Supplementary Online Content

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Supplement 1. Trial protocol

This supplementary material has been provided by the authors to give readers additional information about their work.

Trial Number:	NTR3593	
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1 INTRODUCTION

Idiopathic achalasia is a rare motility disorder of the oesophagus with an annual incidence rate of 1 per 100,000 persons.[1] Achalasia is characterised by aperistalsis of the oesophageal body and dysrelaxation of the lower oesophageal sphincter caused by progressive destruction and degeneration of the neurons in the myenteric plexus. This leads to subsequent retention of food and saliva in the oesophagus, resulting in the typical symptoms of achalasia such as dysphagia, chest pain, regurgitation of undigested food and weight loss. At the long term, incomplete oesophageal emptying and reflux result in an increased risk for development of squamous cell carcinoma of the oesophagus.[1,2] The cause of the neuronal degeneration found in achalasia is unknown.[3]

Treatment of achalasia is focused on symptom relief, which is obtained by destroying the occluding function of the spastic lower oesophageal sphincter. Usually, the first step is endoscopic dilation of the lower oesophageal sphincter using a pneumatic balloon.[4,5] However, a disadvantage of this treatment is the high chance of symptom recurrence which requires subsequent treatment sessions. Also, approximately 3% of the endoscopic pneumodilations (PD) is complicated by a perforation, which is a potentially life-threatening situation.[6] When symptoms recur after endoscopic balloon dilation a surgical myotomy can be considered. During a surgical myotomy the circular muscle fibers of the lower oesophageal sphincter are cut laparoscopically and this results in a lower recurrence rate than pneumodilation.[7] However, this technique can also be associated with severe complications, is more invasive and is more expensive as it involves laparoscopic instrumentarium. Currently, endoscopic pneumodilation is the first choice of treatment in patients with achalasia and surgical myotomy is generally performed in case of symptom recurrence after initial pneumodilation.

Recently, per-oral endoscopic myotomy (POEM) has been introduced as an alternative to surgical myotomy.[8] The POEM technique is entirely endoscopic and is performed under total anesthesia at the endoscopy suite. Using an endoscopic knife, an entry to the submucosal space is made in the oesophagus and after creating a submucosal tunnel towards the lower oesophageal sphincter the circular muscle layers are cut. At the end of the procedure the mucosal opening is closed with clips. In our centre we have now treated more than 10 patients successfully with POEM and we were able to confirm the positive findings in symptom improvement and lower oesophageal sphincter pressure reduction reported by the German and Japanese pioneers of the technique.[8,9]

2 HYPOTHESIS

We hypothesize that POEM has a higher long-term efficacy than PD in treatment of therapy-naive patients with idiopathic achalasia.

3 AIM

To compare the efficacy of POEM to the efficacy of PD as the initial treatment of symptomatic idiopathic achalasia.

4 STUDY DESIGN

This is a multi-centre randomised clinical trial in which a new treatment (POEM) will be compared to the gold standard (PD). The primary endpoint will be measured at two years after treatment and follow up will be extended up to five years.

5 PRIMARY OUTCOME

- Treatment success, defined as:
  - An Eckardt score of 3 or less
  - The absence of the need for endoscopic or surgical retreatment in the period between the first treatment session (first and optional second dilation within first 3 months) and the endpoint
  - The absence of severe complications associated with treatment.

6 SECONDARY OUTCOMES

- Quality of life and achalasia-specific quality of life
- Stasis in the oesophagus, measured with a timed barium oesophagogram
- Presence of reflux symptoms, reflux oesophagitis and excessive oesophageal acid exposure
- Lower oesophageal sphincter pressure and integrative relaxation pressure (IRP4), as measured with high-resolution manometry
- Complications of the treatment, defined as any unwanted events that arise following treatment and/or that are secondary to the treatment. Complications are classified as “severe” when these result in admission > 24 hours or prolongation of an already planned admission of >24 hours, admission to a medium or

intensive care unit, additional endoscopic procedures, or blood transfusion or death. Other complications are classified as “mild”.

- The need for endoscopic or surgical retreatment after the initial treatment session

7 POPULATION

7.1 *Subjects*

Adult patients with symptomatic idiopathic achalasia that have not undergone endoscopic or surgical treatment for achalasia before.

7.2 *Inclusion criteria:*

- Presence of achalasia, as shown on oesophageal manometry
- Eckardt score > 3
- Age between 18-80 years
- Signed written informed consent
- ASA class I or II

7.3 *Exclusion criteria*

- Previous endoscopic or surgical treatment for achalasia, except botulinium toxin injections
- Previous surgery of the stomach or oesophagus
- Known coagulopathy
- Presence of liver cirrhosis and/or oesophageal varices
- Presence of eosinophilic oesophagitis
- Presence of Barrett’s oesophagus
- Pregnancy at time of treatment
- Presence of a stricture of the oesophagus
- Presence of malignant or premalignant oesophageal lesions
- Presence of an extensive, tortuous dilated oesophageal body (S-shape)
- Presence of a diverticula in the distal oesophagus

8 METHODS

8.1 *Study protocol*

Study enrolment and randomisation

In the AMC, patients will be approached that visit the outpatient clinic of the Motility centre of the Gastroenterology department. Patients should be diagnosed with achalasia by manometry using the predefined manometric criteria and have not undergo surgical or endoscopic treatment for achalasia before. Eligible patients will be given a verbal explanation of the study. Each patient will receive a patient information brochure about the study and an informed consent form for participation. Patients will be given sufficient time to read the information and ask questions. Before any study procedures or randomisation are initiated the patient must sign the informed consent form.

There is no time frame for the randomisation. When participants are recruited for the study the time to consider participation in the study is unlimited. Before randomisation the patient must have signed the informed consent form. Randomisation will be done using a web-based program and is stratified for each centre, so that the number of patients treated with POEM or pneumatic dilation is similar for each centre. The randomisation for the two treatments will be 1:1.

Baseline

At baseline, patients will undergo oesophageal manometry, timed barium oesophagography and upper endoscopy. A venous blood withdrawal is performed to screen for abnormalities in blood count, chemistry lab and clotting. If any of these tests have been performed within the last 6 months and of high quality (at the discretion of the investigator) it is not required to repeat this. Questionnaires regarding symptoms and quality of life (see 8.4) are filled in by the patients.

General follow up

Patients that are randomised to endoscopic balloon dilation will be asked to fill in an Eckardt score three weeks after the dilation. If this score is still more than 3, they will be scheduled to undergo a second pneumatic dilation, but now using a 35 mm balloon (figure 1). Manometry is performed if the Eckardt score is 3 or less. If the manometry

shows an IRP of more than 10, patients will also undergo a second pneumatic dilation (with a 35 mm balloon).

Manometry and timed barium oesophagography are performed and questionnaires are filled in all patients 3 months after treatment and at 1, 2 and 5 years after treatment. Twenty-four hour pH-impedance monitoring is performed one year after treatment to evaluate oesophageal acid exposure. Upper endoscopy is performed at 1, 2 and 5 years after treatment.

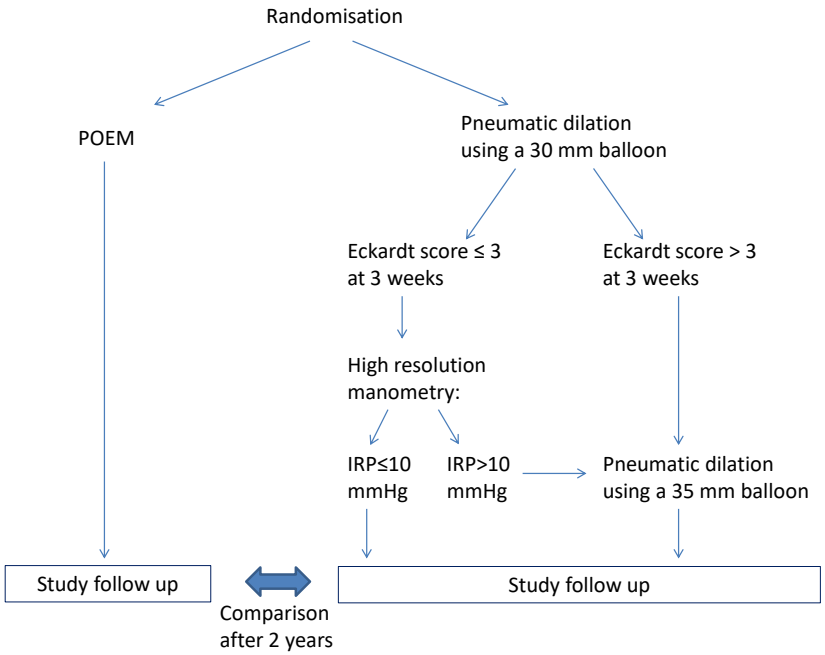

Figure 1 Treatment algorithm used in this study

	Baseline	3 weeks*	3 months	1 year	2 years	5 years
Blood count, chemistry, clotting	X					
Questionnaires	X	Eckardt*	X	X	X	X
Timed barium oesophagography	X		X	X	X	X
Manometry	X	If Eckardt >3*	X	X	X	X
Upper endoscopy	X			X	X	X
pH-impedance monitoring				X		

*Table 1 Schedule of baseline and follow-up examinations; * only for patients randomised to balloon dilation*

8.2 *Pneumodilation (PD)*

In this study pneumodilation will only be performed by experienced endoscopists, that have performed over 20 pneumodilation procedures. Patients are asked to use clear fluids only starting 24 hours before the procedure and nil per mouth starting 8 hours before the procedure. Under fluoroscopic guidance a Rigiflex balloon (Boston Scientific) is positioned at the esophagogastric junction and dilated at a pressure of 5 PSI, followed by dilation with 8 PSI for one minute (Figure 2).[8,10] The initial pneumatic dilation is performed using a 30-mm balloon. Three weeks later the symptoms of patients are evaluated using the Eckardt score. If the Eckardt score is still higher than 3, a subsequent dilation with a 35-mm balloon is scheduled. If the Eckardt score is less than 3 a subsequent high-resolution manometry is scheduled. If this shows an integrative relaxation pressure (IRP4) of more than 10 mmHg, a subsequent dilation with a 35-mm balloon is scheduled as well. In total, patients will thus undergo one or two pneumatic dilations in the first 6 weeks. A second dilation within this 6 week period is not considered a failure but considered part of the regular treatment. PPI are taken orally in a single daily dose for two weeks after each dilation.

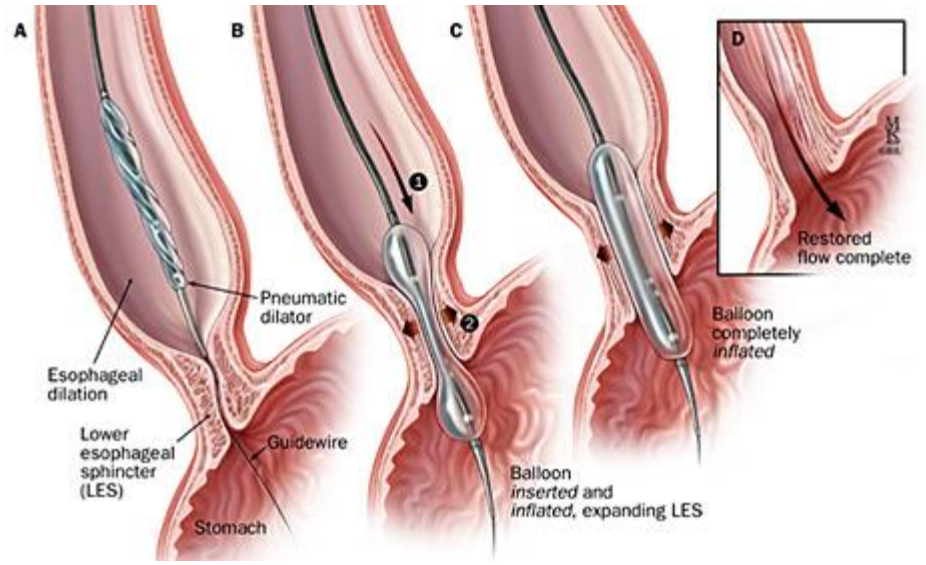

Figure 2 Schematic outline of a pneumatic balloon dilation

8.3 *Per-oral endoscopic myotomy (POEM)*

In this study POEM will only be performed by experienced endoscopists, that have performed over 10 POEM procedures. Patients are admitted two hours prior to the POEM procedure and are discharged the next day. Patients are asked to use a diet with clear fluids starting 24 hours before the procedure and nil per mouth starting 8 hours before the procedure. On the day of the procedure, antibiotics and double dose PPI (proton pump inhibitor) are administered intravenously. A PPI will be taken orally for two weeks in a single daily dose starting at the day of treatment. POEM is performed under general anesthesia and with endotracheal intubation. The mouth, throat and esophagus are rinsed with saline and chlorhexidine (40–60 ml). POEM procedures are then performed as described by Inoue et al. (figure 3).[8]

A forward-viewing upper endoscope (GIF H180J; Olympus, Hamburg, Germany) is used with a transparent distal cap (MH 588; Olympus). Carbon dioxide gas is used for insufflation during the procedures. An endoscopic dissection knife (KD-640L TriangleTipKnife; Olympus) is used to access the submucosa, to create the submucosal tunnel, and also to divide circular muscle fibers over a minimum length of 6 cm in the esophagus, and 2 cm onto the cardia according to the standards of surgical myotomy. An electrogenerator (Erbe Vio 300D; Erbe Elektromedizin, Tübingen, Germany) is used

with Endocut Q mode (effect 2) to open the mucosa, and spray coagulation mode (effect 2, 50 watt) to dissect the submucosa and divide the muscle fibers. A coagulating forceps (FD-410LR Coagrasper; Olympus) is used for hemostasis as needed. Closure of the mucosal entry site is performed using standard endoscopic clips (HX-110UR EZ Clip Reusable Rotatable Clip Fixing Device and HX-610-135L Single Use Clips; Olympus).

On the next day postoperative fluoroscopy is performed to rule out a leak at the esophageal closure site before discharge. Patients are kept nil per mouth until after the fluoroscopy and are kept on a liquid diet for an additional 24 h. Patients are discharged with single dose PPI and a soft diet for 2 weeks.

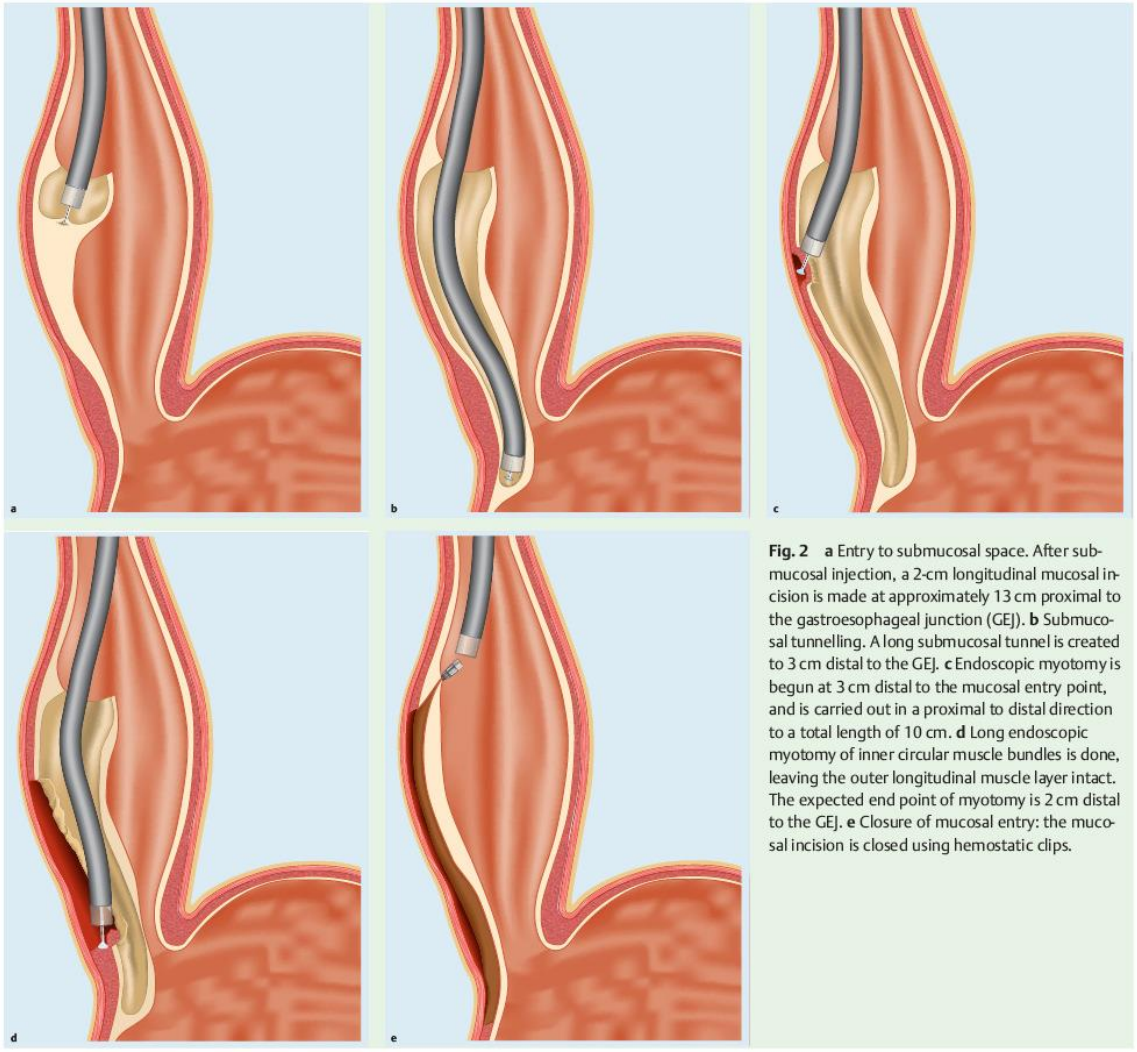

Fig. 2 **a** Entry to submucosal space. After submucosal injection, a 2-cm longitudinal mucosal incision is made at approximately 13 cm proximal to the gastroesophageal junction (GEJ). **b** Submucosal tunnelling. A long submucosal tunnel is created to 3 cm distal to the GEJ. **c** Endoscopic myotomy is begun at 3 cm distal to the mucosal entry point, and is carried out in a proximal to distal direction to a total length of 10 cm. **d** Long endoscopic myotomy of inner circular muscle bundles is done, leaving the outer longitudinal muscle layer intact. The expected end point of myotomy is 2 cm distal to the GEJ. **e** Closure of mucosal entry: the mucosal incision is closed using hemostatic clips.

Figure 3 Schematic outline of the POEM procedure [11]

8.3.1 *Risk of complications in POEM from recent clinical studies*

So far there is limited information about the complications related to the POEM procedure because it is a relative new procedure and long-term follow-up is not yet available. Serious adverse events are not described in the previous studies that performed POEM. The main preoperative complications that are described are subcutaneous emphysema, pneumoperitoneum and pneumothorax. Transmural openings into the mediastinum and into the peritoneal cavity caused emphysema, pneumoperitoneum and pneumothorax. During POEM the inner circular muscle layer is separated from the outer longitudinal muscle layer, leaving the longitudinal muscles intact.[9] The longitudinal muscle fibers are extremely thin, so minor damage can lead to transmural dissections into the mediastinum and peritoneal cavity.

Subcutaneous emphysema was treated conservatively and in all cases the emphysema resolved spontaneously in 2-3 days after surgery. The treatment of the pneumoperitoneum occurred in all patients during the operation. A needle or canula of 18G was placed in the abdominal wall which gave directly relieve.[8,9] A pneumothorax was a rare complication and in all cases thoracic drainage was administered during the operation which gave immediately relieve. Other described rare complications preoperatively were a minor bleeding, controlled by endoscopic coagulation, and small perforations which were clipped.

Postoperative complications were rare. One article described pneumothorax as an important postoperatively complication.[12] The treatment was in most patients conservatively and in some patients a thoracic drainage was administered, dependent on the lung compression volume. An uncommon postoperative complication was a delayed hemorrhage, one day after the operation. This occurred in one patient and was probably caused by a bleeding in the submucosal tunnel. A three-cavity tube was placed by endoscopy into the stomach and lower part of the esophagus to compress the bleeding. After four days the tube was removed without further complications. Another rare complication was a superficial ulcer (Forrest III) at the cardia that was detected with a control endoscopy two days after POEM. This was only seen in one patient. The patient had to continue PPIs and the hospital stay was extended. The control endoscopy 7 days after the procedure showed healing of the ulcer.

The average follow-up after the procedure described in the different articles was 3-5 months. No serious complications were observed during this follow-up period. Furthermore none of the patients developed recurrent symptoms and symptoms of gastro-esophageal reflux or reflux esophagitis were minimal.

8.3.2 *Risk of complications in POEM in the first treated patients of the AMC*

In the AMC the POEM procedure is performed in more than 10 patients. There were no serious adverse events (SAEs) preoperative or postoperative. Preoperative two adverse events occurred in different patients. In one patient a minor bleeding occurred during the cutting of the circular muscle layer which was easily controlled by endoscopic coagulation. To be certain that the patient didn't develop a rebleed, the patient stayed longer at the recovery for close monitoring. Another adverse event that occurred during the procedure was a pneumoperitoneum due to small transmural dissections into the mediastinum. The pneumoperitoneum caused a temporary elevation of intraperitoneal pressure which was relieved with an 18G canula, placed in the abdominal wall during the procedure. The adverse events didn't extend the hospital admission and reintervention was not needed.

Postoperative complications didn't occur. At this moment the follow-up period of the treated patients is 1-6 months. None of the treated patients developed recurrent symptoms so far and also gastro-esophageal reflux symptoms aren't registered.

8.4 *Questionnaires*

- Eckardt score, which is the sum of symptom scores for dysphagia, regurgitation, chest pain and weight loss. Each symptom is scored from 0 to 3. The minimum score is 0, the maximum 12. (see appendix A for explanation of the calculation of the score)
- Medical Outcomes Study 36-Item Short-Form Health Survey [SF-36], The SF-36 mental and physical summary scores (which range from 0 to 100, with higher scores indicating better well-being) measure general aspects of health quality of life (12).

- The validated Achalasia Disease-Specific Quality-of-Life questionnaire (achalasia-DSQoL).[13]
- The Gastroesophageal Reflux Disease Questionnaire (GerdQ) is a self-assessment questionnaire that can be used for the diagnosis and follow-up of gastroesophageal reflux disease, and measures both symptoms and impact of symptoms on person's daily life

8.5 *Timed barium oesophagography*

In the timed barium oesophagography technique, upright frontal spot films of the esophagus are obtained at 1, 2, and 5 min after ingestion of 100-200 ml of low-density (45% weight in volume) barium sulphate (volume of barium determined by patient tolerance).[14] This is a routine clinical test that is used to measure oesophageal emptying and reflects oesophageal function.

8.6 *High resolution manometry of the oesophagus*

High resolution manometry of the oesophagus (pressure measurement) is the gold standard to diagnose achalasia and is used in clinical practice to evaluate the effect of the treatment. High resolution manometry is performed using a catheter that is introduced into the oesophagus transnasally. Patients will swallow 10 small sips of 5 mL of water and presence of peristalsis, spasms and lower oesophageal sphincter pressure and relaxation during swallowing are evaluated. Classification of achalasia will be done using the revised Chicago classification.[15] In routine clinical practise oesophageal manometry is often performed in patients with achalasia.

8.7 *Impedance-pH recording*

It is known that patients that underwent pneumodilation or myotomy are prone to develop gastro-oesophageal reflux disease and often have a high oesophageal acid exposure time.[16] Twenty-four hour impedance-pH recording is performed to assess the degree of oesophageal acid exposure. During the test, a small catheter is introduced transnasally into the oesophagus.[17] This catheter consists of impedance and pH sensors that measure reflux episodes and 24 hour data is stored on a datalogger which patients carry on their belt. Measurements are performed after cessation of acid-suppressive

medication for at least 7 days. Measurements are analyzed for acid exposure time (time with pH<4), number of acid and number of weakly acid reflux episodes and duration of reflux episodes.In the analysis of the pH sginals, episodes with pH < 4 caused by stasis-associated acidification of oesophageal contents will be discarded. Impedance-pH monitoring is a routine clinical test for assessment of oesophageal acid exposure.

8.8 *Upper endoscopy*

The main reason to perform upper endoscopy at baseline is to exclude pseudoachalasia and other causes of dysphagia. After treatment, the main reason to perform upper endoscopy is to investigate whether oesophagitis is present. The degree of oesophagitis is scored according to the LA classification.[18] Upper endoscopy is performed after cessation of acid-suppressive medication for at least 10 days. Upper endoscopy is performed according to the local routine protocol, sedation with midazolam and/or fentanyl is possible if patient prefers this. It is routine clinical practise to perform regular upper endoscopies in patients with achalasia.

8.9 *Withdrawal of individual subjects*

Participants can leave the study at any time 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.

8.9 *Premature termination of the study*

Efficacy data of the study will be monitored by the investigators, mainly by the PI, in cooperation with the DSMB. The study can be early terminated because of clear benefit, harm or futility. Because the first results of the POEM in the AMC and other foreign centres are promising, symptom improvement and lower oesophageal sphincter pressure reduction are comparable to the current two treatments, it is not likely this study will be terminated prematurely. However the aim of this study is to look at the efficacy of POEM versus PD and therefore we need to define stopping regulations for the study of the primary endpoint, treatment success.

The stopping regulation will only be based on the occurrence of severe complications, SAEs, associated with the treatment and re-intervention postoperative. After each

inclusion of 20 participants the study team and the DSMB will discuss the data and review the stopping regulations.The incidence of SAEs in pneumodilation is normally around the 5%. Because POEM is a new procedure at the moment the incidence of SAEs is unknown. One of the stopping regulations concern SAEs and states that the incidence of SAE's in both groups shouldn't exceed 10%. The other stopping regulation is if the incidence of re-intervention exceeds 20%, 1 year postoperative. This is applicable for both treatments. For pneumodilation the incidence for re-intervention is estimated on 10%, 1 year postoperative.

9 SAFETY

9.1 *Section 10 WMO event*

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

9.2 *Adverse and serious adverse events*

Pneumodilation is a safe and regularly performed procedure for patients with achalasia. In this study the procedure will be performed by experienced endoscopists, that have performed over 20 pneumodilations. Complications due to a pneumodilation are rare and the main complication is an oesophageal perforation. The treatment of a perforation is frequently conservatively, total restriction of food and drinks and intravenous antibiotic therapy. In some cases surgery is needed. The incidence of a perforation during pneumodilation is approximately 3%.[6]

POEM is a relative new procedure in the treatment of achalasia. In Germany and Japan the first POEM procedures were performed and in the AMC so far 10 patients are treated with POEM. Because the follow-up of the first patients is only 3-5 months, nothing is known about long-term complications or efficacy. Major complications that can occur during the procedure are a bleeding or oesophageal perforation. Treatment can directly be performed during the procedure by clipping the bleeding or perforation. In

some cases a surgical procedure can be needed. Furthermore POEM can be complicated by minor complications, like pneumoperitoneum and postoperative subcutaneous emphysema. Pneumoperitoneum can be relieved by a puncture of the abdominal wall using an 18-gauge needle during the procedure. Postoperative subcutaneous emphysema is usually self-limiting and additional treatment is not needed. So far the only complications that occurred in the treated patients of the AMC were a minor bleeding that was stopped during the procedure and one patient developed a pneumoperitoneum which relieved by a puncture of the abdominal wall using an 18-gauge needle during the procedure.
All the additional measurements that are performed before and after treatment are safe procedures and routinely performed in the clinical setting. Possible complications are mainly due to placement of the catheters and endoscope. The catheters can give discomfort in the nose and pharynx. Furthermore in rare cases a mucosal bleeding of the nose, caused by the catheter, can occur which never need extra treatment. The endoscope can give discomfort in the pharynx.

All adverse events reported spontaneously by the subject or observed by the investigators will be recorded in a database. The Data Safety Monitoring Board will be informed about the adverse events.

All serious adverse events (SAEs) will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol. The SAEs will be reported within 15 days after the sponsor is first notified of the SAEs.
The SAEs that result in death or are life treating will be reported expedited through the web portal *ToetsingOnline* to the accredited METC that approved the protocol. This will not occur later than 7 days after the coordinating investigators and principal investigator have knowledge of the SAE(s). This first report is preliminary and within 8 days after submission of the first report a final report will be submitted.

9.3 *Follow-up of adverse events*

All adverse events 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 another medical specialist. Furthermore a Data Safety Monitoring Board will be informed about the adverse events that occur.

9.4 *Data Safety Monitoring Board (see also the DSMB charter)*

A Data Safety Monitoring Board (DSMB) is established. In total the DSMB will consist of four members, an epidemiologist, a surgeon, a paediatrician specialised in gastroenterology and a gastroenterologist. None of the members have a conflict of interest with the sponsor of the study. Personal details of the DSMB members can be found in the DSMB charter which also describes in detail the function, aims and responsibilities of the DSMB. In short the DSMB will act in an independent, expert and advisory capacity to monitor participant safety and evaluate the efficacy and the overall conduct of the study. The DSMB will be informed about adverse events and serious adverse events that occur during the study. The advice(s) of the DSMB, in case it influences the set-up of the study, will be notified upon receipt by the sponsor to the METC that approved the protocol. With this notification a statement will be included indicating whether the advice will be followed.

10 STATISTICAL ANALYSIS AND RANDOMISATION

We aim to perform an intention to treat analysis. After testing for normality, pairwise comparisons will be performed between the two treatment arms for all primary and secondary outcomes. Categorical variables will be compared using the Chi-square test. The success rates of the two treatment arms will be compared using log-rank tests on Kaplan-Meier estimates.

Randomisation will be done using a web-based online available program and is stratified for each participating centre.

11 SAMPLE SIZE ANALYSIS

Recently reported complication free success rate of a two step PD strategy is 68% at two years.[6] Long term outcome data of POEM is lacking but at three months a success rate of 94% has been described.[9] Assuming success rates of 70% for PD and 90% for POEM after two years, we estimated that with 62 patients in each group, the study would have 80% power to detect a significant difference in success rate between PD and

POEM with a two-sided alpha level of 0.05. To cope with an estimated 5% loss to follow-up, we aim to enrol 130 patients.

12 PRIVACY

The data of the subjects are coded in order of participation. The code and the data are stored in different locations. The code can only be seen by the investigators. Qualified authorities can get insight in code and data, but only when accompanied by the investigators. Data will be stored 20 years after closure of the trial.

13 ETHICAL CONSIDERATION

The protocol of this study will be submitted to the Medical Ethical Committee of the Academic Medical Center and will not start before formal approval has been granted. Participants will be given oral and written explanation about the study, before they give written informed consent. Subjects are allowed to withdraw informed consent without providing arguments.

The study will be registered at ClinicalTrials.gov and the results will be published in a peer-reviewed scientific journal.

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15 APPENDIX A

Calculation of the Eckardt score

Each patient has to answer four questions that concern different symptoms. Per symptom they have to mark the degree of severity of the specific symptom. Each symptom is scored from 0-3 and the Eckardt score is the sum of symptom scores. The minimum score is 0 and the maximum score is 12. A high Eckardt score indicates severe complaints due to achalasia.

Score	**0**	**1**	**2**	**3**
Questions/Symptoms				
Dysphagia (difficulty or pain during swallowing)	No **(0)**	Occasionally **(1)**	Daily **(2)**	At each meal **(3)**
Regurgitation (food is coming back in to the mouth)	No **(0)**	Occasionally **(1)**	Daily **(2)**	At each meal **(3)**
Chest pain	No **(0)**	Occasionally **(1)**	Daily **(2)**	At each meal **(3)**
Weight loss	0 kg **(0)**	0-5 Kg **(1)**	5-10 kg **(2)**	> 10 kg **(3)**

16 ADDENDUM

Treatment failure in the POEMA Trial

Description of treatment failure

Study subjects are considered treatment failures in case the **Eckardt score is > 3 within the first 2 years of follow-up, retreatment is indicated or a treatment related SAE occured** after the initial treatment. This means that the study subjects did not achieve the primary endpoint, 2 years after the initial treatment, due to recurrent symptoms.

The vast majority of failed study subjects will need retreatment and the indication for retreatment should be based on the symptoms of the subject (Eckardt > 3) in combination with:

- Considerable LES pressure or IRP (> 10mmHg) on HRM.
- Significant stasis on timed barium esophagogram.
- Clinical judgement and expert opinion of the treating physician.

Treatment of treatment failures *(see algorithm below)*

POEM procedure

Study subjects failed on POEM will be retreated with pneumodilation. The first step is to perform a pneumodilation with a 30 mm rigiflex balloon in a single session. The effect of the pneumodilation should be evaluated by the Eckardt score. In case the Eckardt is >3 a new pneumodilation should be scheduled with one step larger balloon size. There is no limit to the number of pneumodilations that can be performed after a failed POEM.

Pneumodilation with 30 and 35 mm balloon

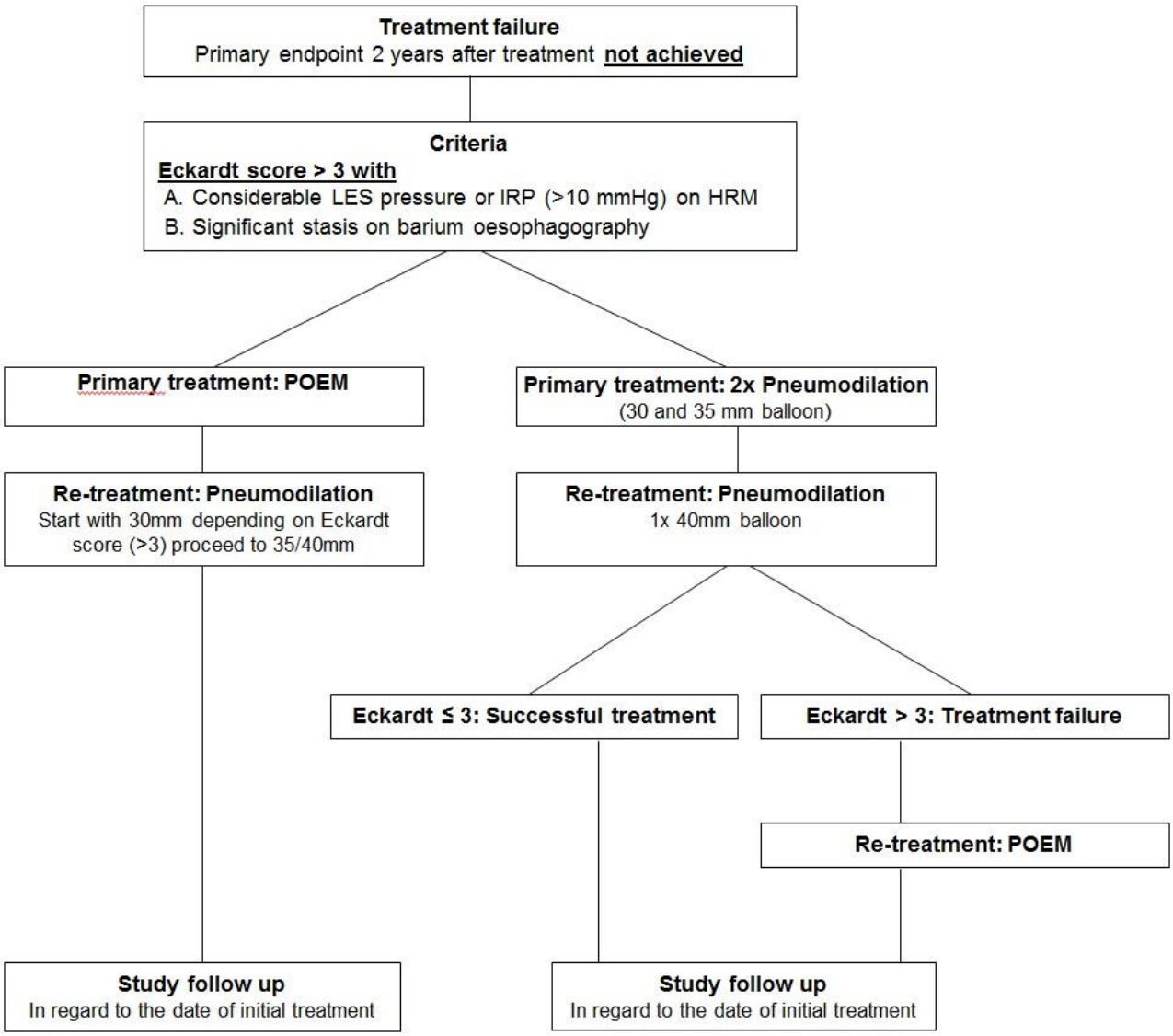
Study subjects failed on the initial pneumodilations (30 and 35 mm rigiflex balloon) within the first year of follow-up will be retreated with a pneumodilation using a 40 mm rigiflex balloon. In case subjects fail more than 1 year after the initial pneumodilations they will be retreated with a pneumodilation using a 35 mm and 40 mm rigiflex balloon.

This is in contrast with the previous versions of the protocol concerning treatment failure that stated that these patients should be subsequently treated with a POEM procedure. The reason to retreat the patients first with a third pneumodilation of 40 mm is that the optimal pneumodilation protocol is used in this way. After the additional pneumodilation(s) symptoms should be evaluated by the Eckardt score. In case the Eckardt is >3 the patient can be scheduled for a POEM procedure.

Follow-up of treatment failures

In principal, study subjects that failed on the initial treatment (2x pneumodilation or POEM) achieved the primary endpoint at that moment. For these patients page 49, study termination, of the CRF should be filled in.

It is very important to continue to collect the data of the treatment failures because sub-analyses of these data can be performed at the end of the study. Therefore, follow up will be the same as the study protocol; follow-up should be scheduled with regard to the date of the initial treatment.



Treatment failure algorithm