Study protocol: Patients with **E**sophageal Carcinoma undergoing Minimally Invasive Ivor Lewis Esophagectomy **wi**th or without **i**ntraoperative Endoscopic Pylorus Balloon **D**ilatation: A Randomized Controlled Trial Investigating the Benefits of Intraoperative endoscopic Pylorus Dilatation (WIDE TRIAL)

Study Type:	Other Clinical Trial according to ClinO, Chapter 4
Risk Categorisation:	Risk category A according to ClinO, Art. 61
Study Registration:	We intend to register our Trial into the ClinicalTrials.gov register. Furthermore, the Trial is registered on BASEC for clinical trials in Switzerland
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Investigated Intervention:	Endoscopic Balloon dilatation during minimally invasive esophagectomy in patients suffering from esophageal cancer
Protocol ID	1.0
Version and Date:	1.3 (dated 18.12.2025)

CONFIDENTIALITY STATEMENT

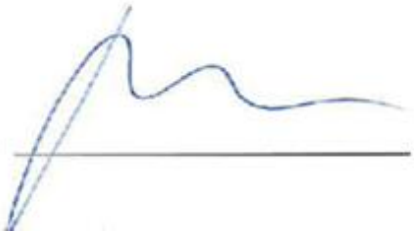
PROTOCOL SIGNATURE FORM

Study Title	Patients with Esophageal Carcinoma undergoing Minimally Invasive Ivor Lewis Esophagectomy with or without intraoperative Endoscopic Pylorus Balloon Dilatation: A Randomized Controlled Trial Investigating the Benefits of Intraoperative endoscopic Pylorus Dilatation
Study ID	2025-01877.

The Sponsor has approved the protocol version 1.0 (dated 09.09.2025) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements.

Sponsor:

Name: Prof. Dr. med. Beat Müller

Date: 10.10.25 Signature: 

Principal Investigator
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Coordinator
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Date: 16.12.25 Signature: 

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GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
ASR	*Annual Safety Repot*
BASEC	*Business Administration System for Ethical Committees*
CRF	*Case Report Form*
CTCAE	*Common Terminology Criteria for Adverse Events*
DGCE	*Delayed gastric conduit emtpying*
FADP	*Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)*
eCRF	*electronic Case Report Form*
FOPH	*Federal Office of Public Health*
GCP	*Good Clinical Practice*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
ICH	*International Conference on Harmonisation*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
SAE	*Serious Adverse Event*
RCT	*Randomized controlled trial*
QoL	*Quality of life*
DGCE	*Delayed gastric conduit emptying*

1 STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Prof. Dr. med. Beat Müller
Study Title	Patients with Esophageal Carcinoma undergoing Minimally Invasive Ivor Lewis Esophagectomy with or without intraoperative Endoscopic Pylorus Balloon Dilatation: A Randomized Controlled Trial Investigating the Benefits of Intraoperative endoscopic Pylorus Dilatation
Short Title / Study ID	**WIDE Trial**
Protocol Version and Date	Version 1.3 (18.12.2025)
Study Registration	The study will be registered at www.clinicaltrials.gov and on the Swiss National Clinical Trials Portal (SNCTP) at www.kofam.ch.
Study Category and Rationale	Clinical trial project category A This is a clinical trial investigating the addition of a commonly used intervention to a standard operation in patients undergoing minimally invasive surgical therapy due to esophageal cancer.
Background and Rationale	For esophageal carcinoma, minimally invasive thoraco-abdominal resection is the standard therapy in a curative setting. Delayed gastric conduit emptying (DGCE) is reported in up to 40% of patients after esophageal resection, making it a significant problem in their treatment. DGCE prolongs recovery and hospital stay which in turn increases the overall costs. DGCE or gastroparesis refers to the stomach's inability to empty its contents into the small intestine in a normal timeframe postoperatively. Mechanical stretching of the pylorus has been shown to reduce the incidence of DGCE in retrospective studies. In open surgery, pylorus dilatation was often performed. However, in the era of minimally invasive surgery, mechanical stretching of the pylorus is technically not possible as in open surgery. There is a need for more and stronger evidence to investigate whether mechanical stretching of the pylorus improves the postoperative course of the patients and lowers the postoperative complication rates.
Risk / Benefit Assessment	This study will provide valuable insight into optimising patient care and reducing complications, given the significant burden of esophageal cancer and its treatment. Reducing DGCE with a simple, safe and often used measure such as balloon dilatation of the pylorus would drastically reduce the morbidity of esophagectomy. Since the balloon dilatation would be done at the beginning of the surgery, risks of the intervention are minimal. Measures such as robust safety protocols, informed consent and privacy measures will be used to protect participants throughout the trial to balance the generally occurring risks of the study and to protect all participants from potential harming.
Objective(s)	Our aim is to investigate if intraoperative endoscopic balloon dilatation reduces the incidence of DGCE in the early postoperative course (until three months postoperatively). Furthermore, we investigate if mechanical balloon dilatation reduces the risk for postoperative complications, hospital stay, time to first bowel movement, and improves quality of life (QoL) after esophagectomy.
Endpoint(s)	Primary endpoint: - Incidence of early DGCE in postoperative course (after 5 and 10 days, measured using radiological and clinical parameters) Secondary: - Incidence of late DGCE (after more than 14 days postoperatively) - Rates of anastomotic leak - Complication rates using Clavien Dindo classification - Hospital stays in days - Time to first bowel movement - Time to first solid food intake - Postoperative Quality of life (assessed with the EORTC QLQ-OES18 questionnaire)
Study Design	This study is a single center, double blinded, superiority randomized controlled trial.
Inclusion- / Exclusion Criteria	Inclusion criteria: - Age >18 years - Histologically confirmed esophageal cancer

	- Planned surgical resection in curative intent as a minimally invasive Ivor Lewis procedure - Provided informed consent Exclusion criteria: - Prior esophageal or gastric resection - Non-curative intent of surgery - ASA Score V - Patients lacking capacity to provide informed consent
Number of Participants with Rationale	Our hypothesis is that intraoperative endoscopic balloon dilatation of the Pylorus reduces the incidence of DGCE. According to our calculation of the required study size for a power of 80%, we need 52 included patients per study arm. To account for potential dropouts or loss to follow-up, an estimated attrition rate of 10% was considered. Consequently, the final target enrolment is increased to 58 patients per group, leading to a total of 116 patients.
Study Intervention	For patients in the intervention group, a balloon catheter will be inserted orally by experienced gastroenterologists under endoscopic control. The pylorus is then dilated to a predetermined size of 30mm using a standard balloon dilatation kit. The intervention will be performed before the gastric conduit is formed.
Study procedures	All patients are treated according to our internal guidelines for esophageal surgery. Baseline data is collected preoperatively. The relevant information concerning the postoperative course of each patient is retrieved from the specific patient charts. These data are collected by ward physicians who do not have access to the study documents and therefore do not know to which group the patients were randomized. After 5- and 10-days, the output of the nasogastric tube will be assessed. Additionally, a radiological X-Ray to assess the width of the gastric tube will be performed. After 3 months patients are asked to fill out the DGCE symptom questionnaire and EORTC QLQ-OES18 questionnaire for a more detailed assessment concerning DGCE specific symptoms and general GI Symptoms and quality of life. Additionally, a radiological passage will be performed after 3 months.
Study Duration and Schedule	December 2025 - June 2028 all patients included and operated. Follow up for 3 months after last operation to assess late DGCE and QoL.
Investigator(s)	Beat Müller, Prof. Dr. med. Clarunis University Digestive Health Care Center Kleinriehenstrasse 30 4002 Basel phone: mail: beat.mueller@clarunis.ch Jennifer Klasen, PD Dr. med. Clarunis University Digestive Health Care Center Kleinriehenstrasse 30 4002 Basel phone: + 41 61 777 73 15 mail: jennifer.klasen@clarunis.ch Lucien Cron, med. pract. Clarunis University Digestive Health Care Center Kleinriehenstrasse 30 4002 Basel phone: + 41 61 777 75 02 mail: lucien.cron@clarunis.ch
Study Center(s)	Clarunis University Digestive Healthcare Centre
Statistical Considerations:	The statistical analysis is performed according to an intention to treat analysis. Chi-square tests is used for categorical variables and t-tests or Mann-Whitney U tests for continuous variables. Multivariable logistic regression will be used to adjust for potential confounders.
Data privacy	Data are collected from patient's electronic data system (Phoenix®/Meona) at St. Claraspital and the University hospital of Basel. Data is then encoded (from 1 to number of patients) and stored onto a Redcap Database with only personalized access.
Ethical consideration	The aim of this randomized controlled trial (RCT) is to demonstrate that intraoperative endoscopic balloon dilation reduces DGCE, thereby improving quality of life, reducing

	morbidity of the patients, shortening hospital stay and lowering treatment costs in patients with esophageal cancer. Endoscopic balloon dilatation is an established, safe and frequently used method. The risk for complications after balloon dilatation is low.
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

2 BACKGROUND AND RATIONALE

Esophageal cancer is the 8th most commonly diagnosed cancer in the world and ranks 6th on the list of cancer entities leading to death. The two most common subtypes of esophageal carcinoma are esophageal squamous-cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) (15). These two types differ not only in their cellular origins but also in their geographic prevalence, associated risk factors, and underlying causes. ESCC arises from the squamous cells that line the esophagus. This type of esophageal cancer is more common in low income countries developing world, particularly in regions of Asia and Africa. The high incidence in these areas is linked to several risk factors, the two most important ones are tobacco use and alcohol consumption. EAC develops from glandular cells located in the lower third of the esophagus, often in the context of Barrett's esophagus. This condition involves the transformation of normal esophageal cells into a type more similar to intestinal cells, usually due to chronic acid exposure. EAC is more prevalent in the industrialized world, especially in North America and Western Europe. The primary risk factors for EAC include obesity, Gastroesophageal Reflux Disease (GERD) and smoking (22).

Men are more frequently affected by esophageal cancer than women. The risk of developing esophageal cancer increases with age. Radical surgical removal of esophageal carcinomas is the only curative therapy available today, especially in EAC. However, the operation is associated with high postoperative morbidity and a high complication rate and a 90-day mortality rate of around 4% (17). Thoracoabdominal resection with creation of a gastric tube or, if possible, transhiatal resection are currently the standard operations for esophageal carcinomas (16). Some of the most important postoperative complications after esophagectomy are anastomotic leak, pulmonary complications such as pneumonia and chylothorax, as well as delayed gastric conduit emptying (DCGE) and dysphagia. DGCE refers to impaired or slowed passage of gastric contents through the conduit, leading to prolonged gastric retention after esophagectomy. It causes symptoms such as nausea, vomiting, regurgitation and inability to tolerate oral intake. DGCE is described in up to 40 percent of patients after esophagectomy and therefore presents a great burden in these patients (8,9). The DGCE can put mental and physical stress on these patients. Also, DCGE may increase the risk of anastomotic leaks through the increased pull on the new esophago-gastric anastomosis. Due to the prolonged recovery, the time until discharge from the hospital and start of rehabilitation is significantly delayed as a result of DGCE. The DGCE also results in higher costs which place an additional burden on the healthcare system.

There are various accepted definitions of DGCE. In 2020, a study involving 33 experts in the field of esophageal surgery attempted to develop a universally applicable definition (10). In the study, the experts defined criteria for early DGCE (<14 days postoperatively) as follows: >500 mL daily nasogastric tube output measured on the morning of post-operative day 5 or later, or >100% increase in gastric tube width on frontal chest x-ray along with the presence of an air-fluid level. Experts describe the following parameters for the presence of late DGCE (>14 days postoperatively): The patient should have at least two of the following symptoms: early satiety/fullness, vomiting, nausea, regurgitation or inability to meet caloric needs by oral intake, and delayed contrast passage on upper gastrointestinal radiograph or timed barium swallow. Furthermore, we learned from this study, that the DGCE syndrome can be defined on the basis of the occurrence of symptoms such as nausea or vomiting. In addition, clinical parameters such as the length of time the gastric tube is in place and the flow rate of the gastric tube as well as radiological parameters can be used as diagnostic tools. The DGCE is associated with the gastric tube remaining in place for a longer period of time. In addition, an increased risk for anastomotic leakage and aspiration is described (17). Various techniques for reducing DGCE have been investigated in the past. In former times, surgical pylorus drainage in the form of pyloroplasty or pyloromyotomy was often a standard procedure for distal esophageal resection. In the era of open surgery, the pylorus was often mechanically dilated using regular forceps, this cannot be down in minimally invasive surgery. Since the widespread adoption of minimal invasive surgery, however, these interventions have been performed less frequently. Another technique that was used was the intraoperative injection of Botox into the pylorus. However, this technique did

not show satisfying results in reducing the rate of postoperative DGCE (12). Overall, there is currently no clear evidence regarding the benefits of individual pyloric drainage strategies (13,14). In a large meta-analysis published in 2022 mechanical stretching of the pylorus performed in different ways (manually, endoscopically or by using a forceps) showed a significant reduction in the rate of postoperative DGCE (15). Another meta-analysis by Mohamed Abdelrahman showed that prophylactic balloon dilatation of the pylorus also reduces the incidence of DGCE (20). The current research situation shows varying results and there is still little clear evidence that either technique is superior to prevent the occurrence of DGCE. Therefore, further studies, especially randomized controlled trials, to identify the optimal technique for reducing the rate of DGCE.

Today, where a large proportion of esophagectomies for esophageal cancer are performed using minimally invasive techniques, DGCE is a significant problem. Recently, a study protocol was published describing another RCT investigating prophylactic pyloric dilatation. In this study, however, dilatation is performed one day preoperatively. Early admission of patients increases health care costs unnecessarily. This emphasizes the need for this study, as we still need to find out when and whether prophylactic pyloric dilatation improves patient outcome (21). If it were possible to prove that intraoperative balloon dilatation of the pylorus could significantly reduce the incidence of DGCE, shorten hospital stay and reduce associated complications, this would be a relevant discovery that could further improve the treatment of esophageal cancer in the era of minimally invasive surgery. By providing high-quality evidence on the efficacy of intraoperative balloon dilatation, the study aims to establish a new standard of care for esophagectomy patients. Positive findings could lead to widespread adoption of intraoperative pyloric dilatation. Moreover, this research could pave the way for further studies with greater statistical power on this topic.

3 STUDY OBJECTIVES AND DESIGN

3.1 Hypothesis and primary objective

The central hypothesis of the study is that intraoperative mechanical balloon dilatation of the pylorus performed by endoscopic balloon dilatation reduces the postoperative incidence of early DGCE.

There are various studies investigating the effectiveness of mechanical dilatation of the pylorus in reducing DGCE. In 2022, an RCT was published which investigated the efficacy of intraoperative balloon dilatation versus pyloroplasty versus no pylorus intervention. In this study, however, all patients underwent open surgery and none of the dilatations were performed endoscopically (19). In the era of minimally-invasive surgery we want to find a measure to reduce the incidence of DGCE during the postoperative course. This study would be, to our knowledge, the first RCT of its kind worldwide investigating intraoperative endoscopic balloon dilatation to prevent DGCE in patients with esophageal cancer undergoing minimally invasive surgery. We investigate the effectiveness of intraoperative balloon dilatation in reducing the incidence of postoperative DGCE in patients undergoing minimally invasive esophagectomy for esophageal cancer. In addition, we will detect potential complications associated with intraoperative balloon dilation of the pylorus as well as to prove that intraoperative balloon dilatation reduces DGCE associated complications, for example pneumonia. Furthermore, we want to analyze if the postoperative quality of life is improved in patients with intraoperative balloon dilatation. The findings of this study will make a substantial contribution to surgical practice and patient care in esophageal cancer.

3.2 Primary and secondary endpoints

The Primary outcome is defined as incidence of early DGCE. Early DGCE is defined as presence of a nasogastric tube with an output of >500ml on day 5 or later and/or >100 % increased gastric tube width on radiological chest X-Ray on

day 5 or later (in comparison with baseline X-Ray upon admission on the ICU). DGCE will be diagnosed using both of these mentioned radiological and clinical tools on day 5 and 10 (10).

As secondary endpoints we define the incidence of late DGCE measured using the symptom orientated DGCE questionnaire and a radiological passage examination after 3 months. Furthermore, we want to investigate potential differences between the two groups concerning the rate of anastomotic leaks, postoperative complications such as pneumonia, duration until first bowel movement after surgery, duration until first intake of solid food, presence of vomiting during the postoperative course and length of hospital stay. In addition, we will analyze the quality of life via symptom orientated questionnaires after 3 months using the EORTC QLQ-OES18 questionnaire.

3.3 Study design

This study will be performed as a prospective single center double blinded randomized controlled trial.

Patients suffering from esophageal cancer scheduled for surgery in curative intent will be randomised to two groups.

Patient Selection and Recruitment

All patients will be treated interdisciplinary by oncologists and surgeons and all patients are being discussed in our interdisciplinary tumor conference. The patients for the study will be screened for eligibility when the decision for curative esophagectomy is made in our “Tumorboard”. Recruiting of the patients is performed during the first surgical consultation and after the determination of the further procedures. During this consultation, the planned esophagectomy and the intervention, the risks as well as the aim and purpose of the study is explained to the patients. Furthermore, the eligibility to participate in the study is assessed. In a second consultation which takes place shortly before surgery, patients can provide the informed consent to participate in the study or not.

Randomization and Blinding

If a patient does not provide informed consent he is excluded from the study and will be treated according to the current gold standard and will then receive surgical therapy without additional intervention.

Enrolled patients will be randomized 1:1 into the intervention group and into the control group using the RedCap randomization tool designed in our RedCap database for the study. Group one will be the intervention group. In this group patients will receive an intraoperative endoscopic balloon dilatation of the pylorus by an experienced gastroenterologist before the gastric conduit is formed. Group two will be the control group where the participants will undergo standard surgical resection without intraoperative balloon dilatation of the pylorus. The outcome assessors in this study are the ward physicians, who record the output of the nasogastric tube and record complications and the radiologists who evaluate the X-rays taken. These medical professionals are blinded for the group assigned. In the surgical reports it is only recorded “Esophagectomy Iwor Lewis WIDE Trial”. Therefore, the outcome assessors are not able to tell if a patient received the additional intervention or not. The data is then, if possible automatically or by hand transcribed into the RedCap database.

Data Collection

After inclusion into the study, baseline data will be collected and stored in a study-specific Redcap Database. This Redcap Database fulfills all regulatories for a study database. In a next step after the operation, surgery-specific data is collected and stored into the redcap database. The surgical reports will not show whether a patient has received an intervention or not. The relevant information concerning the postoperative course of each patient are retrieved from the specific patient charts. These data are collected by ward physicians who do not have access to the study documents and therefore do not know which group the patients were randomized into. After 5 and 10 days, a radiological X-ray of the chest is performed to assess the width of the gastric tube. After 5 and 10 days we also assess whether a nasogastric

tube is in place and, if so, how high the output of the nasogastric tube is. After 3 months we assess the DGCE specific symptoms using the DGCE symptom orientated questionnaire. We also perform a radiological swallow study to record signs, such as delayed contrast passage for late DGCE. Additionally, patients are asked to fill out the EORTC QLQ-OES18 questionnaire to have a more detailed assessment concerning general GI symptoms.

Safety and Unblinding

In case of adverse events, unblinding will be permissible, and procedures for revealing a participant's allocated intervention will be allowed during the trial, also in case of suspension or premature study termination. Unblinding is done by the Surgeon who attended the operation and is therefore not blinded to the group assignment.

3.4. Study intervention

For patients in the intervention group, a balloon catheter will be inserted in the pylorus under gastroscopy guidance during the operation while the patient is in general anesthesia for the esophagectomy by an experienced gastroenterologist. The intervention will be performed intraoperatively before the gastric conduit is formed. The pylorus is then dilated to a predetermined size of 30 mm using a standard balloon dilatation kit. The intervention is carried out according to the standard techniques used by our gastroenterologists and presents the current gold standard in the therapy of DGCE. Hence our gastroenterologists are experienced in performing this intervention. The study intervention will only minimally affect the patient since the only addition for the study is the gastroscopy with balloon dilatation of the pylorus. The time for this intervention is around 20 – 30min additionally.

4 STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

Participants fulfilling all of the following inclusion criteria are eligible for the study:

Inclusion criteria:

- Age >18 years
- Histologically confirmed esophageal cancer
- Planned surgical resection in curative intent as a minimally invasive Ivor Lewis procedure
- Provided informed consent

Exclusion criteria:

- Prior esophageal or gastric resection
- Noncurative intent of surgery
- ASA Score V
- Patients lacking capacity to provide informed consent

4.2 Recruitment, screening and informed consent procedure

All patients are presented to our interdisciplinary "Tumourboard" at the Clarunis University Digestive Healthcare Center after being diagnosed with esophageal cancer. The further treatment procedure is then determined. If a curative treatment procedure with surgery is determined, the patient's suitability for participation is reviewed in a second step. The potential participants are then invited to our surgical consultation. The patient will be informed about the further procedure and the operation. Patients are also given comprehensive information about the study. The consultation will be performed by one of our surgeons from the department specializing in upper gastrointestinal surgery.
The surgeon will explain to each participant the nature of the study, its purpose, the procedures involved, the expected

duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he or she may withdraw from the study at any time and that withdrawal of consent will not affect his or her subsequent medical assistance and treatment.

The participant will be informed that his or her medical records may be examined by authorised individuals other than their treating physician. All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. The patients are then granted between 2 to 8 weeks to think about their consent to participate in the study. During this time the neoadjuvant therapy is administered by our oncologists in the most cases. In a second consultation which takes place shortly before the operation and after the assessment of the anaesthesiologist, patients can provide the informed consent to participate in the study or not after they had sufficient time to make an informed decision. The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure.

The consent form will be signed and dated by the investigator or his designee at the same time as the participant sign and if informed consent is signed this will be noted in the consultation report. A copy of the signed informed consent will be given to the study participant. The consent form will be retained as part of the study records.

The investigator or the sponsor notifies the Ethics Committee of the first study participant, in accordance with art 62 lit. c ClinO, resp. art 38 ClinO. If the first participating person is not included in the trial within two years following the issuance of the authorization, the trial is considered interrupted (art. 23a ClinO). The clinical trial may not be commenced until an application for an extension of the time limit has been approved. The application for the extension is submitted to the CEC as a substantial amendment.

4.3 Study procedures

The study is planned to take place over a duration of 30 months. We perform between 50 to 70 Esophagectomies per year at Clarunis University Digestive Healthcare Centre, with an estimated participating rate of 80 to 90% we should achieve to include 116 patients in around 30 months. Due to the low risk intervention with minimal side effect for the patient, a high participation rate is expected. We plan to start including patients from December 2025. The study starts for each patient from the time when informed consent is provided. The study follow upends after 3 months postoperatively, when we see the participants for a routine check and perform a radiological passage. After completing the last questionnaire 3 months postoperatively, the collection of the requested data is over. Then patients will enter the usual follow-up care program for esophageal cancer. After randomization into the two groups, group one will be the intervention group. In this group, patients will receive intraoperative balloon dilatation of the pylorus by an experienced gastroenterologist. Group two will be the control group where the participants will undergo standard surgical resection without intraoperative balloon dilatation.

For patients in the intervention group a balloon catheter will be inserted under gastroscopy guidance into the pylorus during the operation via the oral way by an experienced gastroenterologist. The intervention will be performed at the beginning of the surgery, before the gastric conduit is formed. The pylorus is then dilated to a predetermined size of 30mm using a standard balloon dilatation kit. Dilatation to 30 mm is the standard treatment for DGCE and was selected in consultation with our gastroenterologists. This intervention will alter the normal operative course only minimally. The only additional step is the pylorus dilatation by an experienced gastroenterologist which requires 20 – 30min of time. Complications are not to be expected since balloon dilatation of the pylorus is a safe and frequently performed procedure (23). In case of a perforation or bleeding, the problem can immediately be treated by the gastroenterologist or the surgeon. For the patient, no additional harm or discomfort will arise since he/she are under general anaesthesia

for the planned esophagectomy already. In short, the potential harm for the patient undergoing the study intervention is minimal.

After the operation all patients are treated according to our internal guidelines for esophageal surgery. Among other things, the guidelines set out standard procedures for oral liquid and food intake, supportive medication, drainage management and gastric tubes. If the course of treatment deviates from the standard, any necessary therapy is adapted according to the patient's needs in consultation with senior physicians. Postoperatively all patients will be transferred to the Intensive care unit for monitoring. The physicians in charge of the intensive care unit then decide when a transfer to the surgical ward can take place. All patients are supported by our physiotherapist as well as our team of nutritionists.

We plan to collect the required data as follows. Surgery-specific data is collected using the information from the clinical information system. These include the duration of the operation, intraoperative complications, details of intraoperative balloon dilatation and anaesthesiologic specialties. The relevant information concerning the postoperative course of each patient are retrieved from the specific patient charts. These data are collected by ward physicians who do not have access to the study documents and therefore do not know which group the patients were randomized into. These data include for example gastric tube and chest tube output, interventions and complications, first bowel movement, time of first solid food intake, days of hospitalization and days spend on the intensive care unit as well as data from postoperative imaging. On the 5th and 10th day we carry out a radiological X-Ray examination of the chest assessing the width of the gastric tube and if the width of the tube is increased in comparison to the baseline X-Ray. Furthermore, we assess the output of the nasogastric tube in millilitres. After 3 months every patient will be seen in our surgical consultation for a routine check-up. There the patients will fill out the DGCE Symptom orientated questionnaire (10) as well as the EORTC QLQ-OES18 questionnaire to assess the Gastrointestinal related Quality of life. In addition, we perform a radiological passage examination to assess the presence of late DGCE. These questionnaires, which are completed on days 5 and 10 as well as after 3 months, together with the radiographic examinations performed at the same time points, represent additional study-specific assessments. They would therefore not be performed in case of non-participation in the study.

4.4 Withdrawal and discontinuation

Patients who withdraw consent and also withdraw of permission to collect further clinical information will be included in the intention-to-treat analysis, but no study-specific follow-up will be performed. All participants who withdraw from the study are no longer involved in the study and no further data collection is performed. If a participant refuses to participate in the study after the hospitalization the participant will be included in the intention to treat analyses. If a patient withdraws the informed consent before the surgery is performed the participant will be excluded from the study.

5 STATISTICS AND METHODOLOGY

5.1. Statistical analysis plan and sample size calculation

The aim of this power analysis was to calculate the minimum required sample size for our randomized controlled trial (RCT) investigating the effect of intraoperative endoscopic pyloric dilatation on the incidence of early delayed gastric conduit emptying (DGCE) within the first 14 days after esophagectomy.

The sample size calculation for this study was based on findings from Boshier et al. (18), which demonstrated a reduction in the incidence of DGCE from 48% to 22% following intraoperative pyloric stretching procedures. To achieve a statistical power of 80% ($1 - \beta = 0.80$) while maintaining a Type I error rate of 0.05 ($\alpha = 0.05$), a power analysis for comparing two independent proportions was performed. The absolute difference in proportions (Δ) was set at 26 (0.48

- 0.22). Using these parameters, the required sample size was calculated to be 52 patients per group, resulting in a total of 104 patients for the study. This ensures sufficient power to detect a statistically significant difference in DGCE incidence between the two treatment groups.

To account for potential dropouts or loss to follow-up, an estimated attrition rate of 10% was considered. Consequently, the final target enrolment is increased to 58 patients per group, leading to a total of 116 patients. This adjustment maintains adequate statistical power even if a subset of participants does not complete the study.

The statistical analysis will be conducted according to the intention-to-treat (ITT) principle. Categorical variables will be analyzed using Chi-square or Fisher's exact test, while continuous variables will be evaluated using either independent t-tests or Mann–Whitney U tests, depending on the distribution. Multivariable logistic regression analysis will be used to adjust for relevant covariates and potential confounding factors.

All statistical analyses will be performed in collaboration with an experienced statistician from our research group using validated software such as SPSS or R. A significance level of $p < 0.05$ will be considered statistically significant for all tests.

6 REGULATORY ASPECTS AND SAFETY

During the entire duration of the study all serious adverse events (SAEs) where it cannot be excluded that the events are attributable to the intervention under investigation are collected, fully investigated and documented in source documents and case report forms (CRF). Study duration is defined from the time when the participant signs the informed consent until the last questionnaire after 3 months has been completed.

6.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

6.2 (Serious) Adverse Events and notification of safety and protective measures

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or a clinical investigation subject which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavourable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A **Serious Adverse Event (SAE)** (ClinO, Art. 63) is any untoward medical occurrence that results in death or is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization or results in persistent or significant disability or incapacity.
Both Investigator and Sponsor-Investigator make a causality assessment of the event to the trial intervention, (see table below based on the terms given in ICH E2A guidelines). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Relationship	Description
Not related	- The event started in no temporal relationship to the project-specific intervention applied and

	- The event can be definitely explained by underlying diseases or other situations. - Causal relationship can be ruled out
Related	- The event started in plausible time relationship to the project-specific intervention applied and - The event cannot be definitely explained by underlying diseases or other situations.

Both Investigator and Sponsor-Investigator make a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

Reporting of SAEs (see ClinO, Art. 63)

All SAEs are documented and reported immediately (**within a maximum of 24 hours**) to the Sponsor-Investigator of the study.

If it cannot be excluded that the SAE is attributable to the intervention under investigation, the Investigator reports it to the Ethics Committee via BASEC **within 15 days**.

Follow up of (Serious) Adverse Events

All participants with a report of an (S)AE's will be followed up until resolution and complete recovery from the (S)AE's.

Notification of safety and protective measures (see ClinO, Art 62, b)

If immediate safety and protective measures have to be taken during the conduct of the study, the investigator notifies the Ethics committee of these measures, and of the circumstances necessitating them, within 7 days.

6.3 (Periodic) safety reporting

Once a year, the investigator submits to the Ethics Committee a list of the safety events including the severity of the events, their causality to the intervention and the safety of the study participants. The investigator also informs the Ethics Committee about the general progress of the clinical trial (ClinO, Art. 43).

6.4 Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.

Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of study site(s) or of study leader and

sponsor (ClinO, Art. 29).

6.5 Notification and reporting upon completion, discontinuation or interruption of the study

Upon regular study completion, the Ethics Committee is notified via BASEC within 30 days (ClinO, Art. 38). The investigator reports the global completion of an international trial to the Ethics Committee within 90 days.

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, e.g.

- Ethical concerns,
- Insufficient participant recruitment,
- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive),
- Alterations in accepted clinical practice that make the continuation of the study unwise, or
- Early evidence of harm or benefit of the experimental intervention

Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38).

A final report is submitted to the Ethics Committee via BASEC within a year after completion or discontinuation of the study, unless a longer period is specified in the protocol (ClinO, Art. 38).

6.6 Insurance

For category A studies: In the event of study-related damage or injuries, the liability of the institution Clarunis University Digestive Health Care Center provides compensation.

7 FURTHER ASPECTS

7.1 Overall ethical considerations

This trial will balance the potential benefits and risks to participants. It will also contribute to the advancement of surgical treatment of esophageal cancer. By prioritizing the safety of participants, protecting their right to privacy, and ensuring their voluntary participation is fully informed, the design adheres to ethical principles. With appropriate mitigation strategies in place for potential risks and a clear path to the generation of meaningful data, this trial has great promise to improve outcomes for future patients without undue burden to current participants.

7.2 Risk-benefit assessment

Risks of balloon dilatation: The intraoperative balloon dilatation procedure may result in mechanical injury, such as perforation (described in 1.5%), bleeding (2-7% but mostly self-limited), or damage to surrounding tissue, which in the worst case may require further surgery or prolong recovery time (23). In our patient collective without underlying pyloric pathology we expect complications to be very rare. Furthermore, inflammation or infection can be caused as a result of dilation, which may increase postoperative complications. In case of serious complications, the problem can be treated immediately since the patient is already under general anaesthesia for the planned esophagectomy and the surgeons and gastroenterologists are already involved and available.

Risks of prolonged surgery: The addition of balloon dilatation to the surgical procedure may slightly increase the length of time under anaesthesia (20 – 30min), which may increase the risk of anaesthesia-related complications such as respiratory or cardiovascular events. Although balloon dilatation itself is a relatively short procedure, extending the operating time adds to the overall complexity of the operation. However, in relation to the operative duration of 6 – 8h, these additional 20 – 30 minutes are minimal and is well within the normal deviation time of a standard minimally invasive esophagectomy.

General surgical risks: Both groups (balloon dilation and control) face the inherent risks associated with surgery for esophageal cancer, including infection, anastomotic leak, pulmonary complications and delayed wound healing. These are standard risks associated with major surgery, independent of the interventions used in the trial.

Minimising procedural risks: Balloon dilatation will be performed by highly experienced gastroenterologists to minimise risks such as tissue injury or perforation. The procedure will follow a standardised, evidence-based protocol to ensure safety and consistency across participants. Any increase in operating time will be minimised through careful planning, and patients will be closely monitored for signs of complications during and after the procedure.

Post-operative care and monitoring: Thorough post-operative care will be provided to all participants, including regular monitoring for complications such as DGCE, infection, or other adverse events. Enhanced recovery protocols will be in place to support patient healing, with early intervention to manage potential complications before they become serious.

Data security measures: Participants' data will be anonymised and stored securely to protect their identity. Access to sensitive data will be restricted to authorised study personnel only.

Informed consent: Participants will go through a detailed informed consent process to ensure that they have a full understanding of the potential risks and benefits of the study, prior to enrolment. They will be informed that they have the right to withdraw from the study at any time, with no impact on their medical care.

The potential benefit for future patients justifies the trial, although it does carry potential risks for participants, particularly related to the balloon dilatation procedure. However, delayed gastric emptying is a significant complication following esophageal cancer surgery with many risks. It contributes to longer hospital stays, increased healthcare costs and reduced quality of life for patients. If this study shows a benefit of intraoperative pylorus dilatation, it will lead to significant improvements in surgical practice and post-operative outcomes by reducing the incidence of DGCE. This study could provide valuable insight into optimising patient care and reducing complications, given the significant burden of esophageal cancer and its treatment.

Above mentioned measures such as robust safety protocols, informed consent and privacy measures will be used to protect participants throughout the trial to balance these mentioned risks and to protect all participants from potential harming.

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

The Sponsor-Investigator is implementing and maintaining quality assurance and quality control systems with written SOPs and Working Instructions to ensure that trials are conducted, and data are generated, documented, and reported in compliance with the protocol, GCP and applicable regulatory requirement(s). All patient and study related data are entered into the electronic Database Redcap.

For quality assurance the sponsor, the Ethics Committee or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the

participant data strictly confidential.

8.2 Data recording and source data

All patient and study related data are entered into the electronic Data base Redcap. For each participant a CRF is maintained. CRFs will provide appropriate coded identification without identifying participants by their name or birth date.

Trial and participant data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other study specific documents, participants are only identified by a unique participant number. The Sponsor-Investigator/PI will decode the data in order to create a decode number that need to be use in the eCRF. The eCRF will be archived in a file. This file will be kept in a safe place accessible only to the Sponsor-Investigator/PI and the project assistant. A copy of this file will also be saved with a password on a separate laptop.

8.3 Confidentiality and coding

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

The investigator has appropriate knowledge and skills in the areas of data security and data protection or is able to ensure compliance by calling in appropriate expertise (Art. 6, ClinO).

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited.

Trial and participant data will be handled with the utmost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other study specific documents, participants are only identified by a unique participant number.

8.4 Retention and destruction of study data and biological material

All study data are archived for 20 years after study termination or premature termination of the study.

9 MONITORING AND REGISTRATION

The institution fulfilling the monitoring duties for this study is Clarunis University Digestive Health Care Center, responsible for ensuring adherence to the study protocol, regulatory requirements, and participant safety throughout the trial. Only the Sponsor-Investigator and the Project Assistant will have access to protocol, dataset, statistical code, etc. during and after the study. Direct access to source documents will be permitted for purposes of monitoring, audits and inspections. This study will be registered in the Swiss National Clinical trial Portal (SNCTP via BASEC).

10. FUNDING / PUBLICATION / DECLARATION OF INTEREST

The initiation of this study will be funded by the Clarunis research funding. Furthermore, grant applications are in progress (Beginner grant Bangerter Stiftung).

After the statistical analysis of this trial the project manager will make every endeavour to publish the data in a medical journal. The sponsor enters and publishes a summary of the trial results in a public register in accordance with ClinO

Art. 65a within one year of completion or discontinuation of the trial. An interruption lasting more than two years is considered a discontinuation of the trial.

For the purpose of publication in the public register the sponsor also ensures that a lay summary of the trial results is entered in BASEC within one year of completion or discontinuation of the trial. The entry is made at least in the national languages of Switzerland in which the study participants were recruited.

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Appendix 1: Schedule of assessments

Study Periods	Screening		In-hospital			Follow up
Days	-X	-14	0	5	10	3 months
Patient Information and Informed Consent		+				
Demographics	X	X				
Medical History	X	X				
In- /Exclusion Criteria	+	+				
Physical Examination	X	X	X	X	X	X
Vital Signs			X	X	X	X
Randomisation		+				
Surgery			X			
Primary Outcome				+	+	
Output Nasogastric tube				X	X	
Radiological passage						+
Radiological Chest X-Ray			X	+	+	
Secondary Outcomes				X	X	X
Adverse Events			X	X	X	X
Quality of life (EORTC QLQ-OES18)		+				+
DGCE Questionnaire		+		+	+	+

Symbol explanations:
X: Routine Examinations in all Esophagectomy patients
+: Study specific/additional Examinations

WIDE TRIAL – CONSORT Flowchart