PROTOCOL TITLE **‘**PERi-operative Selective Decontamination of the Digestive tract to prevent severe infectious complications after Esophagectomy: a Randomized multicenter clinical trial in patients with primary resectable esophageal carcinoma (cT1-4, N0-3, M0)’

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PROTOCOL SIGNATURE SHEET

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DOCUMENT HISTORY

Document	Date of version	Summary of changes
Original protocol version number 1.0	**30.04.2023**	**Initial application**
Protocol version 1.1	**03.03.2024**	**Revised application multiple corrections.**
Protocol version 1.2	**04.04.2025**	**Amendment: changes in PI, changes in logistics and multiple corrections.**
Protocol version 1.3	**30.01.2026**	**Amendment: change of head of department; amphotericin B changes to amphotericin B or Nystatin ; correction**

		inconsistency interim analyses; addition of adjudication committee regarding primary outcome

CONFIDENTIALITY STATEMENT

This document contains confidential information that must not be disclosed to anyone other than the sponsor, the investigative team, regulatory authorities, and members of the Research Ethics Committee.

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
BAPCOC	**Belgian Working Party on Antibiotic Policy (Belgische Gids voor anti-infectieuze behandeling)**
BCR	**Belgian Cancer Registry**
CA	**Competent Authority**
CCI	**Charlson Comorbidity Index**
CCMO	**Central Committee on Research Involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek)**
DAMOCLES	**DAta MOnitoring Committees: Lessons, Ethics, Statistics, A Study Group aiming to investigate the processes of monitoring accumulating trial data and to identify ways of increasing the likelihood that DMCs make good decisions.**
DSMB	**Data Safety Monitoring Board**
DUCA	**Dutch Upper GI Cancer Audit**
ECCG	**Esophageal Complications Consensus Group**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation (Algemene Verordening Gegevensbescherming)**
GMP	**Good Manufacturing Practice**
GI	**Gastrointestinal**
IB	**Investigator's Brochure**
IC	**Informed Consent**
ICU	**Intensive Care Unit**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
INAMI	**French abbreviation for Belgian National Service for Disease and Incapacity Insurance (French: Institut national d'assurance maladie-invalidité)**

KCE	Belgian Health Care Knowledge Centre (Dutch: Federaal Kenniscentrum voor de gezondheidszorg / French: centre féderal d'expertise de soins de santé)
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
PACU	Post Anesthesia Care Unit
RIZIV	Dutch abbreviation for Belgian National Service for Disease and Incapacity Insurance (Dutch: Belgisch RijksInstituut voor Ziekte- en Invaliditeits Verzekering)
rUPS	revised Uniform Pneumonia Score
(S)AE	(Serious) Adverse Event
SDD	Selective Decontamination of the Digestive tract
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
SWAB	Dutch Working Party on Antibiotic Policy (Stichting Werkgroep Antibiotica Beleid)
UAVG	Dutch Act on Implementation of the General Data Protection Regulation (Uitvoeringswet AVG)
WMO	Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen)

1. SYNOPSIS

Rationale: Esophagectomy is a complex surgical procedure, associated with significant morbidity and mortality rates. Most postoperative complications are caused by infections (10–30%). These are thought to arise from (micro-)aspiration of bacteria residing in the oropharyngeal and gastrointestinal (GI) tract, leading to (respiratory) infections. Selective decontamination of the digestive tract (SDD) is a prophylactic antibiotic strategy that aims to prevent postoperative infections. Pathogenic aerobic gram-negative rods and yeasts are reduced, while anaerobic, protective microbiota are preserved. SDD has been shown to lower the risk for respiratory infections in an intensive care setting. Establishing SDD as effective addition to the standard care of esophagectomy patients is expected to increase their chance of survival.

Objective: Robust and prospective evaluation of SDD after esophagectomy as a protective strategy reducing postoperative pneumonia and other infectious complications, anastomotic leakage and mortality.

Study design and population: A randomized, controlled, open-label, multicentre trial, including 854 patients with primary resectable esophageal carcinoma ((y)cT1-4a N0-3 M0) planned for transthoracic esophagectomy.

Intervention: The intervention group receives SDD treatment additional to standard care, comprising two distinct liquids for oral administration: first the 5 ml amphotericin B suspension (100 mg/ml) or the 5 ml nystatin suspension (100.000 IE/ml) and subsequently the 5 ml “SDD base for suspension”, containing both colistin sulphate (20 mg/ml) and tobramycin sulphate (16 mg/ml). Patients take the 5 ml amphotericin B or 5 ml nystatin, followed by the 5 ml “SDD base for suspension”, four times daily for one week, starting three days prior to the surgery. On the day of surgery, intake is limited to an early morning and a late evening dose. All other aspects of care are equal to the control group (standard care without SDD). All participants will be asked to keep a diary and fill out questionnaires.

Main study parameters/endpoints: The incidence of postoperative pneumonia within 30 days after surgery.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Patients undergoing standard care do not experience any added risks due to participating in this study. The intraoperative esophageal sample which will be taken from all subjects to determine the decolonizing effect of SDD treatment will be taken *ex vivo* from the surgical specimen and consequently provides no additional risk for the patient. Potential benefits of the SDD treatment are a lower incidence of infectious complications, such as pneumonia, and as a result shorter hospitalisation and ICU stays, less re-operations,

less re-admissions and lower mortality. SDD can cause (mild) side effects such as vomiting/nausea, diarrhoea, bloating, abdominal pain and loss of appetite.

2. INTRODUCTION AND RATIONALE

Esophageal cancer is an extremely restraining form of cancer, as it affects the swallowing tube (*esophagus)* and impairs the patient's ability to eat. Its global incidence has sharply increased within the last thirty years; in the Netherlands alone, the annual incidence has more than tripled, with now around 3000 newly diagnosed patients per year[1]. In Belgium, around 1600 patients are diagnosed with esophageal cancer each year[2]. At the same time, the overall 5-year survival rate has increased from 5 to 25% due to advanced treatment options. The most common treatment for these patients is pre- or perioperative chemo(-radiation), followed by esophagectomy, which is the surgical removal and reconstruction of the esophagus. In the Netherlands ~30% [3] and in Belgium ~38% [4] of all patients diagnosed with esophageal cancer undergo this surgery every year. Esophagectomy provides the highest chance of cure, but the complex surgical procedure comes with high morbidity (40-60%) and 30-day mortality rates (14 – 36%, depending on the definition used)[5-7]. Most postoperative complications are infections (10-30%), with pulmonary infections posing a major threat to patient survival. Furthermore, surgical-site infections (2,5-5%) and anastomotic leakage-associated infections (10-20%) are a major contributor to the mortality rates after esophagectomies[8, 9]. The postoperative infections are thought to arise from (micro-)aspiration of bacteria residing in the oropharyngeal and GI tract[10]. Besides causing respiratory infections, these pathogens can also induce local inflammation and abscess formation at the level of the enteric anastomosis, resulting in anastomotic dehiscence and eventually anastomotic leakage[11]. Eliminating these pathogens prior to surgery and during recovery potentially decreases the risk of infections and anastomotic leakage.

Selective decontamination of the digestive tract (SDD) describes the prophylactic antibiotic strategy to reduce aerobic gram-negative rods and yeasts of the GI tract, while preserving the anaerobic flora and its protective capacities[12]. The rationale of SDD is to eradicate potentially pathogenic microorganisms from the upper respiratory (SOD) and intestinal tract of ICU patients through an antimicrobial pharmaceutical formulation applied to the oropharynx and the gastro-intestinal (GI) tract. The antimicrobial composition of SOD and SDD aims to supress pathogenic aerobic gram-negative rods and yeasts, while anaerobic, protective microbiota are preserved. This strategy is sometimes advocated as the promotion of "anaerobic colonisation resistance".

SDD consists of the administration of nonabsorbable, topical antimicrobial agents with or without the administration of a short-term course of broad spectrum parenteral antibiotics.

In the intensive care unit, this preventive strategy (SDD) consists of three different components. First, a paste is applied to the oropharynx. As a single component, this is called SOD (selective decontamination of the oropharyngeal tract). Second, a liquid is taken orally or administered via a nasogastric tube. Third, a short (4 day) course of intravenous antibiotics (a third generation cephalosporins such as cefotaxim or ceftriaxon) is added to the regimen. In the Netherlands, most ICUs use the full 3-component SDD strategy, but some only apply the oral component (SOD).

The use of the term SDD may be confusing as SDD is indeed generally referred to as oral paste + intestinal liquid + IV cephalosporin. Within the PERSuaDER-trial however, SDD is referred to as (two components of) an intestinal liquid only.

Many variations of SOD and SDD exist (different combinations of compounds, different combinations of parenteral and non-absorbable orally administered drugs). The most applied combination (the one that is used in the PERSuaDER-trial) is the one that has been used in the Dutch intensive care setting since as early as 1984 and consists of tobramycin, colistin and amphotericin B applied 4 times daily. Next to this, a combination with nystatin as alternative for amphotericin B is extensively used in intensive care setting and has demonstrated not to be inferior to amphotericin B in terms of efficacy[13]. Within esophageal surgery, nystatin is the second most frequently used antifungal agent as part of SDD treatment. In literature, Nystatin has been used in several clinical studies, including trials conducted in the intensive care unit as well as in patients undergoing esophagectomy [14-17]. Our recent literature review revealed no safety concerns regarding the use of nystatin in this population [18]. For further details, please refer to the investigator's brochure. Given the current worldwide drug shortages including many generic medications[19], this protocol has opted for the use of amphotericin B or Nystatin as fungicide, depending on availability for the sponsor.

The Dutch SWAB guideline for patients in ICU [20] comprises all the evidence on SOD and SDD until 2018 and concludes that both SOD and SDD are associated with improved survival in mechanically ventilated patients in ICU (level A1 conclusion). Their use is also associated with a significant reduction of the incidence of ventilator associated pneumonia and ICU acquired gram negative bacteraemia (level A2 conclusion). Additionally SDD and SOD are not associated with ICU acquired infection or colonisation of antibiotic resistant pathogens (level A2 conclusion). Finally SDD and SOD have limited side effects (level A1 conclusion): this will be further discussed in the chapter on safety. The SWAB guideline recommends the routine use of SDD, as in patients who have an expected duration of ventilation upon admission to intensive care of at least 48 hours or an expected length of stay of at least 72 hours.

After 2018, a systematic review and meta-analysis, including both the use of amphotericin B and nystatin as antifungal agent [21] pooled data from 24.389 patients in 32 randomised controlled trials in ICU. The pooled estimated risk ratio (RR) for mortality for SDD compared with standard care was 0.91 (95% credible interval [CrI], 0.82-0.99 and SDD was associated with a reduced risk of ventilator-associated pneumonia (RR, 0.44 [95% CrI, 0.36-0.54]) and ICU-acquired bacteraemia (RR, 0.68 [95% CrI, 0.57-0.81]).

Since the early nineties SDD has been standard of practice in most Dutch ICUs and it is estimated to be currently used in approximately 10.000 ICU patients per year in 2023 (deducted from data from Nice online (Stichting NICE - Nationale Intensive Care Evaluatie (stichting-nice.nl)) This concerns all patients duration of ventilation of at least 48 hours or length of stay of at least 72 hours.
While SDD is nowadays most often used in ICU patients, the application in the peri-operative setting, especially in gastrointestinal surgery, has also been performed since the nineties of the 20th century. The main goal of SDD is to lower the incidence of postoperative infections (especially postoperative pneumonia) and anastomotic leakage. A systematic review revealed a SDD-mediated decrease in postoperative infections and anastomotic leakage in lower GI surgery[22].
In esophageal surgery the concept of SDD was first introduced in 1990 by Tetteroo et al.[23]. The first review on SDD in upper GI surgery was conducted in 2020 by Scheufele et al.[24], showed efficacy without reporting serious adverse effects. Nowadays, four out of the 15 Dutch hospitals (performing esophagectomies) already include SDD in their standard perioperative care regimen for patients undergoing esophagectomy with the aim to reduce postoperative infections. This practice was subject of a recent retrospective cohort study, analyzing data of 496 patients of four Dutch hospitals, of which 179 patients received perioperative SDD. Upon SDD treatment, 45% less patients suffered from postoperative pneumonia (using the rUPS score for postoperative pneumonia [25] and the occurrence of anastomotic leakage was reduced by 50% (10,6% vs. 19.9%) compared to patients not receiving SDD [26]. A complete oversight of all studies with perioperative application of SDD in esophageal surgery, is provided in a systematic review that was performed as part of the Investigator's Brochure (IB) for the PERSuaDER-trial.

In the PERSuaDER-trial, we will apply only the orally administered liquid of SDD. No oral paste (SOD) or intravenous component will be applied. For this study the orally administered liquid of SDD is divided in two liquid formulations. First, the so called 'SDD Base for suspension' a solution containing tobramycin and colistin. Second, the formulation containing amphotericin B or nystatin for which both an SmPC is available.

3. STRUCTURED RISK ANALYSIS

As described in chapter 7 of the study protocol the intervention used in this trial (topical administration of tobramycin, colistin and amphotericin B or nystatin by oral intake) is not expected to be associated with more risks than expected during standard care. This preventative strategy of non-absorbable antimicrobials has been applied in Dutch ICU's and several other ICU's across Europe over the past three decades and is generally considered safe. Safety aspects are further elaborated upon in the IB (Investigator's Brochure).

3.1 Potential issues of concern

a. Level of knowledge about mechanism of action

SDD (Selective Digestive Decontamination) compromises two distinct fluids containing three different non absorbable compounds with antimicrobial activity. Two of these (colistin and tobramycin) have the ability to eradicate gram negative bacteria and one (amphotericin B or nystatin) eradicates fungi (notably Candida spp.) from the digestive tract. Working mechanism for the respective drugs may be found in the Farmacotherapeutisch Kompas and BCFi. Because the active substance of all four antimicrobials is not absorbed, no relevant systemic side effects are expected.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

SDD (Selective Digestive Decontamination) has been used extensively in ICU patients in the Netherlands for the last 20-30 years. In some landmark studies [12, 27] its efficacy has been proven and little to no side effects of SDD have been reported. An extensive report on the safety profile of the SDD components is provided in chapter 7 and in the IB. A variety in composition of SDD exists, but the composition used in this study is the most frequently used in ICU studies and elective (lower) gastro-intestinal surgery[22].

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Not applicable

d. Selectivity of the mechanism to target tissue in animals and/or human beings

As stated above, all pharmaceuticals in SDD are considered non-absorbable and no relevant systemic side effects are expected. To our knowledge no general pharmacological studies have been performed for the combination of compounds taken up in SDD. Toxicity is not extensively studied in the multitude of clinical trials that have been performed in ICU. The Dutch SWAB guideline reviewing all relevant literature states that both SDD and SOD (selective oropharyngeal decontamination) have few but acceptable side effects in ICU patients, however it is recommended to measure aminoglycoside levels in SDD patients receiving continuous veno-venous hemo-filtration (CCVH). Also, in long-term use of SDD, absorption of tobramycin from the gastrointestinal tract takes place[28]. In this prospective observational cohort study by Oudemans et al., 83 of 100 patients had detectable tobramycin levels in the blood (>0.050mg/L) and 12 out of 19 patients undergoing continuous veno-venous hemofiltration (CVVH) showed detectable tobramycin levels, which reached a toxic value (>3.0mg/L) in one patient. The highest tobramycin levels were found in patients during CVVH who also had ischemic bowel disease.

In our study population, patients undergoing CVVH, as well as patients with documented chronic renal failure (GFR < 15 mls/min) or who are on chronic intermittent hemo- or peritoneal dialysis are excluded from the study. If acute renal failure develops during clinical follow up in the postoperative phase of the study (3 days) investigational medication will be stopped. Tobramycin levels may be ordered at clinical indication by the treating physician. SDD in our study will be used only for a maximum of 7 days, which is considered short as compared to the often longtime application in ICU patients (sometimes up to 3-4 weeks). For a detailed description of safety of SDD, see IB.

e. Analysis of potential effect

The non absorbable antimicrobials applied as an intra-oral paste (SOD) has been rarely described to cause obstruction in the esophagus if the paste is not properly removed before applying the next dose[20]. As only enteral liquid (and NOT oral paste) is used in this trial, this risk is considered non-relevant to our study patients.

f. Pharmacokinetic considerations

To our knowledge there are no pharmacokinetic interactions (CYP450, P-gp) and pharmacodynamic interactions (pharmacological/physiological) between the different compounds in SDD. As mentioned above, the compounds are not enterally absorbed, so no systemic side effects may be expected.

g. Study population

Research subjects are patients undergoing elective surgery for esophageal carcinoma. The research subjects are admitted through the General Surgery dept and postoperatively

spend 1-3 days in ICU, medium Care or Post Operative Care units (PACU). The condition of the patients participating in this study is stable, but the operation is an obvious a clinically destabilizing event. For women of childbearing potential at risk for pregnancy, adequate contraception is required.

h. Interaction with other products

Besides binding to sucralfate (see 8.2.1 of this protocol, or for more details the IB), no relevant interaction is expected with other co-medication in these patients. If a patient is using sucralfate, it should be discontinued or switched to a medication with a different mechanism of action. Co medication in these patients is mainly perioperative medication like analgesics (paracetamol, morphine), anesthetic drugs, prokinetic drugs. In this condition all other drugs are administered intravenously in the perioperative period (except for SDD, so no absorption problems are expected). As SDD has no or limited absorption in the circulation, no other interaction is expected.

i. Predictability of effect

Not applicable: in this study the effect is evaluated at the level of patient outcomes (occurrence of infections). However, the level of eradication of relevant microorganisms in the gut is evaluated. Two cultures are taken at the day of surgery and indicate the level of eradication by the orally administered non absorbable SDD indicating patient (non) compliance to the protocol.

j. Can effects be managed?

There are no antidotes or antagonist available for these drugs. Theoretically, an allergic reaction to one of the antimicrobial compounds can occur, however this was only once reported in a patient undergoing esophagectomy and was poorly described[23]. Allergic reactions to the separate components has been described for colistin, amphotericin B and tobramycin but in these reports no difference were made between the oral (non-absorbable) and parenteral compounds. Only one case report is published regarding acute generalized skin rash secondary to the use of an oral suspension of nystatin [29]. It is clear that allergic reactions to the respective compounds are rare but they exist and lead to the exclusion of patients with documented allergies to these drugs.

3.2 Overall synthesis of the direct risks for the research subjects

3.2.1 SDD regimens are widely used and risks are well documented

SDD regimens have been used extensively in ICU patients to prevent bacterial infections and are used as standard care in ventilated ICU patients in the Netherlands[30-32].
As these antimicrobial agents are not, or at the most poorly, absorbed from the gut, systemic effects are rarely expected. The applied dose of colistin, tobramycin, amphotericin B and nystatin in this trial is comparable as the one used in previous studies

on SDD and is in fact the most commonly used SDD regimen, applied as standard of care in ICU's in the Netherlands.

There are only a few case reports on serious adverse reactions during the use of topical antibiotics. These adverse reactions represent three cases of esophageal obstruction by intra orally applied SOD paste in ICU patients[33].
This low risk is also applicable for the most feared -ecological- complication of antibiotic therapy: the induction of development and spread of multidrug resistant microorganisms; a 2013 systematic review showed no relationship between the use of SDD and the development of antimicrobial-resistance in pathogens in patients in the ICU, suggesting that the perceived risk of long-term harm related to SDD cannot be justified by the available data[34]. The risks for patients in non ICU settings are poorly described in the literature. A general description of the safety of SDD can be found in chapter 7 and the IB including the results of a systematic review related to the effectivity and the safety of SDD in patients undergoing elective esophagectomy.

3.2.2 Risks in a severely ill ICU patient population extrapolated to the outpatient ambulant patient group in our study

Participants in the PERSuaDER-trial are adult patients undergoing elective surgery. There is extensive experience with the use of topical antibiotics in adults in the ICU. ICU patients are generally severely ill and suffer from multiple organ failure. In contrast with ICU patients, the condition of the patients in this trial is considered to be stable and patients are usually in a relatively healthy condition because they are eligible to undergo elective surgery. It is likely that the side effects of SDD found in ICU patients are related to the severity of illness and/ or the duration of exposure:

- e.g. elevated levels of tobramycin were predominantly found in patients who received SDD for a long period of time and toxic levels were found in patients with Continuous veno-venous hemofiltration (CVVH) and in a patient with ischemic bowel disease

- Renal dysfunction is common in ICUs where multiple organ failure often comprises acute kidney injury (AKI) which is multifactorial in origin. It is unlikely that AKI in these patients can be attributed to increased levels of tobramycin (colistin, nystatin or amphotericin b) Since the use of topical antibiotics is considered to be safe in ICU patients, it is highly likely that the SDD regimen is safe in ambulant patients as well.

3.2.3 Exclusion of patients at risk

To minimize possible risks, well-described exclusion criteria are used:

- Systemic side effects of SDD are not to be expected, however, for women of childbearing potential at risk for pregnancy, a pregnancy test should be performed prior to the start of treatment with IMP's. Women with a positive pregnancy test are excluded from the trial because of a lack of studies on in vivo effects that confirm topical antibiotics to be safe in these patients.

- Patients with known sensitivity to the components of the study treatment or patients that are unable to take the medication orally are excluded for safety reasons as well.

- Patients with chronic renal failure or undergoing chronic intermittent or continuous dialysis (CVVH) are excluded from participating because of the risk of increased serum tobramycin concentrations described in the literature. In addition, systemic aminoglycosides may enhance muscle weakness caused by existing neuromuscular diseases as myasthenia gravis and Parkinsons disease. Although aminoglycosides are only used in an oral poorly absorbable form in this study, patients with these degenerative neuromuscular diseases will be excluded from the study.

- Patients who are known to be colonized with or have infections caused by microorganisms resistant to tobramycin and / or colistin or against carbapenems are excluded from this trial

Furthermore, all patients will receive complete information on the trial and are made aware of possible complications and side effects. For questions or advise, patients will receive contact information of their treating physician or member of the research team.

4. OBJECTIVES

Primary Objective: The primary aim of the PERSuaDER-trial is to evaluate the effect of SDD on infectious complications after esophagectomy, focussed on the prevention of pneumonia. We hypothesize that the intervention will decrease the rate of post-operative pneumonia by one third.

Secondary Objective(s): The secondary objective is to evaluate additional benefits, such as reduction of other infectious complications including anastomotic leakage, quality of life during the recovery period, and risks of SDD. Furthermore, outcomes will be used for a cost-effectiveness analysis.

5. STUDY PLAN AND DESIGN

5.1 Trial Design

We will perform a multicentre randomized controlled pragmatic trial in patients with primary resectable esophageal carcinoma (cT1-4a, N0-3, M0) undergoing esophagectomy. In this open-label study, patients will be randomly allocated to a control cohort receiving regular care or an intervention cohort, receiving standard care plus SDD (Figure 1). Additionally, all patients receive intravenous perioperative antimicrobial prophylaxis, applied according to the local hospital guidelines and based on national guidelines issued by the Dutch Working Party on Antibiotic Policy (SWAB) and the Belgian equivalent (BAPCOC) for perioperative prophylaxis. All patients will keep a subject diary to track side-effects and symptoms. They will also fill out questionnaires at fixed time points. The trial design does not include a placebo as blinding would greatly increase the complexity and costs of the trial. The proposed approach allows for a pragmatic trial that enables its implementation during routine clinical practice; a key element to obtain a clinically relevant readout on treatment effectiveness.

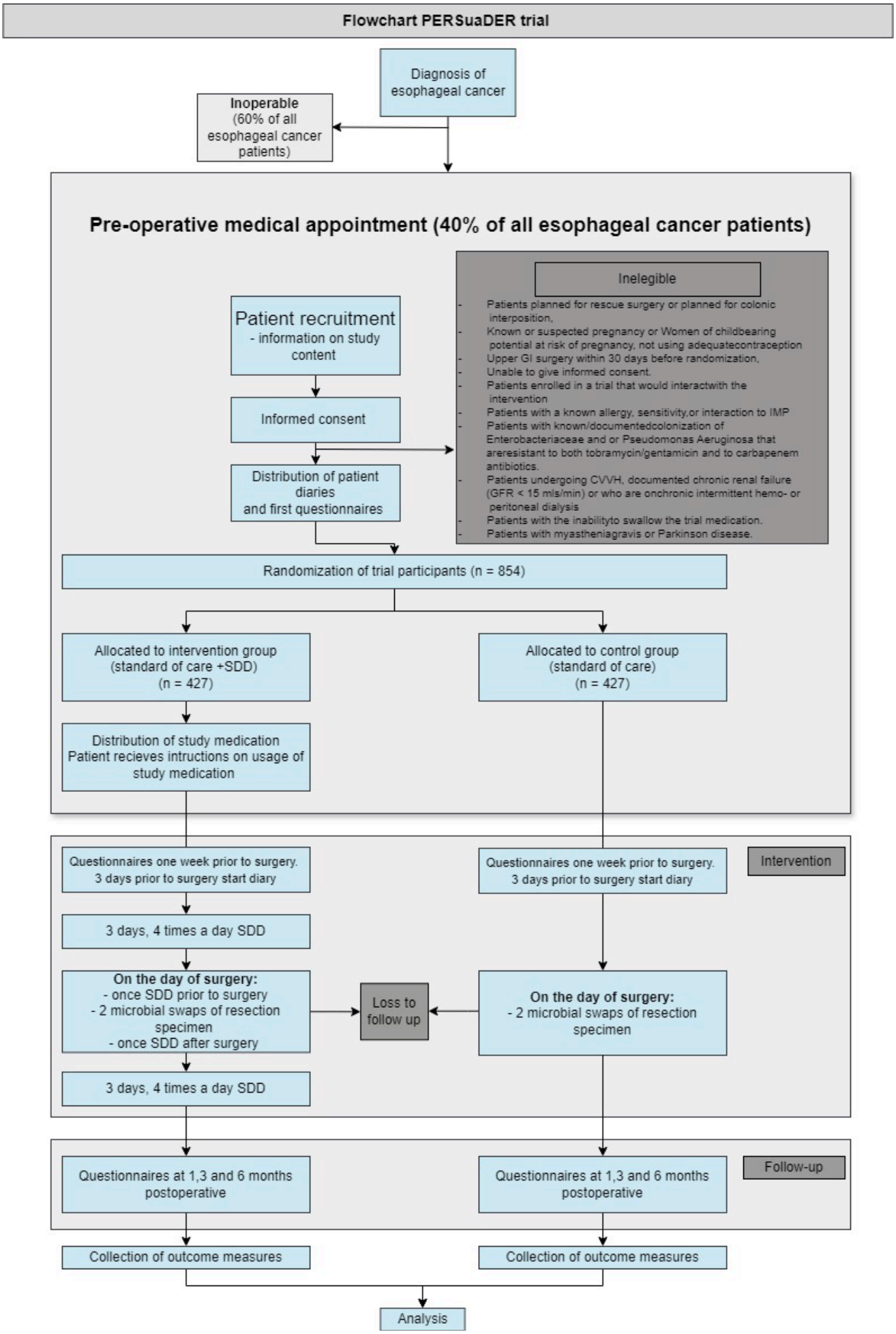


Figure 1| Overview of the study design and the main procedures that subjects will undergo during the research.

5.2 Number of Patients

We are aiming to enrol a total of 854 patients, equally divided between the intervention- and control group.

5.3 Overall study duration and follow-up

The intervention starts three days prior to the surgery, lasting for a total of seven days. Patients will be followed-up for further outcomes (infectious complications, anastomotic leakage, re-operation and quality of life). All patients will be enrolled for a total of six months and three days.

5.4 Patient participation

In the Netherlands, we collaborate with SPKS (http://spks.nl/), a foundation for people with esophageal or gastric cancer which is connecting and supporting patients and exists for more than 25 years. In Belgium, we work with 'Contactgroep Spijs' (https://www.contactgroepspijs.be/). 'Contactgroep Spijs' is a patient peer group that has been recently erected to connect Flemish patients diagnosed with and subject to an operation involving a resection of esophagus and/or stomach; no other francophone nor national patient group is currently existing in Belgium. To gather input and feedback, we have been and will be in regular contact with (former and current) esophageal cancer patients from these organizations (for more information see below).

<u>Involvement in the creation of the trial</u>

Patient representatives from both patient organizations were involved during essential parts of the creation process of the trial: (writing of) the study protocol, discussion on the core study outcomes, the assessment of the impact of the study actions on patient experience throughout the perioperative recovery track, the assessment of the willingness of patients to participate in the study, and the development of patient information. Based on their feedback some patient-related issues and concerns have been amended, e.g. voiced concerns regarding antibiotic resistance.

Furthermore, the scope of the project and its research plan have been discussed with and approved by both patient organizations. Importantly, patient representatives did not foresee any special difficulties in recruiting patients or regarding the willingness of patients to be randomized across conditions (standard care vs. standard care + perioperative SDD). Feedback and questions were continuously discussed in written form via email and a final pre-submission meeting was set up with two representatives of each patient peer group in order to discuss the final trial design and discuss any open issues and questions.

6. STUDY POPULATION

6.1 Population (base)

Patients with primary resectable esophageal carcinoma planned to undergo transthoracic esophagectomy at the 19 participating Dutch and Belgian centres will be recruited. In total, 832 patients with primary resectable esophageal carcinoma are annually planned to undergo transthoracic esophagectomy at the participating centres. To recruit 854 patients for the study at a realistic, expected recruitment rate of ~35%, we will recruit patients for 39 months to draw from a source population of approximately 2681 patients. Therefore, we are likely to recruit the planned number of patients from the defined source population. In case of stagnating inclusion, other centres with the intention to participate will be added to this study by amendments.

In total, approximately 1200 patients undergo transthoracic esophagectomy in the Netherlands and Belgium every year. We expect the study population of both participating countries to have comparable patient characteristics. In recent years, in both the Netherlands and Belgium, the mean age of patients was ~67 years, the majority being male (~77%) and Caucasian (>90%). Patients present with varying degrees of comorbidities (Charlson Comorbidities Index, CCI, 0:45%, 1:22%, 2+:32%), and health status (ASA physical status classification score 1: 8%, 2: 59%, 3+: 34% for the Netherlands and ASA 1: 2,5%, 2: 43%, 3+: 54% for Belgium)[3].

6.2 Inclusion criteria

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

- Diagnosis of primary esophageal adenocarcinoma or squamous cell carcinoma (cT1b-4a, N0-3, M0) in the mid or distal esophagus or at the level of the gastro-esophageal junction scheduled for undergoing transthoracic esophagectomy with curative intent or for esophageal reconstruction with a gastric or jejunal interposition
- Age ≥ 18 years,
- Able to give written informed consent.

6.3 Exclusion criteria

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

- Patients planned for rescue surgery,
- Patients planned for colonic interposition,
- Known or suspected pregnancy,
- Patients who have undergone upper GI surgery within 30 days before randomization,

- Unable to understand the study information, study instructions and give informed consent.
- Patients enrolled in a trial that would interact with the intervention,
- Patients with a known allergy, sensitivity, or interaction to components of the investigational medicinal product,
- Patients with known/documented colonization of Enterobacteriaceae and or Pseudomonas Aeruginosa that are resistant to both tobramycin/gentamicin and to carbapenem antibiotics,
- Patients undergoing CVVH,
- Patients with documented chronic renal failure (GFR < 15 mls/min) or who are on chronic intermittent hemo- or peritoneal dialysis,
- Women of childbearing potential at risk of pregnancy, not using adequate contraception,
- Patients with the inability to swallow the SDD,
- Patients with pre-existing degenerative neuromuscular diseases like, but not limited to, myasthenia gravis or Parkinson disease.

7. *STUDY TREATMENTS*

The investigational medicinal product will consist of two distinct liquids for oral intake of 5 ml antifungal suspension containing amphotericin B (100 mg/ml) or 5 ml nystatin (100.000 IE/ml), followed by 5 ml SDD base suspension consisting of colistin sulphate (20 mg/ml), and tobramycin (16 mg/ml). In the Netherlands, where they are widely used in daily ICU patient care, these products are available as a magistral preparation or as extemporaneously compounded medicines but not as products with a market authorization.
The composition of these compounds has been chosen to decolonize the digestive tract, i.e. to eradicate potential pathogens causing postoperative infections. Colistin and tobramycin have activity against Enterobacterales, a group of gram negative enteric bacteria which are common causative pathogens of nosocomial respiratory tract infection. Amphotericin B and nystatin are antifungal drugs that are effective against Candida spp. that potentially causes postoperative wound infection, empyema and complicates anastomotic leakage associated infections. Many different compositions of SDD have been suggested but the two used in this study was most broadly studied, both in ICU patients as in lower GI surgery.

7.1 Name and description of Investigational Medicinal Product

The combination of the investigational medicinal products, composed of 5 ml 100 mg/ml amphotericin B or 5 ml nystatin (100.000 IE/ml) and 5ml of the second drink containing 20 mg/ml colistin sulphate and 16 mg/ml tobramycin sulphate, as used in this study, is called “SDD”[35]. SDD consists of commercially available and approved antimicrobial drugs that are not or minimally absorbed from the GI tract.

7.2 Summary of findings from non-clinical studies

No preclinical studies with this SDD formulation exist. However, preclinical studies with the individual drugs have been performed extensively, as all active pharmaceutical ingredients of SDD are available in products with a market authorisation in Europe. Extensive information on these separate compounds can be found in the IB.

7.3 Summary of findings from clinical studies

Selective decontamination of the digestive tract is a prophylactic antibiotic strategy that aims to prevent infections by reducing GI colonization with aerobic gram-negative rods and yeasts, while preserving anaerobic microbiota. SDD consists of oral, non-absorbable antimicrobial agents, e.g., colistin, tobramycin, amphotericin B or nystatin. A large number of studies has shown that SDD reduces the number of infections of ICU patients. The most recent systematic review and meta-analysis pooled data from 24.389 patients in 32 randomised controlled trials

in ICU[21]. The pooled estimated risk ratio (RR) for mortality for SDD compared with standard care was 0.91 (95% credible interval [CrI], 0.82-0.99 and SDD was associated with a reduced risk of ventilator-associated pneumonia (RR, 0.44 [95% CrI, 0.36-0.54]) and ICU-acquired bacteraemia (RR, 0.68 [95% CrI, 0.57-0.81]).
In the intensive care unit, this preventive strategy (SDD) actually consists of three different components. First, a paste is applied to the oropharynx. As a single component, this is called SOD (selective decontamination of the oropharyngeal tract). Second, a liquid is taken orally or administered via a nasogastric tube. Third, a short (4 day) course of intravenous antibiotics (a third generation cephalosporins such as cefotaxim or ceftriaxon) is added to the regimen. Many variations of SOD and SDD exist (different combinations of compounds, different combinations of parenteral and non-absorbable orally administered drugs) but the most applied combination (the one that is used in the PERSuaDER-trial) are the ones that has been used in the Dutch intensive care setting since as early as 1984 and consists of tobramycin, colistin and amphotericin B or nystatin applied 4 times daily. Within the PERSuaDER-trial however, SDD is referred to as the orally administered liquid only.

Another recent systematic review showed that perioperative application of SDD (like in the PERSuaDER trial only an orally ingested SDD, no oral paste, no intravenous component) decreased the rate of postoperative infections and anastomotic leakage after colorectal surgery[36]. In esophageal surgery, two studies have reported SDD to reduce gram-negative colonization and to decrease postoperative infection rates[22, 26]. A recent retrospective cohort study comprising 496 patients in four Dutch hospitals with and without SDD after esophagectomy showed that patients who received perioperative SDD were roughly half as likely to develop postoperative pneumonia and or anastomotic leakages than patients receiving standard care without prophylactic antibiotics[26]. A systematic review of all current available literature on perioperative SDD (including both the use of nystatin and amphotericin B) in patients undergoing esophagectomy has been conducted, for we refer to the Investigator's Brochure [18].

7.4 Summary of known and potential risks and benefits

A recent meta-analysis assessed 1384 studies to select 4 small randomized clinical trials on the use of SDD in upper GI surgery[24], showing a reduction of postoperative anastomotic leakage and pneumonia. SDD treatment was not associated with an increase in postoperative mortality. Due to the low amounts of participants included in these studies, and the associated low power, a large-scale study on the use of SDD in upper GI surgeries is needed. The perceived risk of long-term consequences by the antibiotic prophylaxis specific to SDD cannot be justified by the currently available evidence[30, 34]. Please refer to the IB for more details.

7.5 Description and justification of route of administration and dosage

SDD is performed in line with previous studies and Dutch national guidelines [37] and the proposed combination and dosage reflects current prophylactic antibiotic strategies of ICU settings. Adhering to the pragmatic trial setup, the medication will be administered orally as this enables the patients to start with the medication at home. If ingestion of the SDD is not possible in the initial postoperative period, the SDD can be given through the nasogastric tube. In the literature, there is substantial variation in the application of the components of SOD (oropharyngeal paste) and SDD (enteral suspension) during the perioperative phase of esophagectomy. In all studies pre-operative application of SDD suspension is performed as a single intervention. Application of paste in mouth and throat (SOD) is considered unfeasible as the (sticky) paste is considered unpleasant in awake patients. Next to this, it is undesirable in patients with potential esophageal obstruction due to the tumour. In sedated and intubated patients (such as is the case in ICU patients) oral paste (SOD) is part of the standard of therapy.

7.6 Dosages, dosage modifications and method of administration

SDD, according to the Dutch national guidelines[37], is performed in line with previous studies and[12, 27, 30].

The intervention group receives SDD treatment additional to standard care, comprising two distinct liquids for oral administration: first, the 5 ml amphotericin B suspension (100 mg/ml) or 5 ml nystatin (100.000 IE/ml) and subsequently the 5 ml “SDD base for suspension”, containing both colistin sulphate (20 mg/ml) and tobramycin sulphate (16 mg/ml). Patients take the 5 ml amphotericin B or nystatin, followed by the 5 ml “SDD base for suspension”, four times daily for one week, starting three days prior to the surgery. On the day of surgery, intake is limited to an early morning and a late evening dose.

Each patient will receive only one antifungal agent (either amphotericin B or nystatin) for the entire duration of the study, and no switch between antifungal agent will occur within individual patients. The selection of the antifungal agent is based on market availability at the time of patient inclusion. Amphotericin B is the initially specified antifungal agent according to the original study protocol. Due to market shortages, nystatin has been introduced as an alternative antifungal agent through a protocol amendment. During periods in which amphotericin B is unavailable, nystatin will be used according to the study protocol.

7.7 Preparation and labelling of Investigational Medicinal Product

The investigational medicinal products will be produced, labelled, and released in line with current GMP guidelines and the clinical trial regulation 536/2014. This will be done by the Apotheek Spaarne Gasthuis (ASG).After production and labelling, the IMP's are sent to the pharmacy of the Radboudumc who will be responsible for storage and further distribution to the participating centres. All shipments of the IMP's are carried out by certified couriers with temperature registration as required by the GDP criteria. The pharmacies of the participating centres are responsible for storing and distribution of the IMP's to the individual patients.
In the Netherlands, participants will receive the study medication by mail, send to their home address or at the hospital pharmacy. Belgian participants will receive the IMP's during their visit to the outpatient department.
In the event of reported temperature excursions during the storage and/or distribution of the study medication, the site needs to contact the sponsor to be able to take appropriate measurements.

7.8 Auxiliary medicinal product(s)

Not applicable

8. OTHER TREATMENTS AND RESTRICTIONS

8.1 Concomitant therapy

8.1.1 Permitted medication(s)

Due to the pragmatic nature of the trial, there will be no prohibition of concomitant medication.

8.1.2 Prohibited medication(s)

Sucralfate is able to binds to components of SDD, and could lower the efficacy of bowel decontamination. If a patient is using sucralfate, it should be discontinued or switched to a medication with a different mechanism of action.

8.2 Lifestyle restrictions

8.2.1 Contraception measures

For women of childbearing potential at risk for pregnancy a pregnancy test will be performed prior to start of treatment with the IMP's. Women with a positive pregnancy test will be excluded conform our exclusion criteria. During the administration of IMP's, appropriate anticonception should be performed according to CTFG recommendations [38]related to contraception and pregnancy testing in clinical trials. If a patient gets pregnant during the follow-up, she will be excluded. Follow-up of pregnant patients will be done in routine prenatal care.

8.2.2 Other requirements

Not applicable.

9. TRACEABILITY, STORAGE, ACCOUNTABILITY AND COMPLIANCE

9.1 Traceability and storage of the study treatment(s)

ASG is responsible for manufacturing the study medication, which will be transported to the trial pharmacy of the Radboudumc according to GDP. The trial pharmacy of the Radboudumc will take care of the distribution to the pharmacies of the participating centres. The study medication will be stored in the hospital pharmacy conform local pharmacy guidelines. After randomization and prescription the medication is sent or given to the study participant. Furthermore specific documentation of prescribed amounts and doses taken is available in the patient's electronical medical records and patient's diary.

9.2 Accountability of the study treatment(s) and compliance

In the 3 preoperative days no check will be performed apart from the reminder prior to the start, as not to interfere with the pragmatic nature of the trial patients will be asked to hand in the empty vials of the SDD basis for suspension and Amphotericin B or Nystatin upon admission. A member of the research team, will pull up the remaining amount of both IMP's, this will be recorded in the source documents and in the eCRF. During the hospital admission, study medication will be administered by the nursing staff .If a patient experienced any problems swallowing the SDD this should be noted as well.

The local pharmacy is responsible for the drug accountability log. Returned vials need to be weighted and amounts need to be recorded. Vials need to be kept guaranteed until the monitor has done a check.

10. STUDY ASSESSMENTS AND PROCEDURES

10.1 Screening procedure

The treating physician will approach all patients undergoing an esophagectomy for esophageal cancer about the possibility of participating in the PERSuaDER-trial. If the potential participant has consented to be contacted by members of the research team, they will be informed about the study, and additional information regarding the trial will be provided. After the patient has read the letter, any remaining questions will be answered. Once the patient decides that they have had sufficient time to consider their decision and all questions have been answered satisfactorily, the patient will be asked to return their signed consent in the provided return envelope. At the time the ICF forms are handed over to potential participants, verbal permission will be requested to contact them again after one week if the ICFs have not been returned, to inquire if there are any uncertainties that can be addressed. If the potential participant does not agree, they will not be contacted again.

Once the signed informed consent papers are received, patients will be, screened for the inclusion and exclusion criteria, randomized, followed by the distribution of questionnaires, a diary, and, if allocated to the intervention group, study medication.

In a few cases, there might be limited time between the outpatient department visit and the actual day of surgery. We anticipate that this will only be applicable if a patient is scheduled for surgery within 10 days. To provide these patients with the opportunity to participate in the PERSuaDER-trial, the study team will provide them with the informed consent documents, along with the questionnaire and diary, during their outpatient visit. If there hasn’t been a response from the patient and there is a risk of time constraint for randomization and provision of the study medication, a member of the study team will contact the patient by phone. We will inquire whether they wish to participate in the study and, if so, whether they have already sent the signed informed consent papers. If this is not the case, the patient will be request to send a photo of the signed document before sending the form by mail. After receiving this confirmation, patients will be screened for the inclusion and exclusion criteria, randomized, followed by the distribution of questionnaires, a diary, and if allocated to the intervention group, study medication will be sent.

With this approach, we aim to provide these patients with sufficient time to contemplate their informed consent and make a thoughtful decision regarding their participation in the trial.

10.2 Randomisation, blinding and treatment allocation

After informed consent and screening for the inclusion and exclusion criteria took place, randomization will be performed by the randomization module in CASTOR EDC (www.castoredc.com). Block-randomization with variable block size will be used, stratified by the three main confounding factors in esophageal surgery: hospital, site of anastomosis and Charlson Co-morbidity Index (CCI), because all three factors have a significant known

influence on patient related outcomes. Patients are allocated in a 1:1 ratio to receive either usual care alone or usual care plus the SDD treatment policy. As an open label study, allocation of the intervention will not be blinded. Analysis of the outcome parameters will be blinded.

10.3 Study procedures and assessments

An overview of the study procedures is given in Table 1.

Table 1: Schedule of assessments and study procedures – PERSuaDER-trial flow chart

	Timepoint	Preoperative medical appointment			Hospital admission	Surgery	Postoperative care					
		1-6 weeks until surgery	D-3	D-2	D-1	D0	D1	D2	D3	D30	D90	D180
Assessment/ Study procedure	Location	Outpatient clinic	Home		Hospital					Home		
Information on PERSuaDER, study content and consent (research staff)		x										
Collection informed consent		x										
Screening for the inclusion and exclusion criteria		x										
Randomization		x										
Dispersion and instruction on intervention medication at hospital pharmacy (or for Dutch patients sent home, depending on timing informed consent), distribution of questionnaires and diary.		x										
SDD intervention: Amphotericin B or Nystatin and “Basis for SDD”QID (except on D0: BID)			x	x	x	x	x	x	x			
Patient diary			x	x	x	x	x	x	x			
Resectional specimen swabs						x						
Outcome assessment (infectious complications, anastomotic leakage mortality, re-operation, re-admission and LOS in hospital and ICU)						x	x	x	x	x	x	x
QoL questionnaires		x								x	x	x

Abbreviations: BID, twice daily; ICU, intensive care unit; LOS, length of stay; QID, four times a day; QoL, quality of life.

Intervention

After signing the informed consent, screening for in- and exclusion criteria will be conducted, after this, randomization takes place using Castor. Once randomized for SDD, patients will receive SDD medication and instructions by the hospital pharmacy or the research staff (preferably in the same hospital visit). If there is any delay in randomization or in de distribution of the study medication form the hospital pharmacy we may send the SDD treatment by mail, but this is possible for Dutch participants only. SDD treatment policy consists of two distinct 5 ml liquids, administered orally four times daily. The oral antimicrobial prophylaxis starts three days before the day of surgery and is discontinued at day 4 after surgery. On the day of surgery, intake is limited to an early morning and a late evening dose. Patient will be reminded by the local research staff to start with study medication 3 days prior to the operation date. A daily check by a nurse will take place for compliance but only during admission; in the 3 preoperative days no check will be performed apart from the reminder prior to the start, as not to interfere with the pragmatic nature of the trial. Patients will be asked to hand in the empty vials of the trial medication upon admission. When the patient is admitted to the hospital prior to the day of the operation or on the operation day, in-hospital prescribers will continue SDD until the third postoperative day included.

Patients of the control group will not receive any placebo treatment.

Microbial assessment

Two microbial samples will be taken (using CE (conformité européenne) marked IVD's (invitro diagnostics)) from the esophageal resection specimen (one proximal and one from the distal part) for culture to evaluate effectiveness and compliance of SDD application in control as well as in the intervention group. All responsible laboratories have ISO 15189 certification.

10.3.1 Main study parameter/endpoint

The primary outcome parameter is the incidence of postoperative pneumonia within 30 days after surgery. Pneumonia will be defined by the following criteria:

- Positive sputum culture

OR

- Presence of a new progressive radiographic infiltrate plus at least 2 of the following clinical features:
    - Fever > 38.5°C
    - Leukocytosis (>11.0) or leukopenia (<4.0)
    - Purulent secretions

Ambiguous cases regarding the primary outcome of the study, as defined above, will be reviewed by the adjudication committee. The adjudication committee consists of two independent physicians with relevant clinical expertise sufficient to adjudicate the following ambiguous cases. The committee will be blinded for treatment.

Ambiguous cases are defined as:

- Cases in which only a positive sputum culture is reported, without meeting the other criteria for the definition as defined above.
- Cases with clinical suspicion of pneumonia in which all other criteria of the definition are negative. Clinical suspicion is defined in the eCRF as a binary variable (yes/no).
- Cases fulfilling the above-mentioned pneumonia criteria, but without clinical suspicion of pneumonia and/or a potential alternative cause (e.g. anastomotic leakage).

10.3.2 Secondary study parameters/endpoints

Secondary outcome measures are

1. the incidence of all postoperative infectious complications within 30 days after surgery as registered in DUCA (postoperative pneumonia (rUPS and American Thoracic society definition as well), *Clostridium difficile* infection, urinary tract infection, wound infection/abscess requiring wound opening or antibiotic treatment, central line infection requiring line removal or antibiotic treatment, intra-thoracic/intra-abdominal abscess, generalised sepsis as defined by Evans, Rhodes [39]), any other infections requiring antibiotics. All these complications are then graded according to the Clavien-Dindo classification [40];

2. the incidence of anastomotic leakage within 30 days after esophagectomy for which endoscopic, radiologic, or surgical re-intervention is needed. This corresponds to the definition of the ECCG of anastomotic leakage type II and III (Low, Alderson [41]. Anastomotic leakage is defined by contrast leakage on CT-scan with intravenous and oral contrast (swallow CT-scan) upon clinical suspicion, by endoscopy or by drainage of ingested materials into the chest tube (thoracic anastomoses) or ingested materials or saliva into cervical wound (cervical anastomosis) or signs of anastomotic leakage during re-intervention or autopsy;

3. the all-cause mortality within 90 days after surgery;

4. the rate of re-operation within 30 days after surgery;

5. the postoperative length of stay on the intensive care unit (ICU), including re-admissions within 6 months after surgery;

6. the postoperative length of the total hospital stay, including re-admissions for any reasons within 6 months after surgery;

7. the quality of life (QoL) a week before, 30 days-, 3 months- and 6 months after surgery. In the Netherlands, most of the study centres participate in POCOP[42]. POCOP is an online registry for patient related outcome measures (PROMS) or paper-based survey methods, including internationally validated EORTC OG25, QLQC30 and EuroQol-5D-5L questionnaires

[43-45]for patients undergoing esophagectomy. The follow-up of the PERSuaDER-trial we will temporarily remove the patient from the POCOP registration aiming to limit the burden on the patient and to keep the follow-up as high as possible. If consent was obtained to do so, filled in questionnaires will be shared with the POCOP database at the end of the follow-up period. In the Belgian medical centres, the above-mentioned questionnaires will be collected using paper or electronical forms, whichever are available in the respective institutions. If a patient prefers paper forms, a printed version will be provided;

8. Direct and indirect costs. The in-hospital and societal costs up to 6 months after surgery will be estimated with the help of the validated medical consumption questionnaire and the validated productivity cost questionnaire, developed by the iMTA[46, 47]. For Belgium a database cross linkage with the RIZIV/INAMI expenses is foreseen based on data pseudonymized by a Trusted Third Party and handled by KCE. The Belgian national patient identifier number will be used for data linkage with the expenses database of the health insurance provider, but will be withdrawn from the dataset by KCE before the analysis is performed.

All incidence endpoints will also be analysed as cumulative incidence.

10.3.3 Other study parameters (if applicable)

The following patient characteristics will be collected/determined at baseline

1. Patient parameters: sex, age, BMI, ASA classification, smoking, use of medication, comorbidities (e.g. Charlson Comorbidity Index) and history of thoracic or abdominal surgery, and ECOG performance status (Eastern Cooperative Oncology Group).
2. Preoperative tumour characteristics: tumour location and clinical TNM stage
3. Neoadjuvant treatment and type of neoadjuvant treatment
4. Pre-operative pulmonary condition (if assessment is performed)
5. Lab parameters: Albumin (prior to surgery), Hb (prior- and during surgery), Creatinine (pre- and post surgery), inflammatory biomarkers like CRP and PCT and white blood cell count are registered when available to evaluate pots surgical infectious complications.

11. STUDY DISCONTINUATION AND COMPLETION

11.1 Definition end of trial

The trial will be ended 6 months after the last patient underwent surgery.

11.2 Criteria for temporary halt and early termination of the clinical trial

Reasons for termination of a trial by the DSMB may include, but are not limited to:

- Failure of the investigator to comply with the protocol;
- Safety concerns;
- Inadequate recruitment of patients by the investigator.

In case the study is ended prematurely, the sponsor will notify within 15 days each Member State concerned of the end of the clinical trial in all Member Stated concerned and in all third countries in which the clinical trial has been conducted through CTIS (CTR: Article 37(3))

11.3 Discontinuation/withdrawal of individual subjects

11.3.1 Withdrawal of individual subjects

Subjects 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 intervention for urgent medical reasons.

11.3.2 Replacement of individual subjects after withdrawal

Patients will not be excluded from the study or replaced if the planned esophagectomy is cancelled (1-2% of all scheduled esophagectomy procedures). Withdrawn patients will be asked for consent for access to their medical records and reuse of these data (collected in usual care) in the study.

11.3.3 Follow-up of subjects withdrawn from treatment

Patients who withdraw from treatment will be offered to undergo standard of care treatment according to the institution’s guidelines and are followed up in existing registries (IKNL/ POCOP), unless they specifically indicate that this is not allowed and withdraw from consent.

11.4 Arrangements for subjects after their participation in the clinical trial ended

Not applicable

12. SAFETY REPORTING

12.1 Definitions

12.1.1 Adverse Events (AEs)

Adverse events are defined as any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

12.1.2 Serious Adverse Events (SAEs)

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

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- Is an important medical event that may be considered an SAE when - based on appropriate medical judgement - it may jeopardise the subject and may require medical or surgical intervention to prevent one of the above outcomes.

Context specific serious adverse events are defined as a SAE known as a complication of the disease, operation or study intervention.

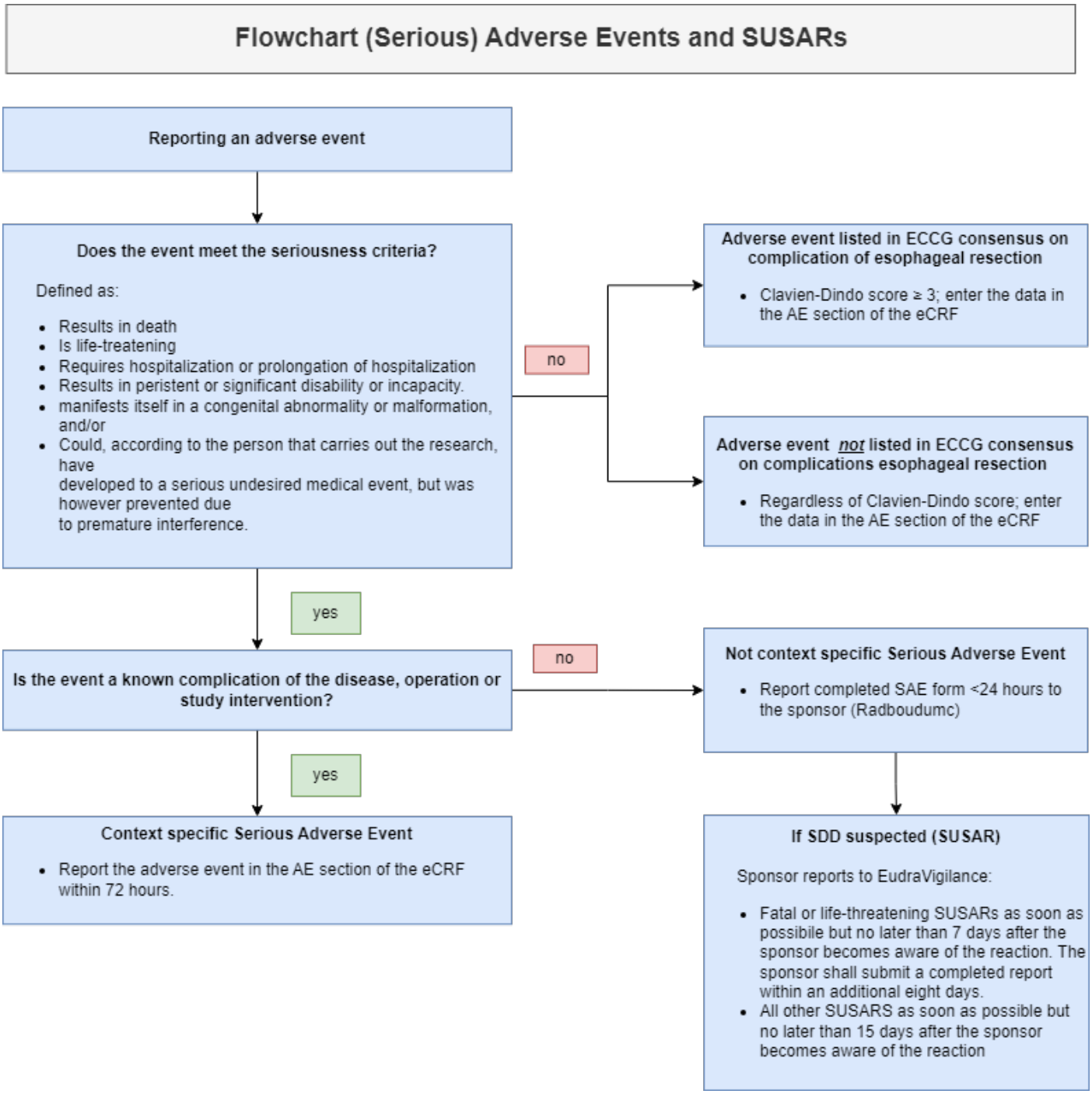
12.1.3 Suspected unexpected serious adverse reactions (SUSARs)

Unexpected adverse reactions are SUSARs if the following three conditions are met:

- The event must be serious;
- There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
- The adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information, see for more information paragraph 7.2 to 7.6 of the protocol.

12.2 Reporting of SAEs/SUSARs

See flowchart below



12.2.1 Reporting of AEs

Esophageal surgery is associated with considerable morbidity and mortality, therefore numerous AEs and SAEs will occur within our study. It is clear that reporting all AEs has no added value and will not enhance patient's safety. Therefore, we agreed to only note in the eCRF the AEs listed in the ECCG consensus on complications of esophageal resection from Clavien-Dindo score 3 onwards.

AEs not documented in the above mentioned ECCG consensus will be entered in the eCRF regardless of Clavien-Dindo score.

12.2.2 Reporting of SAEs/SUSARs by the investigator to the sponsor

The context specific serious adverse events needs to be reported in the AE section in the eCRF within 72 hours after becoming aware (to avoid an incomplete annual safety report). If there occur SAEs/SUSARs which cannot be reasonably expected from the surgical intervention, study intervention or the disease for which the surgical intervention is planned, the investigator will report to the sponsor within 24 hours.

12.3 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.

12.4 Reporting of SUSARs to the Eudravigilance database

The sponsor takes responsibility for the electronic reporting of SUSARs in Eudravigilance without delay.

The period for the reporting of SUSARs to the EMA by EudraVigilance will take into account the seriousness of the reaction and will be as follows:

- In the case of fatal or life-threatening SUSARs, as soon as possible and in any event not later than 7 days after the sponsor became aware of the reaction.
- In the case of non-fatal or non-life-threatening SUSARs, not later than 15 days after the sponsor became aware of the reaction.
- In the case of a SUSARs which was initially considered to be non-fatal or non-life threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than 7 days after the sponsor became aware of the reaction being fatal or life-threatening.

Where necessary to ensure timely reporting, the sponsor may, in accordance with section 2.4 of Annex III, submit an initial incomplete report followed up by a complete report (CTR: Article 42(2)).

12.5 Annual safety report

The sponsor will submit an annual safety report of the investigational medicinal product used in the clinical trial in CTIS, once a year throughout the clinical trial. The annual safety report will be submitted to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions.
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

12.6 Unblinding procedure for safety reporting

Not applicable

12.7 Temporary halt for reasons of subject safety

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 submit the notification through CTIS without undue delay of a temporary halt but not later than in 15 days of the date of the temporary halt. It shall include the reasons for such action and specify follow-up measures. The study will be suspended pending a further positive decision by the concerned member state (CTR: Article 38). The investigator will take care that all subjects are kept informed.

12.8 Urgent safety measures and other relevant safety reporting

Where an unexpected event is likely to seriously affect the benefit-risk balance, the sponsor and the investigator will take appropriate urgent safety measures to protect the subjects. In addition the sponsor will notify the Member States concerned, through CTIS, of the event and the measures taken. That notification will be made without undue delay but no later than 7 days from the date the measures have been taken (CTR: Article 54).

12.9 Data Safety Monitoring Board (DSMB)/ Data Monitoring Committee (DMC)

To monitor safety, futility, and efficacy, an independent DSMB will be appointed. A DSMB charter is created according to DAMOCLES guidelines.
The DSMB has access to the gathered primary and secondary endpoint data. All deceased patients will be evaluated by the DSMB for cause of death and whether this could be related to a study intervention. After every meeting, the DSMB reports to the trial steering committee to discuss results. The DSMB advice will be sent to the Principal Investigators of Raboudumc and UZ Leuven. Should these PIs 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.
Interim analysis will be performed, if these interim analyses lead to an unambiguous conclusion this may cause an earlier termination of the trial.

13. STATISTICAL ANALYSIS

13.1 Description of statistical methods

Categorical data will be presented as number (proportion), continuous data as mean (standard deviation) if normally distributed or as median (inter quartile range) otherwise.
All patients randomized will be analysed for the primary and secondary analyses, irrespective of the intake of SDD (intention-to-treat analysis). See paragraph 13.6 for detailed analysis per study parameter.

13.2 Analysis sets

Data of all patients included in this trial, patient in the intervention group as well as control group will be included in the analysis.

13.3 Participant demographics and other baseline characteristics

The following demographic and baseline characteristics of participants will be analysed: Gender, age, length/weight (BMI), comorbidities (e.g. Charlson Comorbidity Index) and history of thoracic or abdominal surgery, health status (ASA classification), ECOG-performance status (Eastern Cooperative Oncology Group), preoperative T-stage, preoperative N-stage, preoperative M-stage, neoadjuvant therapy (radiotherapy, chemotherapy or chemoradiotherapy), Tumour type and location.

13.4 Randomisation and blinding

Randomization will be performed by the randomization module in CASTOR EDC (www.castoredc.com). Block-randomization with variable block size will be used, stratified by the three main confounding factors in esophageal surgery: hospital, site of anastomosis and Charlson Co-morbidity Index (CCI). Patients are allocated in a 1:1 ratio to receive either usual care alone or usual care plus the SDD treatment policy. As an open label study, allocation of the intervention will not be blinded. Analysis of the outcome parameters will be blinded. Patients will be randomized by the clinician after signing the informed consent, if help is needed they can contact the research coordinators.

13.5 Sample size, trail power and level of significance used

Based on contemporary registries and literature we assume an incidence of postoperative pneumonia in the control group of approximately 22%. The sample size calculation is based on the primary objective of the trial to demonstrate that the intervention will result in a clinically relevant decrease of the rate of postoperative pneumonia by 40% to an incidence of 13% (superiority) with 90% power and a two-sided alpha of 0.05. We performed sample size calculation for the group sequential design using the Design package in R (Keaven Anderson (2021). gsDesign: Group Sequential Design. R package version 3.2.1. https://CRAN.R-project.org/package=gsDesign) with two interim analyses after 30% and 60% of the planned

number of participants completed follow-up for the primary endpoint, two-sided, asymmetric, beta-spending with binding lower bound. The Hwang-Shih-DeCani spending function will be used for both upper and lower bound. This considers the two interim analyses as well. The calculated sample size results in a total sample size of 814 study participants (407 per arm). Despite the short study intervention, some early deaths may already occur in this time frame. Therefore, we include upfront a loss to follow-up rate of 5%, including cancelled surgery after randomisation, and will for this loss add net 20 subjects to each group. As such the total required sample size of 854 participants will be needed.

The following R syntax was used:

```
require(gsDesign)
# parameters
p1 <- .22
p2 <- p1 * 0.6 # .13.2 (40% reduction)
power <- .9
alpha <- .05
# sample size calculation using time-to-event approach
lambdaC <- 1 - (1 – p1) ^ (1 / 30) # assume constant hazard - cumulative incidence 22.0%
lambdaI <- 1 - (1 – p2) ^ (1 / 30) # assume constant hazard - cumulative incidence 13.2%
# group sequential design: 2 interim at 30 and 60%
# the default Hwang-Shih-DeCani spending function from the gsDesign package is used
gsSurv(k = 3, test.type = 3, alpha = .025, beta = .1,
    hr = lambdaI / lambdaC, hr0 = 1,
    lambdaC = c(lambdaC, 0), S = 30, minfup = 30, # after 30 days, no events counted
    gamma = 1, # constant enrolment (1 per unit time)
    eta = 0, # no loss to follow-up for primary calculation
    timing=c(.3,.6,1)
```

13.6 Planned analysis

13.6.1 Primary study parameter(s)

For the analysis of the primary outcome, incidence of postoperative pneumonia within 30 days after surgery, we will use Cox regression (cause-specific hazard ratio which defines the effect on the daily hazard), with censoring for death and putative loss to follow-up, and we will adjust for the stratification variables (see 10.2) by including the stratification variables as strata in the regression. A sensitivity analysis will be performed using Fine & Gray regression (sub distribution hazard ratio which defines the effect on cumulative incidence) considering mortality

as a competing events and censoring for putative loss to follow-up, also including the stratification variables as strata.

13.6.2 Secondary study parameter(s)

Secondary outcomes will be analysed using logistic regression (all-cause mortality and rate of re-operation), time-to-event analysis (incidence using Cox regression and cumulative incidence using Fine & Gray regression), or linear regression (length of stay and quality of life), as appropriate. In all analyses, adjustment will be performed for stratification variables (see 10.2). Per protocol analyses will be performed in addition to the intention-to treat analyses, which includes all patients that received SDD or no SDD in accordance with the randomized allocation. Safety evaluation will be performed in the safety population which includes all subjects from the SDD group that received at least one dose of SDD and all subjects from the control group. Exploratory subgroup analyses will be performed for age, sex, body mass index, ASA score, pre-operative radiation of the surgical site, tumour type and classification, surgical technique, duration of surgery, timing of intravenous perioperative antimicrobial prophylaxis and type of antifungal medication (Amphotericin B or Nystatin); the size of this subgroup will depend on the availability of the antifungal agents at the time of treatment.

Cost-effectiveness and quality of life will be analyzed alongside the trial comparing SDD to usual care over a time horizon of 6 months from a societal perspective. Data on quality of life and absence from work will be collected. Patients will receive the following questionnaires by electronic mail or on paper: the EORTC-QLQC30, EORTC-OG25 and the EuroQol 5D-5L.[43-45] Patients are asked to fill in these questionnaires at 4 timepoints; baseline (1-6 weeks prior to surgery),1, 3, and 6 months postoperative. Dutch patients will be asked for permission to share their data with the POCOP registry (Prospective Observational Cohort Study of Oesophageal-gastric Cancer Patients).

Direct and indirect costs will be measured at baseline, 3 months, and 6 months with the help of the validated medical consumption questionnaire and the validated productivity cost questionnaire, developed by the iMTA[46, 47]. Belgian administrative medical consumption data is used where possible instead of these questionnaires. Prices for detected volumes of care will be based on the standardized Dutch and Belgian prices published in the manual for costing studies. For volumes of care where no standardized price is available, prices will be based on activity based costing or national reimbursement tariffs. Long-term productivity losses will be valued using the friction cost method. Quality-adjusted life years will be calculated in each arm using the EQ-5D-5L utilities estimated by means of the Dutch valuation tariff (no exact Belgian tariff is available at the time of writing this protocol) and the area under the curve will be estimated. Overall costs will be compared between the groups, and mean

differences, including of 95% confidence intervals, will be calculated. Incremental cost-utility ratios (ICURs) will be calculated by dividing the estimated differences in costs by the differences in QALYs. Uncertainty will be addressed by means of bootstrap simulations (n=1000). Results will be graphically presented by a cost-effectiveness plane and a cost-effectiveness acceptability curve varying on a range of willingness to pay values. Furthermore, the influence of differences in Belgian and Dutch cost prices or volumes of care will be explored in a sensitivity analysis as well as the influence of using EORTC based utilities.

13.6.3 Other study parameters

Baseline demographics, comorbidities, medication use, and laboratory values will be described as mean ± standard deviation for continuous data and number + percentage for categorical data.

Explorative subgroup analyses will be performed to assess differences in efficacy between men and women and age groups.

In addition, patients in both intervention and control group will be asked to fill in a diary during (SDD) treatment. This allows us to explore potential side effects and real-life experiences of patients, that is not captured in the current literature. With this diary, we will mainly focus on monitoring the side effects and therapy adherence of the patients.

13.7 Interim analysis

We will use a group-sequential design for the analysis of the primary endpoint, based on asymmetric testing design (superiority and futility). Analysis of the primary endpoint will take place after 30% (N=256), 60% (N=512) and 100% (N=854) of the planned sample size have been randomized and completed 30-day follow-up for the primary endpoint or have withdrawn or died. Including follow-up, data entry, cleaning, and analysis, it is anticipated that the interim data can be presented to the DSMB approximately three months after 30% and 60% of participants underwent surgery. The analysis at each interim analysis will include all randomized participants (intention to treat population), whereby participants still in follow-up will be censored at the date of their last follow-up. Recruitment will be terminated if the z-score crosses either the solid or the dashed line (Figure 2).

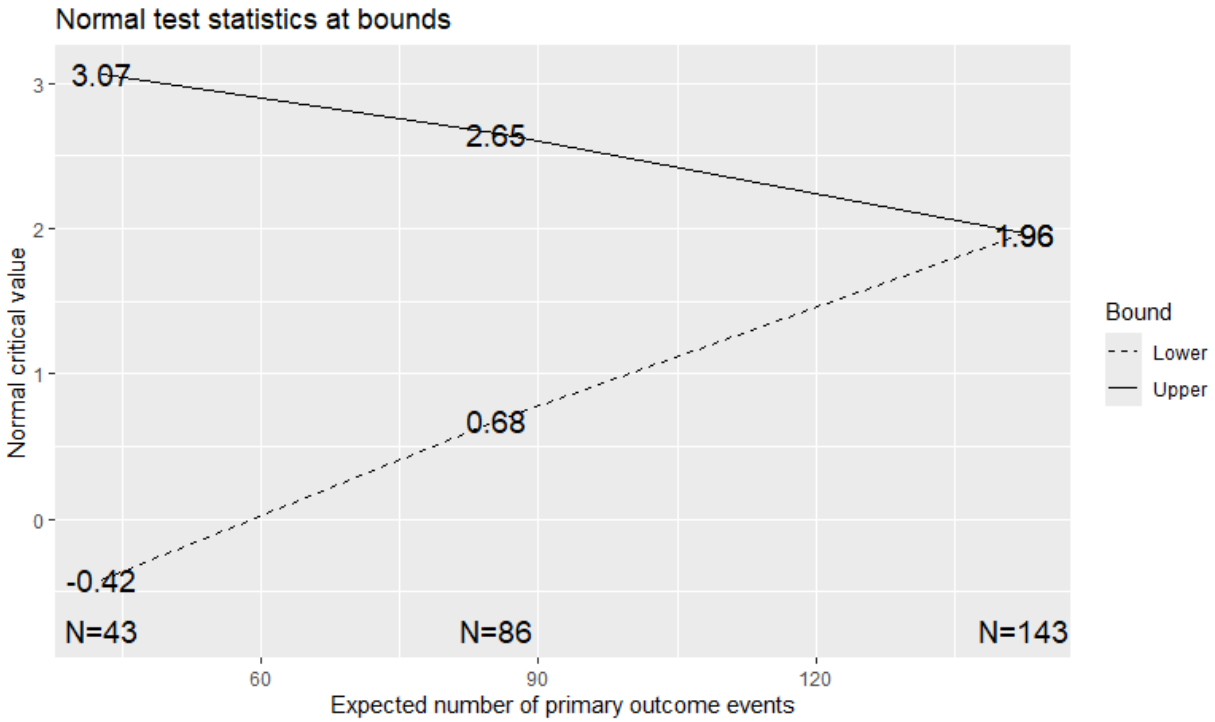


Figure 2| Stopping boundaries for the group-sequential design. The x-axis gives the expected number of primary endpoints at each (interim) analysis under the alternative hypothesis, which corresponds to an event rate of 0.22 and 0.13 for the control and intervention arm, respectively interim analysis 1: after 256 patients of the planned sample size have been randomized and completed 30-day follow-up for the primary endpoint or have withdrawn or died; interim analysis 2: after 512 participants, final analysis: after completing enrolment for the planned sample size.

13.8 (statistical) criteria for termination of the trial

See interim analysis.

13.9 Procedure for accounting for missing, unused and spurious data

The amount of missing data will be described. Missing data in variables that are planned to be included in multivariable models will be imputed using multiple imputation. Missing outcome variables and missing data in planned subgroup variables will not be imputed.

13.10 Procedure for reporting any deviation from the original statistical plan

All deviations from the original statistical analysis plan will be provided in the final clinical study report.

14. ETHICAL CONSIDERATIONS

14.1 Declaration of Helsinki

The study will be conducted according to this protocol, the principles of the Declaration of Helsinki (2013), the ICH Guidelines for Good Clinical Practice and in accordance with all applicable national legislation.

14.2 Recruitment and informed consent procedures

In paragraph 10.1, we provided a thorough explanation of our screening and informed consent procedure. With this approach, we aim to provide these patients with sufficient time to contemplate their informed consent and make a thoughtful decision regarding their participation in the trial.

14.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable (only patients aged 18 years or older who understand the informed consent procedures will be included).

14.4 Benefits and risks assessment, group relatedness

Many patients undergoing esophagectomy suffer from postoperative (micro) aspiration and are prone to develop infectious complications like pneumonia 7.6-35.9%[26]. These complications cause attributable mortality and an increased length of hospital and ICU stay. Similarly, microorganisms may play a major role in the pathogenesis of anastomotic leakage. Pathogens originating from the GI tract reaching the site of the anastomosis can induce local inflammation with abscess formation, facilitating anastomotic dehiscence and, eventually, anastomotic leakage. Eliminating these pathogens prior to surgery and during recovery may decrease the risk of infections and anastomotic leakage. SDD reduces the presence of infectious microorganisms before the surgery and during recovery.

Possible risks for patients of the control cohort:

- Standard risks associated with esophagectomy (e.g., pneumonia, infections, anastomotic leakage, chyle leakage, arrhythmia, bleeding for which transfusion is required, death). These risks are independent of the participation in this study, as patients would undergo the surgery either way.

Possible risks for patients receiving SDD:

- Standard risks associated with esophagectomy (e.g., pneumonia, infections, anastomotic leakage, chyle leakage, arrhythmia, bleeding for which transfusion is required, death). These risks are independent of the participation in this study, as patients would undergo the surgery either way.
- Risk of mild, but common side effects (~1 in 10 people) related to the intake of IMP's during the treatment period (3 days prior to 3 days post the surgery), such as:
    - vomiting;
    - nausea;
    - diarrhoea;
    - bloating and indigestion;
    - abdominal pain;
    - loss of appetite.

Possible benefits for patients receiving SDD:

- less infectious complications, such as pneumonia;
- less anastomotic leakage;
- shorter hospitalisation and/or ICU stays;
- less re-operations;
- lower mortality;
- better quality of life;
- better long term survival.

14.5 Compensation for injury

The sponsor of the study (Radboudumc) has a liability insurance which is in accordance with the legal requirements in the Netherlands (article 7 of the WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

€ 650.000,-- (i.e. six hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research up to a total of € 5.000.000,-- (i.e. five million Euro) for death or injury for all subjects who participate in the Research and a total of € 7.500.000,-- (i.e. seven million five hundred thousand Euro) for the total damage incurred by the organization for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

For the Belgian centers, the insurance provided by the Belgian Coordinating Centre will be covering no-fault liability for Belgian participants.

14.6 Compensation for investigators

Participating sites will be offered compensation which includes a start-up fee, a per patient fee, and a per patient fee depending on follow-up. Next to this the pharmacy will receive fee covering all their expenditures.

This trial is funded (category 2) by ZonMW and KCE, for details see appendix “compensation for trial participants (P1)”.

14.7 Incentives (if applicable)

Non applicable.

15. ADMINISTRATIVE ASPECTS, MONITORING AND CONFIDENTIALITY

We state that the PERSuaDER trial will be conducted in compliance with the protocol, with Clinical Trials Regulation No 536/2014 and with the principles of good clinical practice.

15.1 Approval initial application and substantial modifications

Before the clinical trial is started all the essential documents will be submitted for the regulatory approval via CTIS.

A ‘substantial amendment’ is defined as an amendment to the terms of the ECTR, 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.

If any substantial modifications to the original documents are made we will submit these via CTIS. A ‘substantial modification’ is defined in the CTR as any change to any aspect of the clinical trial which is made after notification of a decision referred to in Articles 8, 14, 19, 20 or 23 and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

15.2 Monitoring

Monitoring and Quality assurance will be performed according to the respective national guidelines. Dutch participating centres will adhere to the following:

Monitoring to check and ensure adequate study conduct regarding ethical conduct, data collection and documentation, records of study procedures, and compliance with the approved protocol will be performed by the Radboudumc Technology Center Clinical Studies. The monitoring plan will be in line with the guideline ‘Kwaliteitsborging Mensgebonden Onderzoek 2019’ of the Dutch Federation of University Medical Centers (NFU). “verwaarloosbaar risico”.

Belgian participating centres will adhere to the following:

The monitoring for the Belgian sites will be performed by the monitor service of the Clinical Trial Centre of the Belgian Coordinating Centre UZ Leuven in line with the monitoring plan as provided by the sponsor.

15.3 Recording, handling and storage of information

The study will utilize electronic case report forms (eCRF) for data collection. All data will be collected and processed in accordance with the General Data Protection Regulation (EU) 2016/679. All site staff will be trained on correct eCRF completion.

Study subjects will be identified only by their unique subject number which will be used in all correspondence and further administration in the study database. The investigator and the investigation site team shall maintain patient confidentiality in all documentations. An identification log will be kept of all subject numbers linked to corresponding participants. The list will remain at the participating site.

Data validation will be performed by checking the eCRFs with the medical records of all trial patients on the primary outcome by the monitor. Discrepancies will be discussed with the study nurse or site investigator.

Information obtained during the study will be regarded as confidential. The investigator and all members of the study team agree not to disclose or publish such information in any way to any third party without prior written permission from the principal investigator, which will not be unreasonably withheld, except as required by law. The Investigator will take all measures to ensure patient confidentiality.

Study related documents, patient records, signed informed consent forms, and source documents will be maintained at the participating site for 25 years after the end of this study, conform EU CTR. Source data will be entered in the online database Castor and afterwards exported to SPSS for the analyses.

For Belgium only:
After the completion of the study the Sponsor will transfer the pseudonymised study data set of the Belgian patients to KCE. KCE will request approval from the competent chamber of the Information Security Committee (ISC) to have the relevant study data linked with e.g. IMA data by a trusted third party (TTP, eHealth platform) using the patient national number.

The patient information and consent includes wording that the national number will be recorded on site by the investigator for later data linkage, but will not be included in trial database available to the sponsor or any other third party. The patient information and consent will also include that in case the patient is randomized, it is planned that a trusted third party (TTP, eHealth platform) will receive and use the national number to link with IMA administrative data.

To this end, KCE will receive the link between the study number and the national number under pseudonymised form. KCE will never be able to use the link without authorisation of the ISC and the intervention of the TTP. This data linkage is planned to obtain a more complete data set containing costs related to health care paid by the compulsory health insurance and the patient that will be used for the analysis of effectiveness and cost-effectiveness of the intervention by KCE. The processing of personal data for this analysis is necessary for the performance of a task carried out in the public interest, as specified in the law defining KCE's missions and tasks. To the extent the personal data is related to health, the processing is necessary for scientific or statistic purposes, as specified in the law defining KCE's missions and tasks. For all processing related to the analysis of effectiveness and cost-effectiveness of the intervention, KCE is the controller.

KCE and BCC have entered into a research agreement detailing the roles and responsibilities of each party, as well as other legal aspects of this collaboration, including the right to use and access of KCE to the Study Data.
If judged appropriate, KCE will introduce the request to the competent chamber of the Information Security Committee and arrange for the data linkage. For the sake of clarity, the linked data are not part of the Study Data. However, KCE will discuss with the Sponsor and BCC the results of the analyses and the reporting of the linked data.

15.4 Temporary halt and (prematurely) end of study report

The sponsor will notify each Member State concerned of the end of a clinical trial in all Member States concerned and in all third countries in which the clinical trial has been conducted through CTIS (CTR: Article 37(3)) within a period of 15 days. The end of the study is defined as the last patient's last visit.

The sponsor will notify each Member State concerned immediately of a temporary halt of the study, including the reason of such an action through CTIS.
In case the study is ended prematurely, the sponsor will notify each Member State concerned of the end of the clinical trial in all Member States concerned and in all third countries in which the clinical trial has been conducted through CTIS (CTR: Article 37(3)) within a period of 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 each Member stated concerned.

15.5 Summary of the results

Within one year from the end of a clinical trial in all Member States concerned, the sponsor will submit to the EU database CTIS a summary of the results of the clinical trial. The content of the summary of the results is set out in CTR Annex IV. It shall be accompanied by a summary written in a manner that is understandable to laypersons. The content of the summary is set out in CTR Annex V (CTR: Article 37(4)).

15.6 Public disclosure and publication policy

Upon completion of the study, the principal investigator will be responsible for the public disclosure/publication of the study outcome. The results will be reported during symposia, national and international professional meetings. The trial results will be submitted to a high-impact peer-reviewed medical journal regardless of the study outcomes.

Authorship credit will be based on the Recommendations of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). The criteria for authorship are defined as 1. substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2. drafting the article or revising it critically for important intellectual content; and 3. final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Only investigators from centres with high protocol compliance, fast enrolment and complete data sets from all follow-up visits will be considered as authors on publications. If these criteria are accomplished for all projected patients for at least 90%, the local principal investigator and an additional member of the research team will be co-author and two additional members of the research team will be collaborator. If these criteria are accomplished for over 75%, the local principal investigator will be co-author, and two members of the research team will be collaborator. Members of the steering committee will be co-author of the publications. The results of this study will be published in a journal. The coordinating investigator/project leader will have the final responsibility of the main publication. Sub-analysis can be published, after final publication of the main paper, and in consensus with the steering committee. The results of this study will be disclosed unreservedly. Prospective trial registration in a public trial registry before recruitment of the first participant will take place and the protocol will be published.

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