, with the continuous technological advances being made and the appearance of new materials for endoscopic use, doubts have arisen as to which devices are best to use. One clear example of this uncertainty is the choice of stent. To date, most published studies on guided transmural drainage with endoscopy have involved double pigtail plastic stents, with the number and diameter varying depending on the collection type [23,24]. In the past years, some reports have been published on the use of self-expanding covered metal stents offering greater diameter, and therefore greater volume in the drainage of the collection [25–27]. However, both types of stent are intended for bile drainage and are not expressly designed for transmural drainage of abdominal collections and more dedicated stents were investigated [8].

Recently, LAMS designed for the drainage of pancreatic collections have appeared with demonstrated efficacy in a number of studies but also most costly [16–20]. These stents are totally covered and offer a maximum caliber of 15–20 mm, thereby allowing for endoscopic necrosectomy in repeated sessions without the need for replacement. In our experience, they permit transmural drainage of pancreatic collections and endoscopic necrosectomy if it is needed, that is safe and effective, as well as reducing the duration of the procedure [10,28].

However, with the increasing of tendency use of these stents, significant LAMS-related AEs (ie. severe delayed bleeding, buried stent syndrome, obstruction, migration) have been reported in several papers.

To date there is only one comparative prospective study of self-expanding metal stents, LAMS type, versus and plastic stents in the endoscopic treatment of WON-type pancreatic collections, and concluded that there is no significant differences in treatment outcomes between both, and in order to minimize LAMS-related AEs, they recommend a follow-up imaging and LAMS removal at 3 weeks if collection is resolved [29].
The PROMETHEUS trial was promoted by the Spanish Society of Digestive Endoscopy, and include 9 tertiary centers, and experts in the management of WON. Hospital Universitari de Bellvitge has the leadership and main role to centralize the decisions in case of doubts, controversies, in order to reduce heterogeneity.

In conclusion, this randomized multi-center trial is necessary and primordial, to clarify the safety and theoretically superiority of LAMS in the management of WON, compared with the use of plastic stents.

**Trial Status**

*Protocol of submitted version, number and date:* number 2.1; date 2018-June.

*Recruitment:* date of starting 2017-June–27th; and recruitment will be completed at 2020-June.

*Revision Chronology:*

*a-Prometheus 2017-June, original: version 1,* first draft of the study protocol.

*b-Prometheus 2017-September, amendment nº 1: version 2.*

Main amendments: (i) to clarify the second inclusion criteria—in case of more than one collection, the EUS-guided drainage will be limited to ONLY ONE pancreatic collection (WON), that one related to the symptomatology (Table 2); (ii) adding of the ‘Research product security surveillance’ section, according to the definitions set out in the MEDDEV 2.7 / 3 guidelines (rev 3, May 2015) “Guidelines on medical devices: Clinical investigations: Serious Adverse event reporting under Directives 90/385 / EECC and 93/42 / EEC “ (appendix 2); (iii) extension to 9 centers respect to the initial protocol (4 centers) (iv) Procedural technique, rescue section: in case of failure, adding of the possibility to perform a ‘Technical variant’ in LAMS group - an insertion of coaxial plastic pigtail within the metal stent.

Additional changes: (i) adding of new and relevant references; change of the grading AE classification (immediate, early and late); (ii) commercial name of each stent; (iii) Delayed start, from the beginning of 2016 to June 2017; (iv) procedural technique section: additional comments regarding when and how some technical variants can be performed; and technical notes about necrosectomy technique; (v) data management paragraph in the statistical section, (v) call phone at 7 days, and additional new legend explaining the possibility of a second imaging procedure at 8w, only in case of radiological clinical success but with persistence of the collection > 5cm (Table 4, Timeline)

*Prometheus 2018-June, amendment nº2: version 2.1—definitive.*

Minor changes: adding of a new size of LAMS (20-mm in diameter).

AEMPS and CEIC have been notified after every amendment, receiving the acceptance from each institution.

**Abbreviations**

*AE:* adverse event

*AEMPS:* Spanish agency for medicines and health products.
ASA: American society of anesthesiologists classification

CEIC: Clinical research ethics committees.

CRF: Case report form.

CTMD: Computed tomography multidetector.

EUS: Endoscopic ultrasound.

LAMS: Lumen-apposing metal stent.

MRI: Magnetic resonance imaging.

SEED: Spanish Society of Digestive Endoscopy.

WON: Walled-off necrosis.

Declarations
Ethics approval and consent to participate: Ethical approval has been obtained from the Comité Ético de Investigación Clínica del Hospital Universitari de Bellvitge-IDIBELL (Barcelona; ref approval no. 140/15), on date May 17th 2015, number reference 140/15. Written informed consent will be obtained from each patient before randomization. Any subsequent amendments of the protocol need to be approved by the relevant ethical bodies before implementation.
Consent for publication: not applicable.
Availability of data and material: minimal dataset necessary to interpret the findings, can be available from the corresponding author on reasonable request.
Competing interests: M. Pérez-Miranda: consultant and speaker for Medtronic, Olympus, Taewoong, and M. I.Tech
E. Vazquez-Sequeiros is a consultant for Boston Scientific
F. Gonzalez-Huix is a consultant for Boston Scientific.
JB. Gornals is a consultant for Boston Scientific and has received a research grant from Boston Scientific.
Other authors declare that they have no competing interests.
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Authors’ contributions:
JBG, CT and PH drafted the manuscript. RB, FBC, CDL, JME, AGP, FGH, CGA, ASY, AT, MPM, EVS, JVR, SS, JV and JBG have provided a critical review and, as investigators at each institution, will promote an adequate enrolment of patients. JBG and JBC registered the study. JBG and CT contributed in the statistical analysis and interpretation. JBG, MPM, EVS, JV, PH, CT and SV participated in the design of the study. JBG, PH and CT conceived the project, designed the study, revised the manuscript, and approved the final submission. All authors read and approved the final manuscript.

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Tables
Table1: Comparative table of the two kinds of stents used in transmural drainage of pancreatic collections.
| LUMEN-APPOSING METAL STENT | PLASTIC |
|----------------------------|---------|
| ADVANTAGES                 | DISADVANTAGES | ADVANTAGES | DISADVANTAGES |
| - Easy release             | - Expensive | - Economical | - Lesser diameter |
| - Wide diameter            | - Less scientific evidence | - Easy extraction | - Shorter patency |
| - Better drainage of solid waste and necrosis | - Temporary placement | - May be left permanently in place | - High occlusion rate |
| - Direct necrosectomy via stent | - Traumatism caused by the ends | - Greater experience (studies) | - A single stent is for WON |
| - Longer patency           | - Unknown whether permanent placement is possible | - High success rate (>80-90%, all types of collections) | - Multiple-demanding technique (MTGT for WON) |
| - Correct visibility       |                      |                      | - Worse visibility ( |
| - Short therapeutic time   |                      |                      | - Leakage of liquid |
| - Hemostatic effect        |                      |                      | - Migration |
| - Prevents migration       |                      |                      | |
| - Anchoring effect         |                      |                      | |
| - Prevents liquid leakage  |                      |                      | |
| - Easy extraction          |                      |                      | |

Table 2: Selection criteria. WON, walled off necrosis. *Diagnosis of WON based on imaging procedures.
Inclusion criteria:
Patients eligible for the trial must comply with all of the following at randomization
- Age 18 years or more
- Patient with indication (ASGE, Jacobson BC, GIE2005) of drainage of, only one, WON-type*-related to the symptomatology of previous acute pancreatitis
- Patient capable of understanding and signing informed consent form
- Patient understanding the type of study and complying with the follow-up of complementary tests during the study’s duration

Exclusion criteria
- Pregnancy or breast-feeding
- Severe coagulation disorder: INR > 1.5 not correctible with administration of plasma and/or platelets < 50,000/mm3
- Asymptomatic patients, without clinical indication of drainage, except for those with vascular compression involvement
- Non-identification of solid content during EUS procedure
- Failure to sign informed consent form
- Patients with intellectual handicap who are unable to understand the nature and possible consequences of the study, unless there is a competent legal representative
- Patients unable to adhere to subsequent follow-up requirements
- Conditions that preclude upper digestive endoscopy, such as stenosis.

NOTE: if there are several pancreatic collections, it does not exclude the patient from the trial. It is only excluded if there are more than one symptomatic collections, candidates to be drained

Table 3: Number of stents along with technical variations depending on size of WON, observed with EUS during procedure.

| TYPE       | LAMS (n, ø)          | PLASTIC (n, ø)          |
|------------|----------------------|-------------------------|
| WON <10cm  | 1, 10-15-20mm        | ≥1, minimum 1 of 10Fr (+ostomy 8-10mm) |
| WON >10cm  | ≥1, >15mm            | ≥2, minimum 1 of 10Fr (+ ostomy 10-15mm) |

LAMS, lumen-apposing metal stent; WON, walled-off necrosis

Table 4: Data management, Calendar.
| Timepoint/ Stages       | Baseline | Intervention | 24h | 7d ± | 4 w ±3d | 8 w ± 5d (TF) | 16 weeks (4 r ± 10d) |
|------------------------|----------|--------------|-----|------|---------|----------------|----------------------|
| ENROLMENT:             |          |              |     |      |         |                |                      |
| Informed consent       | X        |              |     |      |         |                |                      |
| Clinical history and exploration | X    |              |     |      |         |                |                      |
| Eligibility screen     | X        |              |     |      |         |                |                      |
| Allocation             | X        |              |     |      |         |                |                      |
| INTERVENTION:          |          |              |     |      |         |                |                      |
| Implantation           |          |              |     |      |         |                |                      |
| Removal                |          |              |     |      |         |                |                      |
| INR                    |          |              |     |      |         |                |                      |
| ASSESSMENTS:           |          |              |     |      |         |                |                      |
| Blood test             | X        | X            |     |      |         | X              | X                    |
| Imaging test           | X        | X            |     |      |         | X              | Xª                   |
| Symptomatology         | X        | X            |     |      |         | X              | X                    |
| Visit                  | X        | X            |     |      |         | X              | X                    |
| Telephone contact      |          |              |     |      |         | X              | X                    |
| Adverse effects        | X        | X            |     |      |         | X              | X                    |
| Primary outcome        |          |              |     |      |         | X              |                      |
| Secondary outcomes     |          |              |     |      |         | X              |                      |
| Medication             | X        | X            |     |      |         | X              | X                    |

ªOnly in case of radiological clinical success but with persistence of the collection > 5cm

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

appendix 2 Prometheus Safety definitions AE.docx
appendix 1 SPIRIT_Fillable-checklist-15-Aug-2013.doc