Endoscopic sphincterotomy before fully covered self-expandable metal stent placement for malignant extrahepatic biliary obstruction to prevent pancreatitis: a randomised controlled trial

SphinX trial

Version 14.0; July 2020

PROTOCOL TITLE 'Endoscopic sphincterotomy before fully covered self-expandable metal stent placement for malignant extrahepatic biliary obstruction to prevent pancreatitis: a randomised controlled trial'

Protocol ID	2015_176 MEC AMC
Short title	SphinX trial
EudraCT number	NTR5270
Version	14.0
Date	July 2020
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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CBD	**Common Bile Duct**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CI	**Confidence Interval**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
ERCP	**Endoscopic Retrograde Cholangiopancreatography**
ES	**Endoscopic sphincterotomy**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
NSAIDs	**Non-steroidal anti-inflammatory drugs**
OR	**Odds Ratio**
PD	**Pancreatic duct**
PEP	**Post-ERCP Pancreatitis**
RCT	**Randomised Controlled Trial**
(S)AE	**(Serious) Adverse Event**
SEMS	**Self-Expandable Metal Stent**
USSEMS	**Uncovered Self-Expandable Metal Stent**
FCSEMS	**Fully Covered Self-Expandable Metal Stent**
PCSEMS	**Partially Covered Self-Expandable Metal Stent**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**

Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Self-expandable metal stents (SEMSs) are increasingly being used to treat malignant common bile duct obstruction.[1] This shift towards SEMS placement (and away from plastic stent placement) is accompanied by a change in the complication profile of biliary stent placement, with a sharp decrease in late occlusion and cholangitis, but a slight increase in the incidence of post-ERCP pancreatitis.[1-3] It is hypothesised that endoscopic sphincterotomy (ES) before biliary SEMS placement may reduce the occurrence of post-ERCP pancreatitis by widening the orifice of the major duodenal papilla and reducing compression of the pancreatic sphincter. Data on whether or not to perform ES are conflicting.[4, 5] As a result, the European guideline leaves pre-stenting biliary sphincterotomy to the preference of the endoscopist.[6]

Objective: To investigate the role of endoscopic sphincterotomy prior to biliary fully covered SEMS (FCSEMS) placement in the prevention of post-ERCP pancreatitis.

Study design: A multicentre, open, randomised controlled trial.

Study population: Patients with extrahepatic biliary obstruction caused by (suspected) malignancy requiring FCSEMS placement, or who have an indication for plastic endoprosthesis replacement with a FCSEMS.

Intervention: Patients will be randomised to FCSEMS placement with or without prior endoscopic biliary sphincterotomy.

Main study parameters/ endpoints: The primary endpoint is the rate of post-ERCP pancreatitis. Secondary endpoints are procedural complications, technical success of sphincterotomy and stent placement, as well as re-interventions.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: All patients are consented for ERCP, and for the study, and informed about the complications associated with an ERCP: abdominal pain, bleeding, post-ERCP pancreatitis and perforation (consent for ERCP). The main risks of ES are haemorrhage (2.0%) and perforation (0.3%).[7] In daily practice, whether or not the patient will be subjected to a sphincterotomy depends on the endoscopist's preference. Therefore, the study does not introduce an additional risk for the participant.

The presumed benefit of an ES is a reduction in the post-ERCP pancreatitis rate after biliary SEMS placement, but ES may be accompanied by an increased risk of bleeding and perforation. Therefore, a change in the distribution of complications could be anticipated.

The burden for patients participating in this trial is small, with only two short telephone calls seven and thirty days after the procedure to evaluate possible procedure-related complications.

1. INTRODUCTION AND RATIONALE

Self-expandable metal stents for malignant biliary obstruction

Endoscopic biliary stent placement is a well-established treatment for patients with unresectable malignant biliary obstruction, and is indicated for a selected group of patients in the preoperative setting, including patients with severe jaundice (serum bilirubin >250 µmol/L), in those with biliary obstruction undergoing neoadjuvant therapy, those who need to wait for a definitive surgical treatment for logistic reasons, and in those with acute cholangitis.[6] Several randomised controlled trials (RCTs) and meta-analyses have compared plastic and metal stents for these indications and shown a reduced rate of recurrent biliary obstruction with SEMSs.[1, 2, 8] Moreover, a recent meta-analysis showed a significantly increased survival rate for patients treated with SEMSs for malignant biliary obstruction.[1] Because of these benefits SEMSs are increasingly being used, even though their costs are much higher compared with plastic stents. This shift towards SEMS placement is accompanied by a change in the complication profile of biliary stent placement with a decrease in cholangitis, but an increasing incidence of post-ERCP pancreatitis. Data from a Dutch prospective multicentre study [manuscript submitted] in patients with malignant distal biliary obstruction showed 18% (9/49) pancreatitis in those treated with FCSEMSs, compared to 7% (7/102) after plastic biliary stent placement in a previous study (p=0.016).[3] A decrease in cholangitis with the use of SEMSs has been demonstrated in randomised studies with a reduction from 24.5% to 4.9%.[2, 9] In addition, a retrospective analysis of the incidence of post-ERCP pancreatitis after biliary stent placement in the Freeman Hospital, Newcastle, UK, also showed a trend towards an increased incidence of pancreatitis with the use of covered SEMSs [manuscript submitted]. The theory behind the increased risk of pancreatitis is, that because of the radial expansion of the SEMS the orifice of the pancreatic duct at the level of the major duodenal papilla is compressed or even closed off, which causes an outflow obstruction of the pancreatic duct and thereby induces post-ERCP pancreatitis. The outflow obstruction might even be more prominent with the use of FCSEMSs, where the covering of the stent may also block the orifice of the pancreatic duct.

Consequences of post ERCP pancreatitis

In a selected population with a potentially resectable obstructing tumour preoperative biliary drainage is indicated to resolve cholestasis allowing neoadjuvant therapy, treat severe jaundice, bridge waiting times to surgery, or manage acute cholangitis.[6] In this population the occurrence of post-ERCP pancreatitis is a major concern, because it may result in a delay or even cancellation of the preferred therapy. This may have a major impact on the oncological outcome of these patients. Furthermore, post-ERCP pancreatitis results in hospital admission, reduced quality of life and increased healthcare costs.[10] Post-ERCP pancreatitis

is severe in approximately 10% of cases, and carries an overall mortality rate of 3%.[11] Therefore, to investigate the role of a pre-stent sphincterotomy to prevent post-ERCP pancreatitis may have a major impact.

Endoscopic sphincterotomy to prevent stent-induced pancreatitis

The hypothesis that endoscopic sphincterotomy (ES) before biliary SEMS placement prevents the occurrence of post-ERCP pancreatitis by widening the orifice of the major duodenal papilla and thereby ensuring the outflow of pancreatic juice, has been subject of three RCTs.[4, 5, 12] The most recently published trial included 200 patients with distal biliary obstruction caused by unresectable pancreatic cancer who received a partially covered SEMS (PCSEMS).[12] This trial was powered as a non-inferiority study and showed no difference in post-ERCP pancreatitis (8% vs. 9%) and early adverse events (15% vs. 15%) between ES and no ES.[12] The second trial included 82 patients with inoperable malignant biliary strictures and randomised between uncovered SEMS placement with or without prior ES.[5] A sphincterotomy significantly decreased the risk of pancreatitis: 9.8% versus 31.7% (p=0.014). However, there was a significantly increased incidence of cholangitis in the ES group: 58.5% versus 31.7% (p=0.015).[5] The high incidence of cholangitis in this trial may be explained by the fact that almost half of the patients had malignant hilar strictures, which usually causes more complex biliary obstructions. The authors suggested that procedural techniques and the 10 mm diameter of the SEMS could have contributed to the relatively high incidence of post-ERCP pancreatitis.[5] The third RCT randomised between ES and no ES prior to FCSEMS placement in 74 patients with unresectable distal bile duct obstruction.[4] There were no cases of pancreatitis, but the overall complication rate was significantly higher in the sphincterotomy group: 48.6% versus 10.8% (p=0.006). This difference was caused by the unusually high incidence of bleeding (13.5%) and retroduodenal perforations (10.8%) related to ES.[4] The authors explained that an interventional ERCP in an obstructing tumor is associated with a high risk of complications, but no duodenal perforations related to ES have been reported in other prospective studies.[5, 13-15] Based on these conflicting data, the European guideline on biliary stenting recommends that “the anticipated benefits of pre-stenting biliary sphincterotomy should be weighed against its risks on a case-by-case basis.”[6] It can thus be concluded that the current evidence on a pre-stent ES is confusing.

Aim

The aim of this study is to investigate the effect of a biliary sphincterotomy prior to biliary fully covered self-expandable metal stent placement to prevent post-ERCP pancreatitis.

2. OBJECTIVES

Primary Objective:

- Incidence of post-ERCP pancreatitis, which is defined according to the modified definition of Cotton et al: new or worsened abdominal pain, in association with a serum concentration of pancreatic enzymes (amylase or lipase) that was at least three times the upper limit of normal at more than 24 hours after the procedure, requiring hospital admission or a prolongation of planned admission.[7, 16]

Secondary Objective(s):

- Technical success of stent placement; adequate positioning and release of the stent.
- 30-day morbidity related to ERCP (with or without ES):
  - Severity of pancreatitis defined according to the revised Atlanta classification[17]: mild, moderate or severe.
  - Occurrence of bleeding: clinically relevant (not just endoscopic) bleeding requiring blood transfusion, re-intervention, admission or prolongation of hospitalisation.
  - Occurrence of duodenal and retroperitoneal perforation.
- Stent-related 30-day morbidity: re-obstruction, stent migration, cholangitis, cholecystitis.
  - Cholangitis is defined as meeting both criteria 1 and 2:
    1. Temperature ≥ 38.5 °C with cold chills, **OR**
       Temperature ≥ 39 °C without cold chills
    2. Dilatation of the CBD (>8mm ≤75 years or >10mm >75 years), **OR**
       Progressive cholestasis for >2 days and bilirubin >40µmol/L (2.34 mg/dL)
  - Cholecystitis is defined as: Clinical and radiological signs for cholecystitis with a gallbladder wall >3 mm and/or fluid surrounding the gallbladder.
- 30-day mortality.

3. STUDY DESIGN

This study is designed as an open randomised controlled trial. Patients will be randomly assigned to group I (endoscopic sphincterotomy before FCSEMS placement) or group II (no sphincterotomy before FCSEMS placement).

Time schedule

Oct 2014 – Dec 2015	Preparation
Dec 2015 – June 2021	Patient enrolment
July 2021	End of study period

Setting

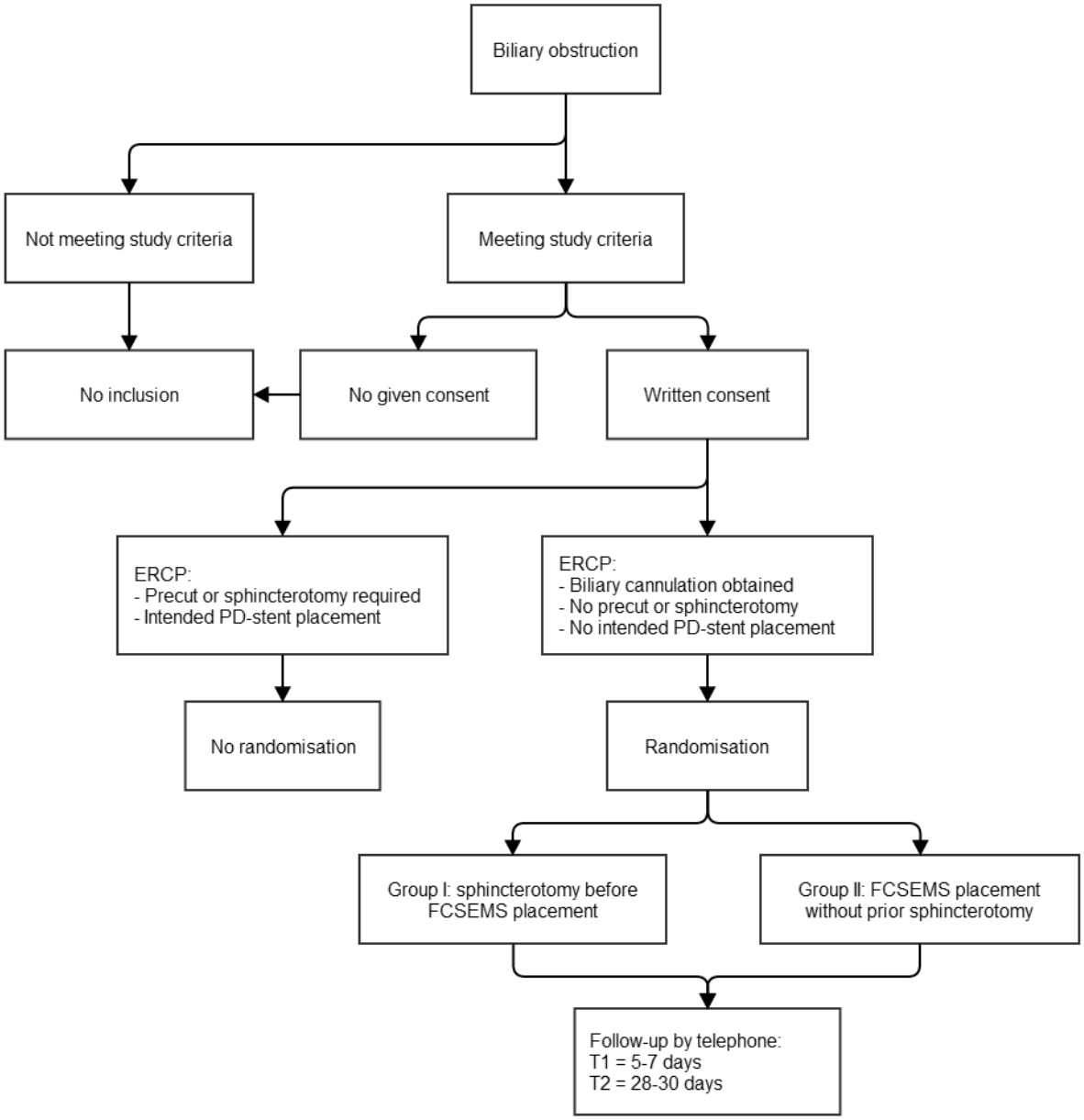
The study will be conducted in an European multicentre setting including university and general teaching hospitals.

Justification of the design

From a methodological point of view, a randomised controlled trial is the best design to evaluate whether sphincterotomy prior to biliary SEMS placement is safe and decreases the incidence of post-ERCP pancreatitis. The current practice is that a sphincterotomy is performed at the discretion of the endoscopist. This decision will depend on the presumed risk of post-ERCP pancreatitis and the previous experience of the operator with performing sphincterotomies. The risk of post-ERCP pancreatitis is influenced by several patient- and procedure-related factors. Randomisation allows homogeneous baseline characteristics and will prevent selection.

From an ethical point of view, it is hypothesised that biliary SEMS placement may increase the risk of post-ERCP pancreatitis and therefore prior sphincterotomy may be beneficial. On the other hand, the endoscopic sphincterotomy procedure itself can be complicated by bleeding and duodenal perforation. The balance between these risks is still unclear. Therefore, we think this RCT is necessary to provide an answer to this clinically very relevant question.

Flow chart study design and main procedures



4. STUDY POPULATION

4.1 Population (base)

Patients with extrahepatic biliary obstruction caused by (suspected) malignancy requiring FCSEMS placement, or who have an indication for plastic endoprosthesis replacement with a FCSEMS.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Indication for fully covered self-expandable metal stent placement
- (Suspected) malignant biliary outflow obstruction
- Biliary stenosis located ≥ 2 cm distal from the hilum
- Age ≥ 18 years
- Written informed consent for the procedure and study participation

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Hilar biliary obstruction, defined as stenosis located within 2 cm of the hilum
- Biliary SEMS or more than 1 plastic endoprothesis in situ
- Precut sphincterotomy or standard sphincterotomy
- Prophylactic pancreatic duct stent, even when the PD-stent is subsequently removed
- Continued use of anticoagulants or antiplatelet drugs with the exception of low-dose aspirin (max. 100mg/day)
- Known clotting disorder
- Patients unable to provide written consent for the study

The in- and exclusion criteria will be reported in de eCRF in Castor EDC.

Considering the logistical challenges of randomising a patient during the procedure, randomisation in Castor is possible without any restrictions (i.e., randomisation can take place before all in- and exclusion criteria are reported).

4.4 Sample size calculation

Primary outcome: post-ERCP pancreatitis

Recently, a Dutch multicentre prospective cohort study was performed, including three regional and two academic hospitals, which studied the outcomes of FCSEMS placement for preoperative biliary drainage in patients with obstructive jaundice due to a peri-ampullary or pancreatic tumour; 18.4% (9/49) of these patients developed pancreatitis [manuscript submitted].[3] The RCT by Zhou *et al*[5], including 82 patients with inoperable malignant biliary strictures, reported a pancreatitis rate of 9.8% in the sphincterotomy group and 31.7% in the group without sphincterotomy before uncovered SEMS placement. So the relative risk reduction after sphincterotomy was 69%. Based on these data the 18.4% risk of post-ERCP pancreatitis after FCSEMS placement can be reduced to 5.7%.

However, the expected effect is probably overestimated, because other observational studies have never reported such a large effect of ES.[18-20] Furthermore, 43% of patients in the trial by Zhou had hilar cholangiocarcinoma and only 26% had biliary obstruction due to pancreatic adenocarcinoma.[5] It is thought that patients with pancreatic head tumours have a lower risk of post-ERCP pancreatitis because of adaptation to the already existing chronic obstruction of the pancreatic duct by the tumour.[21, 22] Therefore, the results from this trial cannot be directly extrapolated to the Western population, where the majority of the eligible study patients will have distal biliary obstruction due to pancreatic head carcinoma. The RCT by Artifon *et al*[4] included 74 patients with distal biliary obstruction, which was caused by pancreatic adenocarcinoma in 81% of patients. No cases of pancreatitis were observed. Other large RCTs comparing covered and uncovered SEMS for malignant distal biliary obstruction, of which around 80% was caused by pancreatic cancer, reported low (≤ 2%) incidence rates of post-ERCP pancreatitis, but in those trials sphincterotomy was performed in 100% and 47% of patients.[21, 22]

To prevent this study being underpowered, we assume a 16% (instead of 18.4%) risk of post-ERCP pancreatitis after biliary FCSEMS placement and a relative risk reduction of 50% (instead of 69%). Using a chi-square test with a 0.050 two-sided significance level α, the power to detect a 50% risk reduction with a background risk of 16% will be 80% when the sample size is 518 patients, 259 patients in each group. In a multicentre setting including high volume referral hospitals, it should be feasible to include 518 patients in a time period of 2-3 years. These results assume that two sequential tests will be made using the Haybittle-Peto stopping rule with a critical p-value at the interim analysis of 0.001 in absence of alpha spending and a final critical p-value of 0.05.

Risks of endoscopic biliary sphincterotomy

A prospective multicentre cohort study in North America reported the 30-day morbidity associated with endoscopic biliary sphincterotomy in 2347 consecutive patients who were subjected to ES:[7]

- Procedure-related (directly or indirectly) mortality: 0.43%
- Overall severe complication rate: 1.6%
- Overall complication rate: 9.8%
- Pancreatitis: 5.4%
- Haemorrhage: 2.0%
- Perforation: 0.3%
- Cholangitis: 1.0%
- Cholecystitis: 0.5%
- Miscellaneous: 1.1%

The risks of an endoscopic sphincterotomy are low and probably primarily related to the clinical indication for the procedure and to procedural characteristics of the ERCP. We assume that the endoscopic sphincterotomy primarily contributes to the risk of bleeding and duodenal perforation. So should the interim safety analysis show a significant increase in these complications, then this will be discussed with the ethics committee.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Standard sphincterotomy (figure 1) requires successful retrograde cannulation of the bile duct with either wire-guided or contrast-guided technique, confirmed by injection of radiocontrast material. The biliary sphincter is then cut by means of electrocautery, with the cutting wire bowed against the roof of the papilla. Any type of regular sphincterotome can be used, according to local protocol. The endoscopic sphincterotomy should be adequate, which means giving way for further rupture of the sphincter when a stent is placed, comparable to the technique used for sphincterotomy combined with large balloon dilatation.

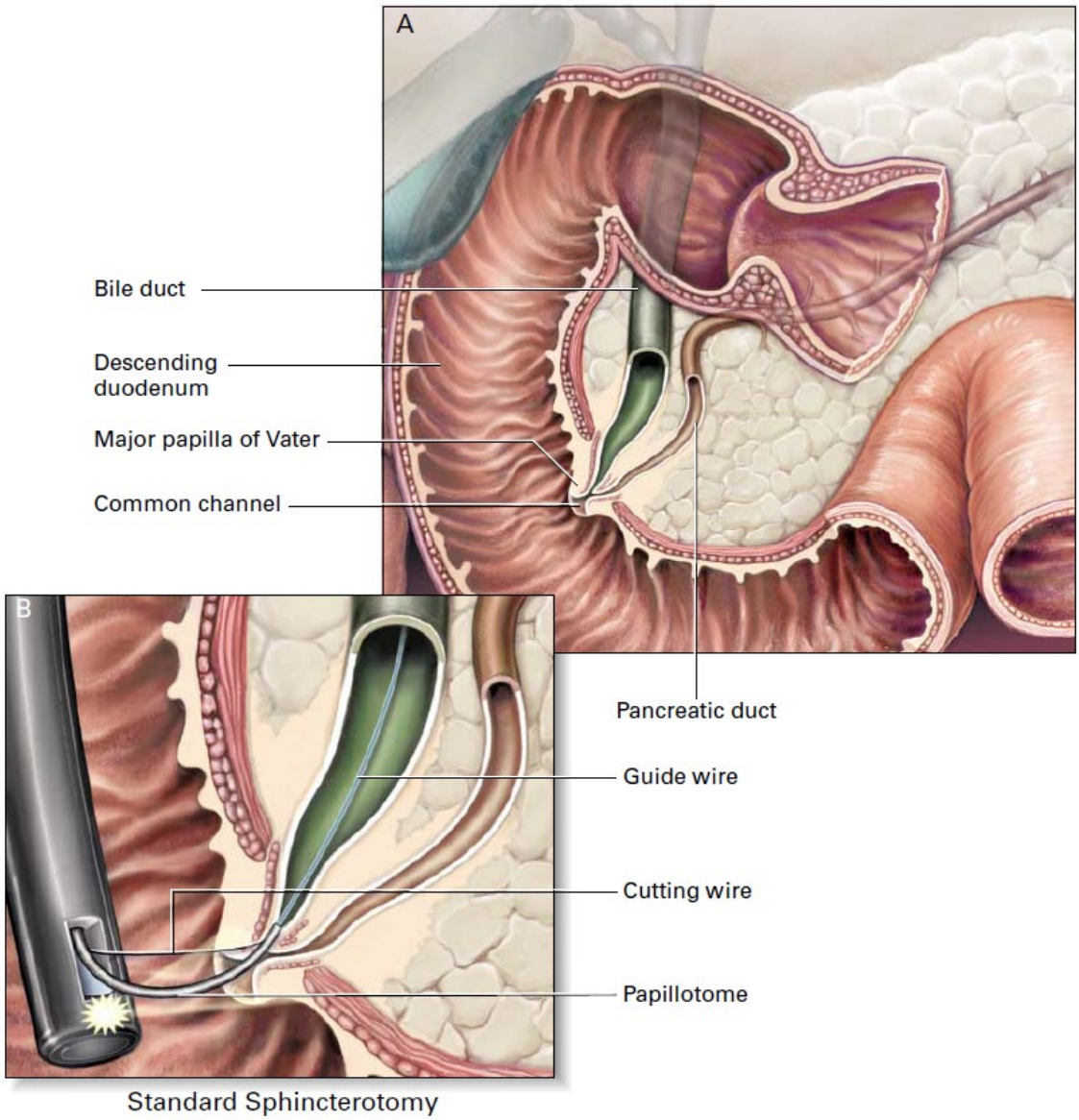


Figure 1. Endoscopic biliary sphincterotomy[7]

5.2 Use of co-intervention (if applicable)

To reduce the risk of post-ERCP pancreatitis, all patients undergoing ERCP receive a standard single dose of a nonsteroidal anti-inflammatory drug (NSAID) peri-procedure, except when NSAIDs are contra-indicated. When the endoscopist decides that a prophylactic pancreatic duct stent is indicated, the patient will be excluded from the trial.

5.3 Escape medication (if applicable)

Escape medication necessary for the management of an acute event, pain or other complaints can be used without any restrictions during the study period.

6. NON-INVESTIGATIONAL PRODUCT

6.1 Name and description of non-investigational product(s)

Fully covered self-expandable metal stents are offered by various manufacturers (Boston Scientific, Cook Medical, Gore, Taewoong Medical, M.I. Tech, etc.), but all share the following properties:

- They consist of a wire mesh of nitinol.
- They are self-expanding and flexible.
- They are covered by a polytetrafluoroethylene or silicone membrane.
- They have looped ends to minimize the risk of tissue trauma.
- They usually have anti-migration features such as flared ends or self-anchoring fins.
- The available stent diameter ranges from 6 to 10 mm.
- The available stent length ranges from 4 to 12 cm.

In this trial we will use the **fully covered Evolution Biliary Stent System** by Cook Medical, Limerick, Ireland. The stent is CE-marked and registered for the use in malignant neoplasms in the biliary tree. The following stent sizes are recommended in this study:

Body diameter (mm)	Stent flange diameter (mm)	Stent length (cm)	Delivery system diameter (Fr)	Minimum accessory channel (mm)
10	11	6	8.5	3.2
10	11	8	8.5	3.2

The merit of a single company stent design is that we exclude heterogeneity due to different stent characteristics. Furthermore, the benefit of a fully covered stent design is that in case of an indefinite diagnosis, FCSEMSs, in contrast to UCSEMSs, provide the option of subsequent stent removal if malignancy is excluded.

6.2 Summary of findings from non-clinical studies

Not applicable.

6.3 Summary of findings from clinical studies

A recently published systematic review of RCTs compared the outcomes of covered and uncovered SEMSs in 1061 patients with malignant distal biliary obstruction.[23] The stent patency rate of covered SEMSs was 81.1% (296/365) at 6 months and 57.3% (209/365) at 12 months, which was similar to the patency rates at 6 and 12 months of uncovered SEMSs (77.5% and 57.3%, respectively). Covered and uncovered SEMSs were equally

safe. The use of covered SEMSs was associated with a significantly lower rate of tumour ingrowth (OR 0.19; 95% CI 0.07-0.55), but showed significantly more tumour overgrowth (OR 1.88; 95% CI, 1.02-3.45) and stent migration (OR, 7.13; 95% CI, 2.29-22.21).[23] There were no differences in the rates of pancreatitis, cholecystitis, perforation, bleeding, or cholangitis; length of hospital stay; or number of recurrent biliary obstructions.[23]

6.4 Summary of known and potential risks and benefits

Previous meta-analyses have already shown the superiority of SEMS over plastic stents in terms of a longer stent patency and less need for reinterventions.[1, 8]

A systematic review of five RCTs that included 781 patients with unresectable distal malignant biliary obstruction, reported the following complications associated with covered SEMS placement after a median follow-up of 212 days[24]:

- Tumour ingrowth: 3.8% (15/395)
- Tumour overgrowth: 7.3% (29/395)
- Sludge formation: 5.6% (22/395)
- Stent migration: 4.0% (13/325)
- Cholecystitis: 2.4% (7/288)
- Pancreatitis: 2.6% (8/310)

A meta-analysis of RCTs, including a total of 1061 patients with malignant distal biliary obstruction, compared the patency and complication rates of covered and uncovered SEMS.[23]

Covered SEMS compared with uncovered SEMS:

- 6 month patency: 81.1% (296/365) vs. 77.5% (276/356); OR 1.82 (95% CI 0.63-5.25)
- 12 month patency: 57.3% (209/365) vs. 57.3% (204/356); OR 1.25 (95% CI 0.65-2.39)
- Recurrent biliary obstruction: OR 0.98 (95% CI 0.49-1.95)
- Stent migration: OR 7.13 (95% CI 2.29-22.21)
- Tumour ingrowth: OR 0.19 (95% CI 0.07-0.55)
- Tumour overgrowth: OR 1.88 (95% CI 1.02-3.45)
- Pancreatitis: OR 1.07 (95% CI 0.44-2.59)
- Cholecystitis: OR 1.34 (95% CI 0.48-3.77)
- Cholangitis: OR 1.07 (95% CI 0.57-2.01)
- Perforation: OR 1.84 (95% CI 0.49-6.87)
- Bleeding: OR 0.46 (95% CI 0.13-1.66)

6.5 Description and justification of route of administration and dosage

FCSEMSs for extrahepatic biliary obstruction are inserted endoscopically.

6.6 Dosages, dosage modifications and method of administration

Not applicable.

6.7 Preparation and labelling of Non Investigational Medicinal Product

The CE-approved fully covered Evolution Biliary Stent is prepared and labelled by the stent manufacturer according to the GMP guidelines.

6.8 Drug accountability

Not applicable. FCSEMSs are being used as standard care.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

Incidence of post-ERCP pancreatitis, which is defined according to the modified definition of Cotton et al: new or worsened abdominal pain, in association with a serum concentration of pancreatic enzymes (amylase or lipase) that was at least three times the upper limit of normal at more than 24 hours after the procedure, requiring hospital admission or a prolongation of planned admission.[7, 16]

7.1.2 Secondary study parameters/endpoints (if applicable)

- Technical success of stent placement; adequate positioning and release of the stent.
- 30-day morbidity related to ERCP (with or without ES):
  - Severity of pancreatitis defined according to the revised Atlanta classification[17]: mild, moderate or severe.
  - Occurrence of bleeding: clinically relevant (not just endoscopic) bleeding requiring blood transfusion, re-intervention, admission or prolongation of hospitalisation.
  - Occurrence of duodenal and retroperitoneal perforation.
- Stent-related 30-day morbidity: re-obstruction, stent migration, cholangitis, cholecystitis.
  - Cholangitis is defined as meeting both criteria 1 and 2:
    3. Temperature ≥ 38.5 °C with cold chills, **OR**
       Temperature ≥ 39 °C without cold chills
    4. Dilatation of the CBD (>8 mm ≤75 years or >10 mm >75 years), **OR**
       Progressive cholestasis for >2 days and bilirubin >40 µmol/L (2.34 mg/dL)
  - Cholecystitis is defined as: clinical and radiological signs for cholecystitis with a gallbladder wall >3 mm and/or fluid surrounding the gallbladder.
- 30-day mortality.

7.1.3 Other study parameters (if applicable)

Aetiology of the stenosis and variables that are associated with the occurrence of post-ERCP pancreatitis:

- Age, sex
- Previous (post-ERCP) pancreatitis
- Number of attempts at biliary cannulation
- Number of guidewire passages into the pancreatic duct
- Number of contrast injections into the pancreatic duct before biliary cannulation

Several ERCP-related data, such as the number of attempts to obtain biliary cannulation and the location of the stenosis (i.e., > 2 cm from the hilum), are not described in the electronic patient file. Therefore, Castor EDC serves as source documentation for these variables.

7.2 Randomisation, blinding and treatment allocation

A stratified randomisation will be performed according to participating centre to achieve approximate balance of important characteristics using a separate randomisation list for each centre. Because of the large sample size, no additional stratification will be performed for other variables affecting the incidence of post-ERCP pancreatitis, such as difficult biliary cannulation or previous plastic stent placement. These variables will be balanced by randomisation amongst the two groups, because their incidence is not rare; primary cannulation fails in approximately 10-20% of patients,[25] and also a significant (~30%) number of patients receive a plastic biliary stent before referral to a tertiary care centre.

Computer generated random numbers will be used to create randomisation lists. Randomisation sets will be prepared and sealed in consecutively numbered opaque and sealed envelopes by an independent research colleague, so the randomisation sequence will be unknown to the investigators and the patients.

Once deep biliary cannulation and subsequent cytology (if indicated) is obtained – without prior precut and when the endoscopist has no intention to place a pancreatic duct stent – the patient will be eligible for randomisation. Patients can be randomised to either group I (sphincterotomy before FCSEMS placement) or group II (FCSEMS placement without prior sphincterotomy) by opening the next sealed envelope. Allocation to treatment I or II is unblinded for both the observer and the patient.

7.3 Study procedures

- Patients with extrahepatic biliary obstruction, who are a candidate for FCSEMS placement, will be identified by their treating physicians.
- Eligible patients will be informed about the study during their visit at the outpatient clinic or by telephone. They will receive the patient information folder at the outpatient clinic or by (e)mail.
- Signed informed consent will be obtained before the scheduled ERCP.
- After informed consent is obtained, patients will be randomly allocated during the ERCP to treatment I (ES) or II (no ES) by opening a sealed randomisation envelope.
- The randomisation envelope is opened after obtaining biliary access and subsequent cytology (if indicated), without prior precut and when the endoscopist has no intention to place a pancreatic duct stent.
- To prevent post-ERCP pancreatitis, all patients undergoing ERCP receive a standard single dose of a NSAID peri-procedure, except when NSAIDs are contra-indicated, which is a standard of care.

- Patients undergoing ERCP will be sedated according to local protocol.
- Antibiotic prophylaxis will be given according to local protocol.
- Patients randomised to group I will undergo biliary FCSEMS placement after endoscopic biliary sphincterotomy.
- Patients randomised to group II will undergo biliary FCSEMS placement without prior sphincterotomy.
- In treatment group I endoscopic biliary sphincterotomy will be performed according to local protocol. The sphincterotomy should be adequate, which means giving way for further rupture of the sphincter when a stent is placed, comparable to the technique used for sphincterotomy combined with large balloon dilatation.
- The 10 mm diameter fully covered Evolution Biliary Stent (Cook Medical) will be used.
- Based on the characteristics of the stenosis, the endoscopist will decide on the optimal length (preferably 6 cm or 8 cm) of the FCSEMS.
- The patient will be discharged after the procedure according to local policy.
- e-CRFs will be completed at baseline, 5-7 days after the procedure and 28-30 days after the procedure. Follow-up consists of a short telephone call or, if available will be retrieved from the patients electronic record.
- To obtain insight in the population that will not be randomised, eCRFs shall be completed up to and including the treatment details during ERCP (page 4 of the CRF) for patients who are not randomised during the baseline ERCP.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time, and for any reason, if they wish to do so, without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.4.1 Specific criteria for withdrawal (if applicable)

Not applicable.

7.5 Replacement of individual subjects after withdrawal

After withdrawal, patients will be replaced by new subjects in order to achieve the calculated sample size.

7.6 Follow-up of subjects withdrawn from treatment

Patients not participating in the study will not be followed-up.

7.7 Premature termination of the study

An interim safety analysis will be performed by the Data Safety Monitoring Board (DSMB) when 50% (n=259) of the 518 patients are included in the trial (chapter 9.4). If the DSMB reports a safety issue, this will be submitted to the medical research ethics committee (MREC). Any advice from the MREC on premature termination of the study for safety reasons will be followed.

The following **stopping regulations** are being applied (see DSMB charter):
The trial will be terminated if there is a statistically significant higher rate of bleeding and/or perforation in the intervention group using Fisher's Exact Test without a clinically relevant reduction in the post-ERCP pancreatitis rate. This balance is a clinical interpretation and will be evaluated by the DSMB.
In absence of a safety issue, the DSMB may still advise premature termination of the study for reasons of efficacy or futility. The Haybittle-Peto rule will be applied at the interim analysis for efficacy, meaning that statistical significance will be assessed at a critical p-value of 0.001 in absence of alpha spending. The trial will be discontinued for futility if 25% of patients in the intervention group develops post-ERCP pancreatitis, which corresponds to a projected expected value of the final test statistic Z of -3.16 and to a conditional power of 0%, assuming a 16% post-ERCP pancreatitis rate in the control group and continuation of the observed trend at the interim analysis. If instead we assume the trend in the second half of the study population to be in accordance with the alternative hypothesis of a 50% reduction in post-ERCP pancreatitis rate, then the conditional power (or probability of observing a statistically significant result in favor of the intervention group) will still remain below 10%.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator will be recorded.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

All SAEs will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the coordinating investigator has first knowledge of the serious adverse events. Local investigators will report SAEs to the coordinating investigator in the AMC as soon as possible after having taken knowledge of a SAE. In case of an elective hospitalisation (i.e., in case of elective surgery, administration of chemotherapy, elective hospitalisation after ERCP), this will not be assessed as a SAE.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report.

8.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

8.4 Data Safety Monitoring Board (DSMB)

A DSMB will be established to perform an interim safety analysis. The committee will consist of independent members, including two clinical experts and a biostatistician, without any conflict of interest related to the study outcomes.

Because an endoscopic sphincterotomy during ERCP is a low risk procedure that is already being performed at the discretion of the endoscopist, the interim safety analysis will be performed by the DSMB when 50% (n=259) of the 518 patients are included in the trial (chapter 9.4). The primary focus of the safety analysis is the occurrence of ES-related bleeding or perforation. The stopping regulations are described in section 7.7.

The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

Further description of the tasks and responsibility of the DSMB is provided in the DSMB charter.

9. STATISTICAL ANALYSIS

9.1 Primary study parameter(s)

The post-ERCP pancreatitis rate in the ES group will be compared to the rate in the non-ES group using Fisher's exact test.

9.2 Secondary study parameter(s)

Comparison between the two treatment groups with regard to 30-day complication rate, technical success rate of FCSEMS placement and 30-day mortality rate will be made using Fisher's exact test.

9.3 Other study parameters

Aetiology of the stenosis, female gender, a history of (post-ERCP) pancreatitis, number of attempts for biliary cannulation, time (in minutes) to biliary cannulation, number of guidewire passages into the pancreatic duct and contrast injection into the pancreatic duct before biliary cannulation will be recorded and assessed as potential confounders.

9.4 Interim analysis (if applicable)

An interim safety analysis will be performed by the DSMB when 50% (n=259) of the 518 patients are included in the trial. The primary focus of the safety analysis is the occurrence of ES-related bleeding or perforation. Because the incidence of bleeds and perforations is expected to be low, a statistical test will be insufficient to detect a statically significant difference between both treatment groups. Therefore, the interim safety analysis consists of a clinical interpretation by the DSMB.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (64th version, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and with the ICH guidelines for Good Clinical Practice.

10.2 Recruitment and consent

Patients with extrahepatic biliary obstruction, who are a candidate for FCSEMS placement, will be identified by their treating physicians. Eligible patients will be informed about the study by their treating physician or the local research coordinator during their visit at the outpatient clinic or by telephone. They will receive the patient information folder at the outpatient clinic or by (e)mail. In this way they will have at least 24 hours to consider participation in the study before undergoing the procedure. A small proportion of patients who present with an acute cholangitis will have an emergency procedure within 24 hours, so only these patients will be asked to consider participation within a timeframe of less than 24 hours. Informed consent will be signed before the scheduled stent placement procedure.

10.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

10.4 Benefits and risks assessment, group relatedness

All patients are consented for ERCP, and for the study, and informed about the complications associated with an ERCP: abdominal pain, bleeding, post-ERCP pancreatitis and perforation (consent for ERCP). The main risks of ES are haemorrhage (2.0%) and perforation (0.3%).[7] In daily practice, whether or not the patient will be subjected to a sphincterotomy depends on the endoscopist's preference. Therefore, the study does not introduce an additional risk for the participant.

The presumed benefit of an ES is a reduction in the post-ERCP pancreatitis rate after biliary SEMS placement, but ES may be accompanied by an increased risk of bleeding and perforation. Therefore, a change in the distribution of complications could be anticipated.

The burden for patients participating in this trial is small, with only two short telephone calls seven and thirty days after the procedure to evaluate possible procedure-related complications.

10.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.6 Incentives (if applicable)

None.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

Patient data will be collected at baseline, 5-7 and 28-30 days after the procedure. The data will be handled anonymously and entered into electronic case report forms (e-CRFs) using Castor EDC. Patients will be coded according to the site and number of inclusion. Therefore, the local investigator keeps a subject identification code list to link the data of the subject. Initials and date of birth will not be collected to prevent that the data in the e-CRF can be linked to the subject. The e-CRFs are completed at 30 days and are stored in Castor EDC. Standard operating procedures will be followed for database management, data verification, and data archiving and retention. The data will be stored for 15 years.

11.2 Monitoring and Quality Assurance

The study will be conducted after careful instructions to the local coordinating investigator on the study procedures, in person or by phone. No additional monitoring will take place.

11.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

11.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.6 Public disclosure and publication policy

The results of this trial, regardless if these are positive or negative, will be submitted for publication to a peer-reviewed scientific journal. The first and second authorship will be assigned to the coordinating investigators E.E. van Halsema and N. Bekkali. The last author will be the principal investigator (J.E. van Hooft). The remaining order of authorship will be decided by number of inclusions per centre. At least 5 patients should be included to earn an authorship and at least 25 patients to have two authorships. A third authorship can be obtained when the patient accrual rate is substantially higher in comparison with the others.

- < 5 patients = acknowledgement
- 5-24 patients = 1 authorship
- 25 or more patients = 2 authorships

The Academic Medical Centre, Amsterdam, the Netherlands, may include an additional three authorships for designing, coordinating and leading the trial.

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

Not applicable.

12.2 Synthesis

Not applicable

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