Elective Adhesiolysis vs. a Wait-and-see Policy to Prevent Recurrences after Conservative Treatment of Adhesive Small Bowel Obstruction

AWARE: Elective Adhesiolysis vs. a Wait-and-see Policy to Prevent Recurrences after Conservative Treatment of Adhesive Small Bowel Obstruction

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Coordinating investigator/project leader	**Dr. Richard ten Broek** **RadboudUMC**
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)	Dr. Richard ten Broek RadboudUMC (Sponsor) Richard.tenBroek@radboudumc.nl
Confirmed as operative Centers in the Netherlands:	Dr. E.B. Deerenberg Franciscus, Rotterdam e.deerenberg@Franciscus.nl Dr. T. Lubbers Maastricht UMC+ tim.lubbers@mumc.nl Dr. S.M.M. de Castro OLVG, Amsterdam S.M.M.deCastro@olvg.nl Dr. K.M. Govaert Pantein, Boxmeer k.govaert@Pantein.nl Dr. F. Aarts VieCuri, Venray faarts@viecuri.nl Dr. E.D. van den Ende ZGT, Almelo e.vdende@zgt.nl Dr. C.S. Andeweg St. Jansdal, Harderwijk CS.Andeweg@stjansdal.nl

Confirmed as operative Centers in Belgium:	Prof. Dr. Albert Wolthuis UZ Leuven (National Coordinating Center) albert.wolthuis@uzleuven.be
	Dr. Najla Bachir Hôpital Erasme najla.bachir@hubruxelles.be
	Dr. Jean-Baptiste Cornille Vitaz Sint-Niklaas cornillejb@gmail.com
	Dr. Jasper Stijns UZ Brussel jasper.stijns@uzbrussel.be
	Dr. Michiel de Maat UZ Antwerpen michiel.demaat@uza.be
Confirmed referral center, potential operative center	Dr. Johan Lange UMC Groningen j.lange@umcg.nl
	Dr. Bas Polle CWZ Nijmegen b.polle@cwz.nl
Confirmed referral centers	Prof. Dr. Pieter Tanis ErasmusMC Rotterdam p.tanis@erasmusmc.nl
	Dr. Flip Kruyt Ziekenhuis Gelderse Vallei Ede

	kruytf@zgv.nl
	Prof. Dr. M.A. Boermeester AmsterdamUMC m.a.boermeester@amsterdamumc.nl
	Jarmilla van der Bilt Flevo ziekenhuis jvdbilt@flevoziekenhuis.nl
	Prof. Dr. Esther Consten Meander Medisch Centrum ecj.consten@meandermc.nl
	Dr. Marnix de Roos Rijnstate Ziekenhuis Arnhem mderoos@rijnstate.nl
	Dr. Gijs van Acker Haaglanden MC gijs.van.acker@haaglandenmc.nl
	Dr. Werner Draaisma Jeroen Bosch Ziekenhuis W.draaisma@jbz.nl
	Dr. Lisanne Posma Slingeland Ziekenhuis Doetinchem l.posma@slingeland.nl
Sponsor (in Dutch: verrichter/opdrachtgever)	**RadboudUMC**
Subsidising party	**ZonMW/KCE**
Independent expert (s)	Maaike Ibelings; gastrointestinal surgeon m.ibelings@etz.nl ETZ Tilburg Department of Surgery Hilvarenbeekse Weg 60 5022 GC Tilburg
Laboratory sites <*if applicable*>	***<please include name and contact data>***
Pharmacy <*if applicable*>	***<please include name and contact data>***

PROTOCOL SIGNATURE SHEET

Name	**Signature**	**Date**
Sponsor or legal representative: ***<please include name and function>*** ***<For non-commercial research,>*** **Head of Department:** ***<include name and function>***	**Prof. dr. C.J.H.M. van Laarhoven** **Surgeon, Head of Department**	
[Coordinating Investigator/Project leader/Principal Investigator]: ***<please include name and function>***	**Dr. R.P.G. ten Broek** **Surgeon, principal investigator**	

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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**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

aSBO Adhesive Small Bowel Obstruction

SUMMARY

Rationale: Adhesive small bowel obstruction (aSBO) is a frequent surgical emergency, associated with 3-8% hospital mortality and a high risk of recurrence (20% at two years of follow-up). ASBO can be treated conservatively or by emergency surgery. In the absence of bowel ischemia or strangulation, conservative treatment is often preferred, to avoid the excess morbidity and mortality from emergency surgery. Recent epidemiological studies, however, demonstrate a considerable higher recurrence risk of aSBO after conservative treatment that is associated with hospital readmissions and lower survival. Elective adhesiolysis following successful conservative treatment might reduce these long-term risks whilst avoiding the high complication rate of emergency surgery.

Objective: We aim to investigate the efficacy of elective adhesiolysis following conservative treatment for aSBO as compared to the current state of the art (wait-and-see policy) to prevent long-term recurrence of aSBO. Further we will evaluate quality of life, healthcare and societal costs.

Study design: Multicenter open-label randomized controlled trial, including 380 patients.

Study population: Adult patients who recovered from aSBO by conservative treatment. Patients that are inoperable for medical, anaesthesiological or surgical reasons are excluded. **Intervention (if applicable)**: The intervention of investigation is elective adhesiolysis. Adhesiolysis is an abdominal procedure in which all adhesions are cut, and adhesion prevention applied to reduce the risk of adhesion reformation. The intervention is compared to wait-and-see policy (the current standard treatment)

Main study parameters/endpoints: Primary outcome is recurrence, defined as readmission for obstructive systems with aetiology of adhesions confirmed by CT. We hypothesize a 50% reduction in recurrence in the intervention arm. Secondary outcomes are morbidity from surgery, health-related quality of life (EQ5D), healthcare costs and societal costs (iMCQ and iPCQ)

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

Patients in the intervention group are exposed to abdominal surgery, which is associated with a moderate risk of minor complications such as wound infection and haemorrhage, and small risk of severe complications such as iatrogenic bowel injury. According to our hypothesis, a potential benefit is the reduction in the risk of recurrences. Recurrence of aSBO is associated with a risk of readmissions, reinterventions, and also increased long-term mortality.

1. INTRODUCTION AND RATIONALE

Adhesive small bowel obstruction (aSBO) is a frequent abdominal surgical emergency causing an estimate of 4,000 hospital admission in the Netherlands and Belgium annually.(1, 2) ASBO is associated with significant morbidity and mortality, in particular when emergency surgery is needed to resolve the obstruction. In a recent Dutch snapshot study in which 34 hospitals participated, mortality after operative treatment was 4.2%.(1) In the NELA report from the U.K., ASBO was the most frequent cause of overall death in emergency abdominal surgery, and the 30-day mortality rate of surgery for aSBO was 7%.(3) In comparison, mortality from conservative treatment consisting of gastric decompression, nill per os, and iv fluids, was only 1.6% in the Dutch snapshot study.(1) The burden of aSBO for society is also huge, although there is relative little specific data on the societal costs and QoL after aSBO. Direct hospital costs for an episode of ASBO are calculated at € 2,277 ± 265 for conservative treated episodes, and € 16,305 ± 2,513 for operatively treated episodes.(4) The majority of patients with aSBO are in working age. In our experience, most patients have an extended sick leave of several weeks after an episode of aSBO, and some may never return to work at all. In a Scandinavian study the prevalence of chronic abdominal pain after an episode of aSBO was 20%.(5)

Because of the increased morbidity and mortality of emergency surgery, an international clinical practice guideline advises a trial of conservative treatment in the absence of signs of acute bowel ischemia or strangulation.(2) Nevertheless, the preference for conservative treatment is increasingly subject to debate. There is a recent body of evidence showing that the risk of long-term recurrence is considerable higher after conservative treatment. In a population study, 2-year recurrence after conservative treatment was estimated at approximately 20%, as compared to 13% after emergency surgery for patients admitted for their first episode of aSBO.(6, 7) The risk of recurrence increases with longer follow-up, and recurrence risks up to 40% have been reported at 10 years of follow-up after an initial episode of aSBO.(8, 9) Recurrence risks of aSBO is even higher in patients with more than one episode in history (30-60%).(10) At long-term follow-up operative treatment is associated with lower risks of recurrence and a subsequent lower risk of mortality (hazard ratio, 0.80; 95% confidence interval, 0.75-0.86).(6) A RCT with 4 years of follow-up demonstrated that the risk of recurrence following operative treatment can further be reduced from 11% to 2.2% when using adhesion barriers.(11) For these reasons, part of the hospitals in the Netherlands and Belgium already treat aSBO more frequently by surgery. Currently, a conservative wait-and-see policy is the standard treatment applied after primary admission with an aSBO. Elective adhesioslysis is already being applied selectively in clinical practice, especially in patients with a recurrent aSBO.

Another alternative strategy might involve elective adhesiolysis after the resolution of aSBO with conservative treatment. Elective adhesiolysis is a reimbursed procedure in the Netherlands and Belgium, primarily performed in expert centers for patients with chronic abdominal complaints after surgery. In selected patients, along with the use of adhesion barriers to reduce the risk of adhesion regrowth, this procedure results in long-term control of chronic symptoms. (12, 13) A recent study from our group suggests that this procedure also effectively reduces the risk of (recurrent) aSBO with more than 65%, while avoiding the morbidity from emergency

surgery.(14) In this study 122 patients with chronic complaints from adhesions were included, of whom 60 had previous episodes of aSBO. In both the entire cohort and the subgroup of patients with previous aSBO, elective adhesiolysis resulted in a significant 3-fold reduction in incidence of aSBO during 5-year follow-up.

The aim of the present study is to assess the efficacy and safety of elective adhesiolysis to reduce long-term recurrence of aSBO, as compared to a wait-and-see policy. Primary outcome is the 2-year risk of readmission for recurrence, secondary outcomes are chronic abdominal complaints, mortality, operative morbidity, quality of life, and healthcare and societal costs (measured by iMCQ and iPCQ). In the selection of outcomes we made sure to incorporate the outcomes from the ASBO core outcome set that a relevant for long-term evaluation.(15)

2. OBJECTIVES

Primary Objective:
To assess the efficacy and safety of elective adhesiolysis with application of adhesion barrier to prevent recurrence of aSBO as compared to wait-and-see.

Recurrence is defined as a hospital readmission for symptoms of bowel obstruction, after exclusion of other causes of bowel obstruction by CT (see outcomes).

Secondary Objective(s):
To assess impact of elective adhesiolysis as compared to wait-and-see on health economics (in accordance to the Dutch and Belgian standards), Quality of Life, chronic abdominal complaints, costs, as well as the cost-effectiveness from a healthcare and societal perspective..

3. STUDY DESIGN

This is a multicenter randomized open-label controlled trial including 380 patients. The setting of the trial is hospital care. The trial will be performed as an open label trial, because of the invasiveness of the intervention that cannot be blinded for. The control group will have a wait-and-see policy which is in accordance to the current state-of-the-art. Follow-up for the primary outcome will be 2 years. In addition a longer-term follow-up of 5 years will be performed using record linking. Cross-over from the control to the intervention group after development of a recurrence are allowed, as we expect some patients might develop a preference not to await further recurrences. The main criterium that has to be met for cross-over from the control group to the intervention group is the recurrence of an aSBO in a control patient. Cross-over will not impact the primary outcome, but may impact some of the secondary outcomes. Cross-overs will be analyzed according to intention to treat.

4. STUDY POPULATION

4.1 Population (base)

4.2 Inclusion criteria

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

- Adult patients aged 18 years and older who have recently recovered from aSBO by small bowel obstruction managed by conservative treatment.
- ASBO is defined as an acute episode of bowel obstruction, causing symptoms of bloating, nausea and abdominal pain, and requiring hospital admission.

In addition, the following criteria have to be met:

- Patients who have previously been operated (high a prior risk of adhesions) are required to have no signs of other causes of bowel obstruction on imaging studies (CT- scan).
- Patients with no previous operation in history (low a prior risk of adhesions) are required to have typical signs for aSBO on imaging studies (abrupt change of bowel calibre, closed loop, or signs of torsion on vessels in the mesentery on CT-scan).

4.3 Exclusion criteria

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

- Patient who are unfit for operation for surgical, anesthesiological or medical reasons as determined by multidisciplinary team assessment or pre-operative screening
- Patients with active malignancy, reducing life expectancy
- Patient who has undergone surgery for previous episodes of aSBO in the past six months.
- Patient who has undergone previous complete adhesiolysis with use of adhesion barriers.
- Pregnancy

4.4 Sample size calculation

Primary outcome is the time to recurrence measured at two years of prospective follow-up. We will perform a superiority trial. Based on previous literature, we expect 20% recurrence in 2-year with wait-and-see policy (based on a mix of patients with a first and recurrent episode of aSBO) and a 10% recurrence rate after intervention, resulting in a hazard ratio (HR) of approximately 0.47.
We estimated that if 378 patients were randomly assigned in a 1:1 ratio (i.e., 189 per group) to the intervention group or the control group, our study would have 80% power to detect an HR for recurrence of adhesive small bowel obstruction of approximately 0.47 at a two-sided α level of 0.05. After rounding the total number of patients up, we aim to include a total of 380 patients. Analysis will be performed by intention to treat basis, using survival analysis. We will use cox regression to be able to apply multivariable analysis to account for covariates such as previous episodes of ASBO.

5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

Elective adhesiolysis will be compared to a wait-and-see policy. Elective adhesioslysis is selectively applied in clinical practice, especially in patients with a recurrent aSBO.

Elective adhesiolysis is a surgical procedure in which all adhesions in the abdomen are released. Elective adhesiolysis is preferably performed laparoscopy, but the precise surgical approach is adjusted to the expected location and extent of the adhesions, presence of a stoma, abdominal wall defects, as well as the surgical history and locations of previous scarring. We expect an open approach or conversion from laparoscopy to open surgery to be required in 10-15% of patients. The typical duration of hospital admission is 1-2 days for laparoscopic adhesiolysis and 5-7 days for open or converted adhesiolysis. Patients typically have one control visit to the outpatient clinical between 2-4 weeks after discharge to assess surgical healing.

In accordance to the surgical protocols of expertise centres for adhesiolysis and the advice of the international clinical practice guideline for aSBO, adhesion barriers are used as part of the standard of care during elective adhesiolysis, to reduce the risk of regrowth of adhesion after their release.(2) The adhesion barriers are registered and authorized medical devices. They will only be used in accordance to their registered and intended use. The application of adhesion barriers is an easy and low-tech intervention that requires no specific surgical skill or learning curve. Information session will be held in all participating centres prior to start of the trial.

The adhesion barrier to be used in laparoscopic adhesiolysis is Icodextrin 4% (Adept^{tm}). This barrier has previously been found to be safe and effective in reducing adhesion formation in abdominal surgery.(16) Specifically, it has demonstrated to reduce the risk of readmission for aSBO when applied during emergency surgery for aSBO.(11) The barrier was also used in a recent cohort, demonstrating reduced incidence of aSBO after elective adhesiolysis.(14)

The barrier to be used in open or converted surgery is hyaluronate carboxymethylcellulose (Seprafilm^{tm}). This barrier has also been found safe and effective in reducing adhesion formation in abdominal surgery. In a meta-analysis the barrier was effective is reducing the risk of future reoperation for aSBO when applied in colorectal surgery.(16)

Despite the existing evidence for the efficacy of adhesion barriers, they have only partly been implemented in hospitals in the Netherland and Belgium. In our group, there was

broad consensus based on the available data that adhesion barriers should be used as part of a good elective adhesiolysis. This consensus was also supported by the surgeons from the participating centres in the Netherlands and Belgium that at present do not use adhesion barriers in their daily routine. Therefore we decided to standardize their use in the trial. Barriers are provided as part of the trial to minimize the risk of difficulties with inclusion, or significant delays in local approval of a lack of availability of adhesion barriers. The use of barriers will be a focus in the implementation plan that will be made by the end of the trial.

No specific intervention or follow-up is performed in the control group of wait-and-see policy. Current standard treatment for patients with a primary aSBO is the wait-and-see policy.

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

The primary outcome of the study is recurrence at 2-years of follow-up. Recurrence is defined as a readmission for symptoms of small bowel obstruction, including lower abdominal pain, bloating and nausea with or without vomiting. In addition imaging by CT-scan should not show indications of other causes of bowel obstruction (such as an incarcerated abdominal wall hernia or tumour), which is over 90% accurate for the diagnosis of ASBO.

The incidence of recurrent ASBO increases over time. We deliberately preferred a 2-year follow-up as the primary outcome, because at this time frame it is feasible to prospectively follow-up on patients with low loss of data, and also ethically to avoid long delays in implementation of results.

6.1.2 Secondary study parameters/endpoints (if applicable)

Secondary outcomes are:

- Recurrence at 5 year (identified by record linking[BE] or general practitioner data[NL])
- Recurrences needing surgery
- Recurrence risks stratified by patients and surgical characteristics (Sex, age)
- Recurrence risk in the operative subgroup stratified for laparoscopic vs open surgery
- Morbidity from elective adhesiolysis:
    - Serious adverse events and complications, graded by Clavien-Dindo score.
    - Intra-operative events (i.e. bowel injury), graded by ClassIntra®

- ICU admission
- Reinterventions within 90 days

Patient questionnaires at 1 and 2 years of follow-up

- Health-related quality of life measured by EQ5D
- Gastro-intestinal related quality of life measured by GIQLI
- Characteristics of abdominal pain
- Costs from healthcare perspective (measured by modified iMCQ)
- Costs from societal perspective (measured by modified iMCQ and iPCQ)
- Cost-effectiveness (incremental cost-effectiveness ratio, i.e. cost per QALY)

Surgical follow-up

- History taking with focus on potential recurrences
    - Review of data from readmission in same hospital
    - Ask patients if there have been readmission to other hospitals
- Assessment of complaints related to obstruction
    - Chronic or recurrent nausea, bloating, abdominal pain
    - Unintended weight loss
- Physical examination focused on abdominal pain and incisional hernia

The full iMCQ and iPCQ questionnaires are quite extensive and elaborate for patients to fill out. Therefore a modified version of these questionnaires is applied, in which only the domains that are potentially affected by ASBO are included, as decided upon during an expert meeting with healthcare professionals and patient representatives. This method is frequently applied in cost-effectiveness research and also increases the number of patients completing the questionnaire.

6.1.3 Other study parameters (if applicable)

At baseline we will collect data on surgical history, co-morbidity, BMI, and substance use. During the surgery we will collect data on surgical approach, intra-operative events graded by Class-Intra, extent and location of adhesions (measured by Peritoneal Adhesion Index), Completeness of adhesiolysis, and use of barrier.

At the follow-up visits we will perform history taking and physical examination focused on identification of potential readmissions for ASBO at other hospitals, chronic complaints, and late surgical complications such as incisional hernia.

6.2 Randomisation, blinding and treatment allocation

Upon inclusion, patients will be randomized 1:1 to intervention or control. The randomization will be stratified for first episode of aSBO vs. recurrent episode of aSBO, and for the operative center. Patient with previous recurrences of aSBO have

an higher risk for recurrences as compared to patients presenting with a first episode. We also plan to perform subgroup analyses for patients presenting with a first or recurrent episode of aSBO. Adhesiolysis is a procedure that is difficult to fully standardize, because the approach and technique can vary based upon location and density of adhesions. Randomization is therefore stratified per center to correct for small differences in decision making regarding surgical techniques and approach. The number of included patients per stratum can be relative small, therefore random permuted blocks with a size of 4 or 6 will be used to ensure balanced randomization between the groups.

This is an open label trial. The marked differences between the intervention and control group do not allow for blinding of subjects, surgeons, and researchers.

6.3 Study procedures

Patients who recovered from aSBO by conservative treatment who meet the above inclusion and exclusion criteria are eligible for inclusion. Potential candidates are identified by treating surgeons and physicians at participating operative and referral centres. The treating surgeon or physician will discuss the option of participating in the study and give a short introduction on what participation entails at discharge. Furthermore, the physician will verbally ask permission to the patient for the study team to contact the patient and schedule an outpatient visit to an operative centre to provide full information on the trial and discuss participation, non-committal. Patients referred to discuss participation in the trial will receive written information about the trial at a minimum of 5 days prior to the outpatient clinic meeting. The outpatient clinic meeting will be scheduled within two weeks from discharge when the patient has fully recovered. At the outpatient clinic history taking and physical examination will be performed by a qualified surgeon and anaesthesiologist to confirm eligibility of the patient to participate. Further, detailed information about the intervention will be provided.
Patients who agree to participate in the study will provide written informed consent to be randomized.

Multidisciplinary team meeting

Patients who are surgical, medical, or anaesthesiological unfit for surgery are to be excluded from the study. There is not a single pragmatic test to assess is a patient is fit for surgery. Therefore a weekly disciplinary team meeting with the experts centres will be conveyed, where cases in which there is doubt about the fitness of patient to undergo elective adhesiolysis can be discussed.

Cross-over of patients

Patients randomized to the control arm of the trail are offered the possibility to cross-over to the intervention group in case they have developed a recurrent episode of ASBO during the study period. A recurrent episode of ASBO is defined as a new episode of acute bowel obstruction during the follow-up after randomization, causing symptoms of bloating, nausea and abdominal pain, and requiring hospital admission, and no other cause for obstruction on CT (as defined in the inclusion criteria under 4.1). Following such recurrent episode, patients in the control arm can decide for cross-over in shared decision making with their treating surgeon and not randomized. Data until the first episode of recurrence will be analyzed according to intention to treat.

Surgery

Patient randomized to the intervention will undergo surgery within 6 weeks following inclusion. Surgery will be performed in accordance to the description of the intervention in chapter 5 of the protocol. Peri-operative care will be performed according to local protocols for elective laparoscopic surgery in the operative centres. Based on previous experiences we expected adhesiolysis to be performed laparoscopically in 70-80% of patients. Average hospital stay following laparoscopic adhesiolysis is 2 days. In converted and open surgery cases, the average stay is 5 days. Operatively treated patients will have a single outpatient visit to evaluate the recovery at 6 weeks post- surgery, or more frequent if a complication has occurred (as appropriate in the care for that complication). No specific follow-up is performed after this single post-operative outpatient visit.

Control arm

For patients randomizing to the control arm no specific follow-up care is performed as per usual care.

Recurrence

Patients will present at their local hospital (referral of operative centre) in case of symptoms of recurrence of bowel obstruction, including lower abdominal pain, bloating, nausea, and vomiting. Although most cases of bowel obstruction are caused by adhesions, especially after previous episodes of aSBO, there are a few other aetiologies of bowel obstruction such as strangulated abdominal wall hernia or tumours. To confirm the adhesive aetiology of small bowel obstruction a CT-scan will be made. CT-scan is known to be more than 90% accurate in distinguishing adhesions from alternative causes of bowel obstruction.(2) A readmission for obstructive symptom with CT or operative confirmation of adhesive aetiology will be scored as recurrence under the primary outcome.

Data collection

Follow-up questionnaires will be sent at 6, 12 and 24 months of follow-up. The questionnaire will include surveys of health-related quality of life (EQ5D), abdominal complaints, healthcare costs (iMCQ) and productivity (iPCQ). In addition the questionnaire will cover potential missed episodes of recurrence (e.g. readmission for recurrence when travelling abroad). In case a potential missed episode of recurrence is identified, additional medical information of the readmission is requested to verify if this was an episode of recurrence.

Table 1 provides an overview of the study procedures and moment for data capture.

Long-term follow-up

We will perform an extended follow-up of 5 years for the primary outcome of readmission based on data from participating centers and general practitioner data. General practitioner data are important sources for the long-term follow-up as patients might present at a different hospital with a recurrence of ASBO. In both the Netherlands and Belgium correspondence from all hospital admissions is held by the general practitioner. After review of data from participating hospitals, short questionnaires will be sent to general practitioners to identify potential readmissions for ASBO outside the group of participating hospitals. We have experience with these questionnaires in previous studies, and this methods has been shown to accurately identify readmissions for ASBO. Additional hospital data is requested to verify diagnosis of ASBO in case a potential episode of recurrence is detected through general practitioner data. Participants will be asked for oral and written consent at inclusion to contact their general practitioner and other hospitals in the future for long-term follow-up.

In Belgium, general practitioner care is not fully centralized. In case it is difficult to obtain the required information from general practitioners, we will use record linkage to identify potential relevant readmissions using the following procedures by KCE.

After the completion of the study the Sponsor will transfer the pseudonymised study data set 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 participant national number.

The participant information and consent include 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 participant information and consent will also include that in case the participant 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 participant 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 Sponsor 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.

Background" means any intellectual property (IP), data, materials, information owned or controlled by the Sponsor or a Site and required to run this Study. Sponsor will identify such Background including the legal restrictions of which Sponsor, or Sites are aware that may affect the use of the Background for the purpose of the Study or the rights granted to KCE under this Agreement.

The Study Data consist of this protocol, including amendments, the electronic forms for data capture, including the annotations and guidance for use, the electronic database of the pseudonymized clinical and non-clinical data collected using data capture, including the log of changes from data entry to database lock, study reports based on these pseudonymized data, and any data or reports generated at a later stage, e.g. based on exploratory analyses or stored samples.

"Foreground" means any Study Data, and any tangible biological, chemical and physical material and inventions, that are generated, acquired, discovered, conceived, developed, created, exemplified or derived as a result of carrying out the Clinical Study, whatever its form or nature, whether it can be protected or not, as well as any Foreground IP. Sponsor acknowledges that the main purpose of the research performed under this Agreement is to generate results that will serve the general public interests, and specifically the interests of the patients and public

healthcare decision making bodies, and, therefore, undertakes not to exploit the Foreground in any way that is or could be detrimental to such interests.

The Sponsor owns the Study Data but provides KCE with a copy of the pseudonymized database after database lock as well as a royalty-free unrestricted license to use the Study Data for non-commercial public health related purposes as detailed in the Agreement between KCE and the sponsor. 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 the results of the analyses and the reporting of the linked data.

Table 1 Overview of Study Procedures

	Screening period	Randomisa-tion	Treatment Period[1]			Midterm follow-up			Long-term follow-up
	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	
	Max 2 weeks af-ter dis-charge	Max 4 days after visit 1	Day of Surgery (max. 6 weeks after randomisation)	Discharge (~1-7 days after surgery)	Outpatient clinic (2-6 weeks after surgery)	6 months	12 months	24 months	5 years
Informed consent	X								
Eligibility Assessment	X[2]	X							
Randomisation		X							
Surgical findings			X						
Registration of Physical ex-amination and history taking[3]	X				X	X	X	X	
Review of electronic patient data	X		X	X					X
QoL questionnaires	X					X	X	X	
Modified iMCQ and iPCQ	X					X	X	X	
General practitioner ques-tionnaire									X

1. Visits 2-4 only apply to the intervention arm of the trial.
2. Screening and assessment as soon as possible after conservative treatment for ASBO.
3. History taking and physical examination focused on readmissions, chronic abdominal pain, and incisional hernia as described above.

6.4 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 for urgent medical reasons.

6.5 Replacement of individual subjects after withdrawal

Our sample size calculations accounted for some loss to follow-up, and subjects who withdraw from the study will not be replaced.

6.6 Follow-up of subjects withdrawn from treatment

Patients withdrawing from the study who randomized to the control arm, or prior the intervention, do not require specific follow-up. Patients withdrawing after the intervention will receive appropriate surgical care. This includes a single outpatient clinic to evaluate recovery at 6 weeks post-operative, as well as care for possible complications of surgery. After full recovery from surgery no specific follow-up is required.

Patient who refrain from surgery after randomization or cross-over from wait-and-see to surgery but do not withdraw from the study as a whole, will be followed according to the study procedures as described above and analyzed based on intention-to-treat.

6.7 Premature termination of the study

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

7. SAFETY REPORTING

7.1 Temporary halt for reasons of subject safety

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

7.2 AEs, SAEs and SUSARs

7.2.1 Adverse events (AEs)

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

Adverse events related to adhesiolysis include complications associated with abdominal surgery such as wound infection, haemorrhage, pneumonia and thrombosis. Further adhesiolysis is associated with a small risk (2-4%) of iatrogenic injury to organs such as the bowel. In case of iatrogenic bowel injury, failure of healing of this injury can results in further negative sequelae including reoperation, stoma, and ICU admission.

7.2.2 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 hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

All SAEs as defined in the protocol must be reported to the Sponsor within 24 hours of the trial staff becoming aware of the event. The sponsor will report the SAEs occurring up to 3 months following treatment through the web portal *ToetsingOnline* to the accredited METC that approved the protocol [NL] and the approving ethical Commission in Belgium. SAEs that result in death or are life threatening will be reported as soon as possible after becoming aware, followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events. In Belgium all other SAEs will reported as part of the yearly progress report.

7.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands and Belgium, as defined in the protocol

7.4 Data Safety Monitoring Board (DSMB) / Safety Committee]

This study adds a moderate risk (“matige kans”) of moderate to slight to moderate damage (“milde tot matige schade”) and small risk (“kleine kans”) of severe damage (“ernstige schade”), consequently adding a moderate risk (“matig risico”) according to the risk classification of the “Nederlandse Federatie van Universitair Medische Centra” (NFU). Continuous safety monitoring will be performed accordingly.

An independent data safety monitoring board (DSMB) will be installed to perform ongoing safety surveillance as described in the charter for the Data Safety Monitoring Committee, attached as a supplement in section K5. Also, resumes of the members of the DSMB are attached in this section. The DSMB will decide on safety and continuation of the study. The DSMB will evaluate the study data and advise the sub-investigator on the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial. The members of the DSMB have no conflict of interest, are not involved in the study, nor are they receiving funds. The DSMB will have full access to the study data.

A planned interim safety analysis will be performed after inclusion of 130 and 260 patients. The DSMB will analyze all cases in which complications graded as grade IIIb or higher on the Clavien-Dindo scale have occurred (Table 1). Criteria for terminating the study is when patients undergoing the intervention, are at an increased risk of developing severe complications with prolonged negative impact on patients health, that is higher than expected based on literature or disproportional to the potential benefit of the operation. The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

Table 1. **Clavien-Dindo scale**

Grade I	Any deviation from the normal post-operative course not requiring surgical, endoscopic or radiological intervention. This includes the need for certain drugs (e.g. antiemetics, antipyretics, analgesics, diuretics and electrolytes), treatment with physiotherapy and wound infections that are opened at the bedside
Grade II	Complications requiring drug treatments other than those allowed for Grade I complications; this includes blood transfusion and total parenteral nutrition (TPN)
Grade III	Complications requiring surgical, endoscopic or radiological intervention Grade IIIa - intervention not under general anaesthetic Grade IIIb - intervention under general anaesthetic
Grade IV	Life-threatening complications; this includes CNS complications (e.g. brain haemorrhage, ischaemic stroke, subarachnoid haemorrhage) which require intensive care, but excludes transient ischaemic attacks (TIAs) Grade IVa - single-organ dysfunction (including dialysis) Grade IVb - multi-organ dysfuncton
Grade V	Death of the patient

8. STATISTICAL ANALYSIS

Data will be analyzed according to the intention-to-treat principle. The primary outcome (difference in incidence of recurrence between groups) will be analyzed using multivariate cox-regression to account for the stratification variables, i.e. first episode vs. recurrent cases; and operating center. Results will graphically be presented using Kaplan-Meier curve.

Surgical findings, and complications in the operative group will be assessed descriptively in a quantitative analysis. Quality of life, gastro-intestinal complaints, healthcare and societal costs will be analyzed using mixed-effect models. Differences with a P-value <0.05 are considered statistically significant.

In case of loss to follow-up, cases are included in survival analysis up to the moment of loss to follow-up. The main potential intercurrent event is abdominal surgery for an indication unrelated to ASBO during follow-up. After this new surgery new adhesions might form that could interfere with the risk of developing an ASBO. Within the 2 year time frame, such unrelated reoperations are expected in approximately 5% of patients. Because of the randomization, we expect both groups to be at equally risk for such event. Our main analysis will be on intention to treat basis, and for this analysis, data from patients with this intercurrent event will be further collected and analysis. As a secondary outcome we will also analysis the data per protocol, in which case patients with intercurrent events are censored.

Another potential intercurrent event is cross-over from the control to intervention group of patients after a recurrence. Patients that cross-over have already reached the primary outcome of a recurrence, and thus this event has no impact on the primary outcome. However, it might impact some of the secondary outcomes. This will be recorded, and accounted for in the secondary analyses.

8.1 Primary study parameter(s)

The primary outcome, incidence of recurrence, is analyzed using survival analysis (Cox-regression) on intention to treat basis.The primary outcome is analysis in the total group, and in the subgroups of patients presenting with a first or recurrent episode of aSBO.

In previous studies, (amongst others: v.d. Beukel et al.) no indications have been found for 'violation' of the assumption for proportional hazards. Stratification is applied on the variables *first episode of aSBO vs. recurrent episode of aSBO*, and *hospital*. No other covariates will be taken into account. We will test two-sided.

After a new surgery for another reason, the risk for aSBO will increase as a consequence of new adhesions that can arise due to this surgical procedure. In this trial, we expect this to be a rare event, and the few times that this will happen, this will probably be spread evenly over the two groups. Therefore, there is no reason for censoring nor removal in the intention-to-treat protocol. Only in the secondary per-protocol analysis these patients will be removed.

8.2 Secondary study parameter(s)

Recurrence as per protocol analysis, Quality of life, gastro-intestinal complaints, healthcare and societal costs will be analyzed using mixed-effect models.

Economic evaluation

Parallel to the clinical trial an economic evaluation will be performed, comparing the costs and effects of elective adhesiolysis and a watch-and-wait policy, in order to determine the most cost-effective approach. The economic evaluation will be performed from a societal and health care payer perspective, adhering to the Dutch and Belgian guidelines respectively.(17,18) The time horizon of the base case analysis of the economic evaluation will be two years. Some of the long-term consequences of aSBO such as chronic pain can continue to cause morbidity and costs beyond the follow-up of the trial. Also new instances of recurrence of aSBO continue to occur at long periods after surgery, beyond clinical trial follow-up. Long-term cost and effects will therefore be evaluated using decision analytical modeling.

Trial-based economic evaluation

The trial-based cost-effectiveness analysis will be conducted with an intention-to-treat

approach and cost-effectiveness is expressed in (incremental) cost per QALY. Costs of the elective surgery will be calculated based on materials needed, operation time and length of hospital stay. Other important health care cost categories are subsequent hospital visits, related adverse events, readmissions, general practitioner, allied health professional visits, and home care services. There may also be patient and family costs, such as out-of-pocket payments, informal care costs and productivity loss. Most health care use is collected as part of the clinical trial. Data on health care use outside of the hospital, informal care and productivity loss are collected the validated iMTA Medical Consumption Questionnaire (iMCQ) and iMTA Productivity Cost Questionnaire (iPCQ), completed by patients at baseline, 6, 12 and 24 months.(19,20) The questionnaires are modified to include those domains that are potentially impacted by ASBO. The Dutch

manual for costing research is used to determine prices for resource use.(21) The EQ-5D-5L survey is used to calculate QALY using area under the curve calculations.(22) The EQ-5D is completed at baseline, 6, 12 and 24 months.

The differences in costs and QALYs between elective adhesiolysis and the wait-and-see-policy are estimated using regression analyses, accounting for baseline imbalances and the correlation between costs and outcomes.(23) If relevant, an incremental cost-effectiveness ratios (ICER) is calculated by dividing the estimated difference in costs by the difference in QALYs, i.e. ICER = Δ costs / Δ QALY. Uncertainty in the costs and effect differences and the ICER, is addressed using non-parametric bootstrapping techniques (with 5000 replicates). The probability of elective adhesiolysis being cost-effective, for various ceiling ratios for the ICER (i.e. willingness to pay per QALY gained) is presented in a cost-effectiveness acceptability curve (CEAC). Several scenario and one-way sensitivity analyses will be performed to further assess the robustness of results. Recommended statistical methods are followed and performed in R Studio.(24)

Model-based economic evaluation

We evaluate the 5-year and lifetime cost per QALY by developing a de novo decision-analytic model. We use the Dutch societal perspective, and the Belgian perspective will be explored. The ZIN guideline for economic evaluations in healthcare will be followed, for example including productivity losses using the friction cost approach.(21)The conceptual model will be developed based on a review of existing cost-effectiveness models and interviews with clinical and patient experts. It will likely be a state transition model, which means that patients can transit through different relevant health states through their lifetime. Data inputs are informed based on trial data and, where not available from the trial, identified through targeted reviews, expert interviews, hospital records, and data linkage. Long-term data on risk of recurrence will be extrapolated from the trial using survival analysis. The model will be developed in MS excel. Validation efforts include technical verification using the TECH-VER checklist, as well as expert interviews.(25) We explore uncertainty through (probabilistic) sensitivity and scenario analyses.

8.3 Other study parameters

Baseline parameters will be compared by independent samples t-test for continues outcomes and chi-square for dichotomous outcomes.

8.4 Interim analysis (if applicable)

An Interim analysis measuring safety outcomes is planned after 140 and 280 patients are included. In this interim analysis, we will primarily evaluate adverse events related to the intervention. Most patients will not have completed follow-up at the interim analysis, and therefore no futility analysis is performed. A data safety monitoring board will be installed to keep an overview of the (severe) adverse events and decide whether the study will be terminated when patients are at an increased risk of developing grade 3b or higher adverse events with prolonged negative impact on patients health.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version October 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO) and applicable local regulations of the participating countries as well as other European guidelines, regulations and acts such as the GDPR (General Data Protection Regulation, in Dutch: Uitvoeringswet AVG).

9.2 Recruitment and consent

Patients are identified by their treating physician or surgeon during admission for aSBO. Patients in whom aSBO resolves with conservative treatment are eligible.

The treating surgeon or physician will discuss the option of participating in the study and give a short introduction on what participation entails at discharge.

The treating physician will verbally ask permission to the patient for the study team to contact the patient and inform further about the trial and schedule an outpatient visit at an operative centre to provide full information on the trial and discuss participation, non-committal. Patients referred to discuss participation in the trial will receive written information about the trial at a minimum of 5 days prior to the outpatient clinic meeting. The outpatient clinic meeting will be scheduled within two weeks from discharge when the patient has fully recovered. Patients who agree to participate in the study will provide written informed consent to participate in the study. Patients remain free to withdraw at will at any time from the study without giving a reason.

Eligible patients that agree to receive detailed information to consider participation will receive the Patient Information Form (PIF),the Informed Consent (IC) form and the patient information brochure from the study team online via e-mail prior (at a minimum of 5 days prior to the outpatient clinic meeting) to the visit to the outpatient clinic. The PIF explains the rationale behind the study, as well as what participation entails. An outpatient clinic appointment at an operative centre is scheduled within two weeks from discharge. During the outpatient clinic meeting, eligibility of the patients will be further assessed by a surgeon and anesthesiologist. The surgeon will also discuss in detail the intervention in the study as well as the prognosis of watchful waiting, and provides a possibility for further questions on the intervention. If patients require more time for a decision about participation a digital follow-up visit is scheduled at 4-5 days. If the patient decides to participate informed consent will be signed digitally or on paper at the outpatient visit, or a digital follow-up visit, by the patient and a representative of the study team.

The intervention will be scheduled at the operative center where the patient has visit the outpatient clinic.

9.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

9.4 Benefits and risks assessment, group relatedness

Based on the hypothesis of the study, participants in the intervention group might benefit from a lower risk of recurrence. Moreover, chronic abdominal complaints are highly prevalent among patients who had an episode of aSBO, and adhesiolysis might also have beneficial effects on chronic complaints. Based on existing literature on acute treatment of aSBO, and elective adhesiolysis in patients with chronic abdominal complaints, a reduction of 50% or more in the risk of recurrence is expected.(11, 14)

On the other hand, patients in the intervention group are exposed to the risk and morbidity related to the operative intervention. Morbidity includes a mean hospital stay if 2 days in laparoscopic cases and 5-7 days in open or converted cases. There is a moderate risk for complications such as wound infection, bleeding, pneumonia and deep venous thrombosis. There is a small risk of severe complication such as iatrogenic bowel injury.

We consider the current study justifiable because the risk of recurrence without intervention is high (20% within 2-year, but the incidence continues to rise to much higher numbers in the longer term), and epidemiological data also shows that recurrences are associated with lower quality of life and even increased long-term mortality.(5, 6)

Prior to the design of the trial we performed a feasibility study. A main focus in the feasibility study was assessment of the willingness of surgeons and patients to randomize between the two arms of the trial, which are very different in nature. Moreover, surgery is an invasive procedure and not all patients will develop recurrence even when left untreated. The surgeons consulted consisted of surgeons that intended to participate in the trial. A focus group of patients was recruited from a recent observational study on ASBO. The patients consulted had conservative treatment for ASBO and would have been eligible for the trial.

Both surgeons and patients demonstrated a high willingness to participate. Surgeons indicated that there is an equipoise between the two options, and expect to be able to explain this clearly to patients. Only 10% of patients in the focus group would not participate because of strong treatment preferences, 60% indicated to certainly participate and overall 90% of patients would consider to participate. Some patients reported that a cross-over option if a recurrence occurred is an important factor for participation. This has been incorporated in the protocol, and does not affect the primary outcome.

9.5 Compensation for injury

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

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

9.6 Incentives (if applicable)

Patients participating in the study are eligible to receive reimbursement for travelling costs related to study visits to the operative centre. In a few cases a deductible for the covering of health insurance might apply to patients randomized to the intervention arm of trial, that they would otherwise not spent. (E.g. in case the admission for aSBO is in another calender year than the surgery). In such cases, patients are entitles to a refund of the deductable. No further incentives or reimbursements are applicable.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

To protect the privacy of the participants, all collected data will be encoded and only the project leader and the executive researcher per centre will have access to the encoding key and the acquired data. The code as used in the cohort is a numerical code. All subjects will be offered full access to their own data and the outcomes of the project can be explained to them. When the trial is completed, aggregate disclosure about the trial results will be provided to the entire cohort at the same time. At the end of the experiment and analyses, all data will be stored for 25 years in accordance with GCP regulations. Detailed information can be found in the Datamanagement Plan.

10.2 Monitoring and Quality Assurance

This study adds a moderate risk (“matige kans”) of moderate to slight to moderate damage (“milde tot matige schade”) and small risk (“kleine kans”) of severe damage (“ernstige schade”), consequently adding a moderate risk (“matig risico”) according to the risk classification of the “Nederlandse Federatie van Universitair Medische Centra” (NFU).

The steering group will monitor the progress of the study every 6 months. The study will further be monitored annually, and at start and closure of enrollment by a qualified monitor independent from the research. Monitoring will be conducted in accordance with moderate risk monitoring guidelines of the NFU, which will be detailed in a monitoring plan.

10.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

10.4 Annual progress report

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

10.5 Temporary halt and (prematurely) end of study report

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

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

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

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

10.6 Public disclosure and publication policy

The study is investigator driven. Results from this study will be used for publication in medical literature, with (optional) open access. Study results will be published in compliance with the prevailing Central Committee on Research Involving Human Subjects (CCMO) publication policy.

Based on the results of the trial we will make an implementation plan for the Netherlands and Belgium. A systematic approach to implementation will be followed, starting with an exploration of all stakeholders and organizations involved, included healthcare providers, health insurance companies, policymakers, and patient representatives. Prior to the start of the project we will organize focus group interviews with all stakeholders to elucidate barriers to implementation that should be addressed in order to increase success of implementation. Upon completion of the study we will again convene with the stakeholder group to evaluate barriers and draft a implementation strategy. Specifically we will focus on the use of adhesion barriers as part of elective adhesiolysis during the implementation. At present, adhesion barriers have only partially been implemented in the Netherlands and Belgium. The implementation plan will focus on implementation of elective adhesiolysis as performed in the trial, and explore potential difficulties with the purchase and use of adhesion barriers in some hospital.

11. STRUCTURED RISK ANALYSIS

11.1 Potential issues of concern

Not applicable

11.2 Synthesis

The chapter “potential issues for concern” is skipped because the current study uses registered interventions and devices (elective adhesiolysis and adhesion barriers) used within the indication and without new combinations with other products or therapies. Adhesiolysis is a common procedure, often performed in combination with other procedures to gain access to the operative field, and also performed in emergency setting for aSBO. The adhesion barriers used have CE clearance and have been approved for over 10 years. They are used for the present indication in expertise centres for adhesion-related disorders.

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