Patient-controlled sedation with propofol versus combined sedation during bronchoscopy – a randomized controlled trial

EudraCT 2015-005274-38

BRONSE
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version 3

Sponsor: Lena Nilsson

Investigational products:

- Propofol (Propofol-®Lipuro 5/10/20 mg/ml, Propofol Sandoz 10/20 mg/ml, Diprivan® 10/20 mg/ml, Propolipid 10/20 mg/ml, Recofol 10/20 mg/ml)
- Midazolam (Midazolam Accord 1/5 mg/ml, Midazolam Actavis 1/5 mg/ml, Midazolam Hameln 1/5 mg/ml, Midazolam Panpharma 1/5 mg/ml, Dormicum® 5 mg/ml)
- Morphine-Scopolamine (Morfin-Skopolamin Meda (10+0.4) mg/ml)
- Glycopyrronium bromide (Robinul® 0.2 mg/ml)

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List of abbreviations

ACCP	American College of Chest Physicians
BAL	Broncho-alveolar lavage
BTS	British Thoracic Society
IC	Informed consent
IMP	Investigational medicinal product
OAA/S	Observer's Assessment of Alertness/sedation
PCS	Patient-controlled sedation

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Synopsis

The study "Patient-controlled sedation with propofol versus combined sedation during bronchoscopy – a randomized controlled trial" (EudraCT number: 2015-005274-38, protocol number: "BRONSE") is a phase IV single centre prospective randomized controlled trial with parallel groups. A total of 300 adult outpatients undergo diagnostic bronchoscopy during sedation and are randomized into three sedation arms (1:1:1); sedation with midazolam and morphine-scopolamine as premedication (clinical routine), sedation with propofol using PCS and morphine-scopolamine as premedication, and sedation with propofol using PCS and glycopyrronium bromide as premedication. The study is partially blinded, the bronchoscopist is blinded regarding given premedication for patients given PCS (two sedation arms). The hypothesis is that PCSincrease the amount of patients ready for discharge, and further that patients characteristics affect the amount of propofol administered. The endpoints are primarily the amount of patients ready for discharge within 2 hours and secondary assessment of patient characteristics using questionnaires, recovery and satisfaction as well as bronchoscopist evaluation and doses of administrated drugs. Finally safety variables are collected such as vital signs and interventions performed to maintain cardiovascular and respiratory stability. Study is planned to start during the first half of 2016 and end during the first half of 2017.

Background information and rational

Bronchoscopy is performed to investigate and diagnose patients with pulmonary disorders at the Pulmonary Clinic at Linköping University Hospital. The patient receives topical anaesthetic, analgesia and sedation during the bronchoscopic procedure according to the recommendations set by American College of Chest Physicians (ACCP) (Momen, M. W., et al. 2011) and British Thoracic Society (BTS) (Du Rand, I. A., et al. 2013) to achieve good patients' satisfaction and procedure tolerance (Momen, M. W., et al. 2011). The standard of care at the clinic today for sedation is the use of benzodiazepine in combination with opioid. Clinical experience has shown that the combination affect the recovery time with a delay of discharge. The combination is frequently used for bronchoscopy but recent studies show a transition to use propofol as sedative agent. The pharmacokinetic properties for propofol are more favourable regarding onset of action and time for recovery (Stolz, D., et al. 2009), and equal level of patient satisfaction compared with benzodiazepine (Yoon, H. I., et al. 2011). Adding an opioid to propofol improve quality of sedation, tolerance to bronchoscopy, reduces coughing and usage of topical anaesthetic (Yoon, H. I., et al. 2011, Du Rand, I. A., et al. 2013) but also increases the risk of respiratory depression (Yoon, H. I., et al. 2011) and may increase the risk of hypoxemia.

The bronchoscopic procedure with sedation will be performed by a team consisting of: one bronchoscopist, who conducts the bronchoscopy; two pulmonary nurses who assist the bronchoscopist; one nurse anaesthetist administrating sedation drugs and monitoring the patient. During the procedure titration of the sedative agent with bolus doses is done. Differences between individuals need for sedation affect the depth of sedation and influence patient tolerance, cardiorespiratory functions and result in pro-longed post-procedural care. Patient Controlled Sedation (PCS) has been used to allow the patient to interact and self-administrate an appropriate dose of sedation to tolerate the procedure (Hwang, J., et al. 2005). PCS using propofol as the only sedative agent may give optimal conditions for both the patient and the bronchoscopic team as well as shorten recovery time which makes an earlier discharge possible.

Except weight, type of procedure and combination with other drugs (Nilsson, A., et al. 2015), little is known about factors that can explain why different subjects administer different amounts of sedative drugs to themselves when using PCS. We aim to address this issue by exploring some patients' characteristics using validated questionnaires. We will look at sense of coherence, coping strategies, anxiety and depression and investigate if there is a connection between these characteristics' and dose requirement during PCS.

Benefit-risk evaluation

Bronchoscopy is undertaken as an outpatient procedure. As soon as the patient fulfils the discharge criteria he/she can leave the hospital. With the use of short acting drug (propofol) for procedural sedation time to discharge can be shortened compared to midazolam, but also time to return to stable vital signs. The latter means that the monitoring period after the procedure can be shortened. By a faster turnaround it is probable that more patients can be handled in the bronchoscopy unit during one day. The risk of having patients to stay in hospital overnight due to a slow recovery is also probably reduced.

Another benefit is most probably the PCS technique itself. The level of sedation is in the hand of the patient himself, and in other studies this has shown to be something that patients put great value in. The PCS allows individually adjusted sedation levels, and the short acting properties of propofol facilitate deeper sedation during shorter specially difficult and demanding periods of the intervention. If insufficient sedation during the procedure occur, rescue medication (opioid) can be used to potentiate propofol and deepen the sedation as well as to give relief of any pain. If the level of sedation still is not acceptable for the patient or bronchoscopist additional propofol is administrated by the nurse anaesthetist. Replacing morphine-scopolamine with glycopyrronium (in sedation arm GP) may affect the pain relief. If the pain relief is insufficient the bronchoscopist may give additional topical anaesthetics and/or request additional rescue medication, as described above.

The most severe risks connected to sedation, especially with deep sedation, are circulatory and respiratory events, but aspiration of gastric contents is also a risk. The same precautions as with general anaesthesia are undertaken. An anaesthesiologist will conduct a preprocedural assessment of the patient and is available for consultation via telephone and will be informed before sedation and bronchoscopy procedure begin. The anaesthesiologist is available within a few minutes if call is made to anaesthesiologist pager.. The patients' vital signs are monitored by a nurse. In a recent meta-analysis of sedation during bronchoscopy it was concluded that the risk of hypoxia during the procedure was not increased during sedation compared to awake procedures (Hong, K., et al. 2015). Only patients planned for bronchoscopy as part of their clinical assessment are included in the study. We believe that the benefits of using the propofol PCS technique outweigh the risks with the trial. Possibly can the PCS technique in the future can be a routine method for outpatient bronchoscopy.

Objective

Our primary hypothesis is that the use of patient-controlled propofol sedation for outpatient bronchoscopy will increase the amount of patients ready for discharge after two hours, compared with sedation using midazolam and morphine. We further hypothesize that patient characteristics affect the amount of propofol self-administered by the patient during patient controlled sedation.

The primary endpoint is the amount of patients ready for discharge within 2 hours, according to the Post Anaesthetic Discharge Scoring System (PADSS) score, after outpatient bronchoscopy.

Secondary endpoints; assessment of self-rated patient characteristics using questionaries' (Sense of Coherence, Coping Strategies Questionnaire, Hospital Anxiety and Depression Scale) and recovery (Post-discharge Surgical Recovery Scale), patients' satisfaction, bronchoscopist evaluation (perception of cough, bronchial secretion and acceptance of procedure), total dose given of topical anaesthetic, analgesia and sedation drugs.

Safety variables; level of sedation, vital signs (arterial oxygen saturation, respiratory frequency, non-invasive blood pressure and heart rate) and interventions performed to maintain cardiovascular and respiratory stability.

Study design

Clinical trial, Phase IV; therapeutic use. The study is a prospective randomized controlled trial with parallel groups conducted in a clinical unit (single centre). It will be partly blinded; the bronchoscopist is blinded regarding given premedication for patients with PCS (two sedation arms). The study will be conducted at the Pulmonary Clinic, Linköping University hospital, according to the Helsinki Declaration principles. Screening will be performed during a planned pre-procedural visit some days to a couple of weeks before the bronchoscopy. The patient receives verbal and written information regarding the study from the pulmonary physician. After having had time to consider participation, the pulmonary physician checks inclusion and exclusion criteria's and obtains an informed consent from the participants. It shall be noted that no study-related procedures will be done prior signed consent. The patient may cancel participation in the study at any time without having the medical care affected. Women of childbearing potential are tested with S-β-HCG pregnancy test, results are checked upon visit 2 before randomization. Self-rated patient assessment forms will be handed out for the patient to fill in at home between visit 1 and visit 2 as well as after visit 2. The patient will be informed to mail them back to the Pulmonary Clinic with attached prepaid envelope.

At day for visit 2 (day of procedure) the patient shall be fasting from solid food for at least 6 hours, and clear liquids two hours before the onset of sedation (according to the Swedish Society of Anaesthesiology and Intensive Care, 2013). Inclusion/exclusion criteria's are rechecked (after results of the S-β-HCG test) and if patient is excluded from the study, treatment will be done according to routine. Each patient who fulfils participation in the study is allocated consecutively a sealed opaque randomization envelope containing instructions of which premedication and sedation shall be administrated before and during the procedure. Randomization is done in blocks with equal distribution between the three groups. An independent statistician produces a randomization list using the computer program STATA. Randomization is done by means of closed, numbered envelopes associated with randomization opened in consecutive order. The envelopes will be prepared by an independent individual, not involved in the study. The randomization number given for each patient shall be documented in their individual CRFs.

There will be three sedation arms; premedication with subcutaneous morphine-scopolamine and sedation with midazolam (group MM) (todays standard of care), premedication with

subcutaneous morphine-scopolamine and sedation with PCS (propofol) (group MP), and premedication with intramuscular glycopyrronium bromide and sedation with PCS (propofol) (group GP). The research subject will be randomized 1:1:1 to one of the three sedation arms and conduct one bronchoscopy with sedation.

If patient is randomized to sedation with PCS (group MP or GP) the nurse anaesthetist will give additional thorough information and instructions how to operate the PCS device before premedication is administrated and the bronchoscopy begins.

The bronchoscopist is blinded regarding the premedication in the both PCS groups (group MP and GP) and therefore shall the premedication be filled in the same type of syringe and be marked only with study number, randomization number and route of administration by pulmonary nurse at clinic. Administration of premedication is done one hour before start of bronchoscopy by the same pulmonary nurse who prepared it. Time, route (subcutaneous or intramuscular) and name of pulmonary nurse who gave the premedication is documented in CRF. During the procedure the type of sedation will be revealed for the bronchoscopist due to difficulties to conceal the technical equipment of the PCS.

During the procedure the anaesthesiologist is available for consultation via telephone and will be informed before sedation and bronschoscopy procedure begins. Furthermore the anaesthesiologist is available within minutes if call is made to anaesthesiologist pager. Before bronchoscopy is initiated (one hour after premedication) the patient is encouraged to start using the PCS until the patient feel comfortable (Sedation scale OAA/S 4/3). At the same time local anaesthetic is administrated nasally and pharyngeally depending on type of bronchoscopy and during the procedure local anaesthetic is administrated with a spray-as-you-go technique to anaesthetize vocal cords and trachea. During the procedure the bronchoscopist may request additional medication to achieve deeper sedation and/or pain relief due to a need that the patient has to be completely still during specially demanding and potentially dangerous parts of the procedure. If requested, the sedation is deepened with additional midazolam (if group MM) by nurse anaesthetist or by awaiting the PCS to deliver additional requests from the patient (if group MP or GP). If pain relief is needed additional topical anaesthetics is administrated by bronchoscopist and/or alfentanil (rescue medication) by nurse anaesthetist (all groups). The bronchoscopy takes approximately 1 hour. When the procedure is finished (bronchopscope is removed=time 0), the patient will monitored by nurse anaesthetist until sedation score OAA/S 5 and thereafter monitored by pulmonary nurse until home readiness score PADSS score ≥9 (approximately 1 to 4 hours) and thereafter discharged to home if outpatient else transferred to ward.

The questionnaire S-PSR is filled out by the patient the in the evening the same day of discharge. The day after discharge the patient fills out the QoR-23 questionnaire. Both questionnaires' are mailed back to the Pulmonary Clinic with attached prepaid envelope.

Before, during and after the bronchoscopy the patient is continuously monitored regarding vital signs. Monitoring of vital signs during bronchoscopy until OAA/S 5 is reached after bronchoscopy will be done by nurse anaesthetist. Monitoring before bronchoscopy and when patient have achieved OAA/S 5 after bronchoscopy will be done by pulmonary nurse. Oxygen (2L, 0,5-1L for patients with chronic obstructive lung disease) is administrated by a nasal catheter during the procedure and if needed post-procedural.

The patients are planned to be discharged the same day as the procedure after post-procedural monitoring is completed and criterions for discharge (PADSS) is fulfilled. Patients who not fulfil the criteria for discharge will have a pro-longed monitoring and stay at the clinical ward until criteria are fulfilled. Any adverse events/serious adverse events that have happened during the visit shall be documented and reported (see further under Registration of safety).

At home (or at ward, if pro-longed stay) the patient fills out the self-rated questionaries' S-PSR (day of procedure) and QoR-23 (day after procedure) which include adverse events/serious adverse events follow-up, which are sent by mail back to the Pulmonary Clinic. Participation in the study ends after this questionnaire and the study ends after last subject last questionnaire (day after bronchoscopy).

Roles in study

	Visit 1 Pre-procedural visit	Visit 2 Day for procedure		
		Pre-procedural	Per-procedural	Post-procedural
Pulmonary physician /bronchoscopist	Screening Inclusion /exclusion criteria Informed consent	Check result of S-β-HCG test Inclusion /exclusion criteria	Bronchoscopy	
Pulmonary nurse		Randomization Premedication Monitoring	Assist bronchoscopist	Monitoring (after OAA/S 5)
Nurse anaesthetist			Monitoring Sedation	Monitoring (until OAA/S 5)
Anaesthesiologist	Preprocedural assessment	Be available for consultation and immediate assistance		

Primary investigator may at any time withdraw a patient if the patient does not follow the procedures in the study protocol. Participation in the study is completely voluntary and the research subject may at any time terminate his/her participation in the study without having to explain why and without incurring any consequences for continued care. Upon termination of participation, treatment continues according to praxis on the clinic. Already collected data may be analysed if the patient does not oppose this.

	Visit 1 Pre-procedural	Visit 2 Day for	Follow-up Day after

	visit	procedure	procedure
Screening - Inclusion criteria - Exclusion criteria	X	X[5]	
Informed consent	X		
Medical history - Relevant medical history and medication that affect the patient's cardiorespiratory stability and / or treatment of pain / anxiety[1]	X		
Self-rated patient questionnaires (handed out)	X (SOC, CSQ-SWE, HADS)	X (S-PSR[2])	X (QoR-23[3])
Randomization - Premedication - Type of sedation during procedure		X	
Procedure - Bronchoscopy - Sedation - Monitoring		X	
Post-procedural monitoring		X	
Adverse events and serious adverse events follow-up[4]		X	X[4]

[1] Relevant data is medical history and medication that affect the patient's cardiorespiratory stability and / or treatment of pain / anxiety
[2] Filled out by the patient in the evening of discharge
[3] Filled out by the patient the day after discharge
[4] Documented by patient in QoR-23 questionnaire
[5] Inclusion/exclusion criteria's are rechecked after S-β-HCG test

The study is planned to start during the first half of 2016 and last visit at the clinic is planned to be during the first half of 2017.

Selection of subjects

Inclusion criteria

- Adult patient (≥18 years)
- Planned bronchoscopic procedure with sedation in an outpatient setting
- The patient have after receiving information about the study given his/her signed informed consent to participate.
- Women of childbearing potential only if use of an effective contraceptive.

Exclusion criteria

- Positive pregnancy test S-β-HCG.
- Known/suspected allergy or contraindication* to any medication within the study.
- Functional disability in both hands which affect the possibility to operate the PCS device.
- Cognitive impairment, unwillingness or language difficulties resulting in difficulty to understand the meaning of participation in the study or to operate the PCS device.

*Contraindications (exclusion of patient is made for each substance):

Propofol

- Hypersensitivity to propofol, peanut, soya or any of the excipients.

Midazolam

- Hypersensitivity to midazolam, benzodiazepines or to any of the excipients.
- Severe respiratory failure or acute respiratory depression.

Morphine-Scopolamine

- Secretion stagnation, respiratory depression. Anxiety during alcohol or hypnotic effect.

- Glycopyrronium bromide Hypersensitivity to glycopyrronium bromide or to any of the excipients.

Lidocaine and Lidocaine-naphazoline

- Hypersensitivity to the active substance, local anaesthetics of the amide type or to any excipients.
- Hypersensitivity of the methyl and / or propyl (methyl / propyl paraben), or the metabolite para-aminobenzoic acid (PABA).

- Pharmaceutical formulations of lidocaine containing parabens should be avoided in patients who are allergic to ester local anaesthetics or its metabolite PABA.

Alfentanil
- Hypersensitivity to the active substance or to any of the excipients listed.

Naloxone
- Hypersensitivity to the active substance or to any of the excipients listed.

Flumazenil
- Hypersensitivity to the active substance or to any of the excipients listed.

Patient withdrawal criterias

Patient is withdrawn from study by primary investigator if any of the following criteria are fulfilled:
- patient withdrawal of informed consent
- if patient safety is jeopardized
- if the procedure is not possible to perform in accordance with the protocol due to insufficient sedation, insufficient pain relief or other circumstances.
- if protocol is violated

Premature termination of the study

The sponsor/primary investigator may terminate the study if:
- the study reveals indications that either of groups has significant anomalous outcomes in relation to the other treatments
- safety for the patients within the study may be affected
- insufficient number of patients can be included in the study
- study drugs according to the protocol cannot be delivered

In case of termination of study by the sponsor, MPA and EPN will be promptly informed and receive a detailed written explanation of the reasons for termination.

Investigational medicinal product(s)

Patient-controlled sedation

The software used in the PCS device (T34L PCA, CME Ltd. Lichtenstein, Germany) used for the procedure has no lockout period or background infusions and size for bolus dose of propofol is set in advance. Administration of the drug is controlled by the patient by using the delivery button that may self-administrate the drug when there is a need for sedation. Repeated administration will increase concentration of the drug which will affect the patient consciousness and level of sedation which results in lower frequencies or none requested bolus doses. When concentration decreases the patient may start to interact with the PCS again and if needed continue the administration. Due to potential discomfort during the initiation of the intervention the patient usually begins using the PCS before the intervention starts. The nurse anaesthetist should during the whole procedure encourage the patient to use the PCS whenever there is need to decrease discomfort.

Propofol (Propofol-®Lipuro 5/10/20 mg/ml, Propofol Sandoz 10/20 mg/ml, Diprivan® 10/20 mg/ml, Propolipid 10/20 mg/ml, Recofol 10/20 mg/ml)
Propofol is a sedative-hypnotic agent used for induction or maintaining anaesthesia or sedation during surgery, diagnostics, or procedures. It produces sedation/hypnosis rapidly (usually within 40 seconds from the start of an injection) and smoothly with minimal excitation; decreases intraocular pressure (IOP) and systemic vascular resistance; rarely is associated with malignant hyperthermia and histamine release; suppresses cardiac output and respiratory drive. For intravenous sedation in diagnostic and surgical procedures: Initially, 6-9 mg/kg/h by infusion given for 3-5 minutes or an alternative dose of 0.5-1 mg/kg by slow injection over 1-5 minutes. Sedation is maintained with 1.5-4.5 mg/kg/h infusion.
The agent is supplied locally from the locked storage (room temperature) at the department of anaesthesia and surgery. An accountability list will ensure the possibility to trace the agent from delivery on the department to administration. Due to use of agent from the local storage no additional labelling of the agent is needed. The agent will be administrated intravenously using a peripheral venous catheter. Based on former experience and knowledge from similar procedures with PCS and the estimated time for the procedure, totally 420 mg propofol 10 mg/ml (=42 ml) is prepared in a 50 ml syringe compatible with the PCS device. The PCS software is set to make it possible to deliver 5 mg propofol (0,5 ml) for each request with a infusion rate of 300 ml/h (6 requests/min or 3 ml/min or 30 mg/min). Dose level is based on previous experiences from procedures with PCS. The agent will only be supplied during the procedure and the patient will be monitored bedside by nurse anaesthetist.

Midazolam (Midazolam Accord 1/5 mg/ml, Midazolam Actavis 1/5 mg/ml, Midazolam Hameln 1/5 mg/ml, Midazolam Panpharma 1/5 mg/ml, Dormicum® 5 mg/ml)
Midazolam is a short acting potent sedating drug used for instance before and during diagnostic interventions together with or without local anaesthetics. It can also be used as pre medication before anaesthesia, to provide anaesthesia or for sedation in connection with intensive care. The drug will be given intravenously. An initial dose of 1.5 mg will be given and additional doses titrated and adjusted to the patient's age and physical status. A maximum of 3.75 mg will be given during a procedure.
The agent is supplied locally from the locked storage (room temperature) at the department of anaesthesia and surgery. An accountability list will ensure the possibility to trace the agent from delivery on the department to administration. Due to use of agent from the local storage no additional labelling of the agent is needed. The agent will be administrated intravenously using a peripheral venous catheter.

Morphine-Scopolamine (Morfin-Skopolamin Meda (10+0.4) mg/ml)
Morphine-Scopolamine is used to reduce pain and receive an anticholinergic effect before invasive interventions. The agent will be given as a subcutaneous injection of 0.5-1.0 ml depending on the age of the patient.
The agent is supplied locally from the locked storage (room temperature) at the clinic. An accountability list will ensure the possibility to trace the agent from delivery on the clinic to administration. The agent will be labelled with patient id and randomisation number by designated pulmonary nurse who will not attend during the procedure. One hour before procedure start is administrated subcutaneously. Dose level is based on previous experiences for reduction of pain and secretion on patients during bronchoscopy.

Glycopyrronium bromide (Robinul® 0.2 mg/ml)

Glycopyrronium bromide is an anticholinergic agent used to reduce secretions in the mouth, throat, airway, and stomach before surgery. It blocks the activity of acetylcholine in the body, which decreases secretions and decreases side effects caused by medicines that may increase the action of acetylcholine in the body. Glycopyrronium bromide decreases acid secretion in the stomach. Hence it can be used for treating ulcers in the stomach and small intestine, in combination with other medications. In anaesthesia, glycopyrronium bromide injection serves as a preoperative antimuscarinic drug that reduces salivary, tracheobronchial, and pharyngeal secretions, as well as decreases the acidity of gastric secretions blocks cardiac vagal inhibitory reflexes during intubation.
The agent is supplied locally from the locked storage (room temperature) at the clinic. An accountability list will ensure the possibility to trace the agent from delivery on clinic to administration. The agent will be labelled with patient id and randomisation number by designated pulmonary nurse who will not attend during the procedure. One hour before procedure start 0.2 mg (=1 ml) glycopyrronium bromide is administrated intramuscular. Dose level is based on previous experiences for reduction of secretion on patients during sedation or anaesthesia. The agent will be supplied before procedure and the patient will be monitored bedside by a nurse anaesthetist.

Coadministration of other medicinal products

Lidocaine (Lidokain FarmaPlus 10mg/ml, Xylocain® 10 mg/ml) and Lidocaine-naphazoline (Lidokainhydroklorid-nafazolin 34 mg/ml + 0,17 mg/ml)
Lidocaine is a local anaesthetic of the amide group. The dosage will be adjusted according to the response of the patient and the site of administration. The lowest concentration and smallest dose producing the required effect should be given. The maximum dose for healthy adults should not exceed 200 mg. The agent is supplied locally from the locked storage (room temperature) at the clinic. The agent will be supplied before bronchoscopy starts and the patient and repeated if needed during the procedure.

Rescue medication

Alfentanil (Rapifen® 0.5mg/ml)
Alfentanil is a narcotic analgesic, in general, as well as adjuvant to regional anaesthesia and for both short (bolus injections) and long (bolus, supplemented by increments or by infusion) surgical procedures. Because of its rapid and short-lasting action, alfentanil is particularly suited as a narcotic analgesic for short procedures and outpatient surgery, but also as an analgesic supplement for procedures of medium and long duration, since periods of very painful stimuli can easily be overcome by small increments of alfentanil or by adapting its infusion rate.
The agent is supplied locally from the locked storage (room temperature) at the clinic. An accountability list will ensure the possibility to trace the agent from delivery on the clinic, by the local pharmacy, to administration. The agent will only be used as rescue medication if sedation with PCS is insufficient and will be labelled according to local regulations (not blinded). Intermittent bolus doses of 0.125 mg (=0.25 ml) alfentanil is administrated intravenously using a peripheral venous catheter. Dose level is based on previous experiences from procedures were additional analgesic is needed. The agent will only be supplied during procedure and the patient will be monitored bedside by nurse anaesthetist.

Naloxone (Naloxon B. Braun 0,4 mg/ml, Naloxon Hameln 0,4 mg/ml, Nexodal 0,4 mg/ml)
Naloxone is indicated for the treatment of respiratory depression induced by natural and synthetic opioids. It may also be used for the diagnosis of suspected acute opioid overdosage. The agent is supplied locally from the locked storage (room temperature) at the clinic. An accountability list will ensure the possibility to trace the agent from delivery on the clinic, by the local pharmacy, to administration. The agent will only be used as rescue medication if suspected acute opioid over dosage occur and will be labelled according to local regulations (not blinded). The dose should be titrated for each patient in order to obtain respiratory response while maintaining analgesia. An intravenous dose of 1.5 - 3.0 micrograms/kg body weight is usually sufficient, but a full two minutes should be allowed between each 100 microgram increment of naloxone administered.

Flumazenil (Lanexat® 0,1 mg/ml)
Flumazenil is used to reverse the effects of benzodiazepines. By reversing the effects of benzodiazepines, it allows the patient to become conscious so that they can breathe unaided. An accountability list will ensure the possibility to trace the agent from delivery on the clinic, by the local pharmacy, to administration. The agent will only be used as rescue medication if suspected acute benzodiazepine over dosage occur and will be labelled according to local regulations (not blinded). The starting dose for adults is 0.2mg administered intravenously over 15 seconds. If the required level of consciousness is not obtained within 60 seconds, a further dose of 0.1mg can be injected and repeated at 60-seconds intervals to a maximum of 1mg during anaesthesia.

The study has no restrictions regarding concomitant medication used by the patient.

Registration of efficacy

Primary endpoint

Discharge assessment

Post Anaesthetic Discharge Scoring System (PADSS)

The PADSS is used to clinically assess if the patient is ready to be discharged after anaesthesia/sedation and consist of five criteria: vital signs, ambulation, nausea and/or vomiting, pain and surgical bleeding (see further appendix 3). Each criterion is given a score ranging from 0 to 2. Only patients who achieve a total score of 9 or more are considered ready for discharge. A measurement of the PADSS score is done by pulmonary nurse every 15 min after bronchoscopy is finished (time =0 is when bronchoscope is removed) for 2 hours and thereafter every hour until two consecutive PADSS scores ≥ 9. When this is reached the patient may be discharged. It takes less than 1 minute to complete the assessment.

Secondary endpoints

Assessment of self-rated patient questionaries'

Sense of coherence (SOC)

The SOC is a theoretical formulation that provides a central explanation for the role of stress in human functioning. It is a self-rating scale and consists of 29 items (see further appendix 5). Scores are set by the patient for each question from 1 to 7 and codification of the items follows giving scores on a sub-scale level as well as a total score. The questionnaire used in the study is in Swedish language and will be handed out after informed consent is given and filled out by the patient between visit 1 and visit 2. It takes approximately 5 minutes to complete the questionnaire. The questionnaire will be mailed by the patient in a prepaid envelope to the Pulmonary Clinic.

Coping Strategies Questionnaire (CSQ-SWE)

The CSQ-SWE is the Swedish version of "The coping strategy questionnaire" and is a 50-items self-rated questionnaire used to assess cognitive and behavioural strategies to cope with pain (see further appendix 6). Each coping strategy subscale consists of six items measured with a numerical rating scale ranging from 0 ("never do that") to 6 ("always do that"). Subscale scores and total score is calculated. The questionnaire will be handed out after informed consent is given and filled out by the patient between visit 1 and visit 2. It takes approximately 5 minutes to complete the questionnaire. The questionnaire will be mailed by the patient in a prepaid envelope to the Pulmonary Clinic.

Hospital Anxiety and Depression Scale (HADS)

HADS is used to assess patents' experience of anxiety and depression. It is a 14-item self-rating scale and consists of seven questions for the subscales anxiety and depression (see further appendix 7). Each item is scored 0-3 and a total score for each subscale is calculated. The questionnaire used in the study is in Swedish language and will be handed out after informed consent is given and filled out by the patient between visit 1 and visit 2. It takes approximately 2 minutes to complete the questionnaire. The questionnaire will be mailed by the patient in a prepaid envelope to the Pulmonary Clinic.

Post-discharge Surgical Recovery Scale (S-PSR)

The modified Swedish version S-PSR is based on the "Post-discharge Surgical Recovery Scale" and is a 14-item questionnaire to assess the recovery post-discharge regarding the patients' health status and activity (see further appendix 2). Each item is rated using a semantic differential scale and the total sum is multiplied by 100. The possible range is 10-100, with higher score indicating a more favourable postoperative recovery. The assessment is done by the patient at home (or at ward if pro-longed hospital stay is necessary) in the evening on the day of bronchoscopy. It takes approximately 2 minutes to complete the questionnaire. The questionnaire will be mailed by the patient in a prepaid envelope to the Pulmonary Clinic.

Modified version of Quality of Recovery (QoR-23)

The questionnaire "Quality of Recovery" (QoR-23) is a 23 item questionnaire to assess recovery after day surgery regarding the patients' emotional state, physical comfort and physical independence (see further appendix 4). Each item is rated on a five-point scale (1-5) and the scores are summed. A higher score indicate a better quality of recovery. The assessment is done by the patient at home (or at ward if pro-longed hospital stay is necessary) in the morning the day after bronchoscopy. It takes less than 1 minute to

complete the assessment. The questionnaire will be mailed by the patient in a prepaid envelope to the Pulmonary Clinic.

Patients' satisfaction
After patient has recovered according to the protocol and before discharge, the patient assesses their overall satisfaction with the procedure using the Likert-type scale (1. Very dissatisfied, 2. Dissatisfied, 3. Neither satisfied nor dissatisfied, 4. Satisfied, 5. Very satisfied). The patient may comment any cause which made the satisfaction score high or low and if the patient would like to receive the same method of sedation during a future bronchoscopy.

Bronchoscopist evaluation
After completion of the procedure the bronchoscopist assess their perception of cough, bronchial secretion respectively circumstances for a smooth performance of the bronchoscopy of procedure using the Likert-type scale (1. Very dissatisfied, 2. Dissatisfied, 3. Neither satisfied nor dissatisfied, 4. Satisfied, 5. Very satisfied).

Requested/given bolus doses from PCS
Each time the patient is requesting a bolus dose of propofol from the PCS it will deliver a pre-set dose. If an additional dose is requested before the first dose has been completely delivered (due to multiple requests) an additional dose will not be delivered. All requests, delivered or not delivered, will be recorded in the PCS software and transferred to the CRF.

Total dose given of topical anaesthetic, analgesia and sedation
The total dose of given medication of topical anaesthetic, analgesia and sedation will be registered for each patient. For patients using the PCS requested respectively given bolus doses of propofol will be registered.

Procedure safety variables
Vital signs
Vital signs (arterial oxygen saturation, respiratory frequency, non-invasive blood pressure and heart rate) will be recorded every five minutes as well as any interventions performed to maintain cardiovascular and respiratory stability.

Level of sedation
Level of sedation is assessed by the nurse anaesthetist using The Observer's Assessment of Alertness/Sedation (OAA/S) scale (Chernik, D., et al. 1990) by specifying sedation level score between "Does not respond to mild prodding or shaking" (score 1) to "Responds readily to name spoken in normal tone" (score 5) (see further appendix 1).

Level of sedation is measured by the nurse anaesthetist in 5 minutes intervals until procedure completion.

Interventions
When the pre-defined safety limits (see below) are breached during the procedures appropriate interventions has to be undertaken by the nurse anaesthetist and registered.

Pre-defined safety limits and interventions		
Symptom	**Definition**	**Intervention**

Respiratory depression	Respiratory rate < 8 breaths/min according to surveillance monitor **OR** visual count by nurse anaesthetist	Encourage patient to breath
Low oxygen saturation	Oxygen saturation < 90%	Increase oxygen flow
Obstructed airway	Obstructive apnea	Apply chin lift
Apnea	Apnea according to surveillance monitor **AND** oxygen saturation < 90% **OR** apnea > 30s detected visually by nurse anaesthetist **AND** oxygen saturation < 90%	Assisted ventilation with mask and addition of at least 50% O_2
Bradycardia	Heart rate < 40 beats/min	Give atropine 0,5 mg
Hypotension	Non-invasive systolic blood pressure < 90 mmHg	Give ephedrine 5 mg

Registration of safety

Safety variables regarding the level of sedation and vital signs are described above. A nurse anaesthetist is present during the whole procedure until sedation level OAA/S 5 is reached, thereafter and before procedure a pulmonary nurse is present. Bronchoscopist and anaesthesiologist are available via telephone and/or pager and can be present within a few minutes.
All of the drugs are administered by routes and given in doses in accordance with approval from the Swedish Medical Products Agency. The personnel involved in the procedure are all familiar with the use of the drugs being studied.

Incident

The definition of an incident is any untoward event or unintended response to the study drug, irrespective of dose. Incidents should be reported whether they are related to the procedure or not, even a slight cold, a sprained foot etc. Exceptions that will not be reported as an incident is the most common adverse reactions reported in FASS from each study agent (see table below) or events considered to be part of the normal post-procedural process such as local pain from upper airway, hoarseness, fever, cough etc.

Propofol	
Body system	**Adverse reaction**
Central and peripheral nervous system	Headache when awakening
Heart	Bradycardia
Vascular	Hypotension
Respiratory, thoracic and mediastinal	Transient apnea during induction
Gastrointestinal	Nausea and vomiting during awakening
General symptoms from site of administration	Local pain at induction

Midazolam	
Body system	**Adverse reaction**

Psychiatric	Agitation, excitation, anger
Central and peripheral nervous system	Unconscious movements, hyperactivity
Heart	Bradycardia
Vascular	Hypotension
Respiratory, thoracic and mediastinal	Respiratory depression, apnea
Gastrointestinal	Nausea and vomiting
General symptoms from site of administration	Local pain at induction

Morphine-Scopolamine

Body system	**Adverse reaction**
Psychiatric	Euphoria, confusion, hallucination
Central and peripheral nervous system	Dysphoria, disorientation, dizziness, respiratory depression
Eye	Difficult accommodation, meiosis
Heart	Tachycardia, hypertension
Vascular	Hypotension
Respiratory, thoracic and mediastinal	Bronchoconstriction
Gastrointestinal	Nausea and vomiting, dry mouth
General symptoms from site of administration	Urticaria, itching

Glycopyrronium bromide

Body system	**Adverse reaction**
Central and peripheral nervous system	Drowsiness
Eyes	Visual disturbances
Heart	Tachycardia, palpitations, ventricular arrhythmia
Gastrointestinal	Dry mouth

Lidocaine and Lidocaine-naphazoline

Body system	**Adverse reaction**
Vascular	Hypotension, hypertension
Central and peripheral nervous system	Dizziness, paresthesia
Heart	Bradycardia
Gastrointestinal	Nausea and vomiting

Alfentanil

Body system	**Adverse reaction**
General	Chills, pain at the injection site, fatigue
Circulatory	Bradycardia, tachycardia, hypotension, hypertension, decreased blood pressure, high blood pressure
Airways	Apnea
Musculoskeletal	Muscle rigidty
Central and peripheral nervous system	Drowsiness

Neurological	Movement disorder, dizziness, sedation, dyskinesia
Psychiatric	Euphoric mood
Eyes	Visual disturbances

Naloxone	
Body system	**Adverse reaction**
Central and peripheral nervous system	Dizziness, headache
Vascular	Hypotension, hypertension
Heart	Tachycardia
Gastrointestinal	Nausea and vomiting

Flumazenil	
Body system	**Adverse reaction**
Central and peripheral nervous system	Dizziness, headache, agitation, tremor
Eyes	Diplopia, strabismus, increased amount of tear fluid.
Vascular	Hypotension, orthostatic hypotension
Gastrointestinal	Nausea and vomiting
Skin	Sweating
General	Fatigue, pain at the injection site

All incidents that investigator, identifies as incident will be documented in the medical record and incident report until day after procedure due to short exposure to IMP and short half-life of IMP.

In the incident report the following grading is used to rate the severity of an incidence:
- Mild = aware of the symptoms but they are tolerable
- Moderate = symptoms partially affect daily activities
- Severe = symptoms significantly affect daily activities

The investigator assesses the relationship between the incidence and the study drug, as defined:
- Likely = good reasons and sufficient documentation to suspect causality
- Possible = causality cannot be dismissed
- Unlikely = Another reason is more likely
- Not evaluable = causality cannot be confirmed

Serious adverse events
Investigator of the study will determine if the incidence is a SAE or not. Criteria for being a SAE:
- Death
- Life-threatening condition
- Conditions that require hospitalization or prolongs time at hospital
- Conditions which cause a lasting or significant disability or incapacity
- Congenital malformation or congenital defect

- Other serious medical event according to investigator

The investigator shall report all SAE to the sponsor within 24 hours. The sponsor will decide whether the SAE is considered as a SUSAR, which promptly shall be reported to the Medical Products Agency and the Ethics Review Board.

Annual safety report
Annually, while the study is ongoing, the sponsor reports a safety report to the Medical Products Agency (MPA) and Ethics Review Board (ERB). The report defines the time period reported and summarizes number of patients that have completed/discontinued/withdrawn, all SAEs, all SUSARs, changes in the study drugs safety information (Summary of Product Characteristics (SmPC)) as well as a summary regarding the safety of the patients within the study concerning the risk-benefit since the study was approved.

SUSAR-report
A SUSAR is a suspected serious unforeseen incident, undesirable severe reaction to a study drug (which has not been previously reported).

A SUSAR that is fatal or life-threatening shall be reported as soon as possible and no later than 7 days after it has become known to the sponsor. Relevant follow-up information will be forwarded within another 8 days. Other SUSARs shall be reported as soon as possible and no later than 15 days after they come to the sponsor's knowledge. The sponsor shall inform all investigators participating in the study about the SUSAR.
Report regarding SUSARs to the MPA will be done using the CIOMS form which will be scanned and snet electronically via email to mpa@registrator.se by sponsor.

Pregnancy
Women of childbearing potential will be asked about pregnancy. Pregnant women and women with positive S-β-HCG will be excluded in the study. All sedation arms include drugs, midazolam or propofol, classified as “Category C” during pregnancy. The accumulated doses of propofol or midazolam given as sedation during bronchoscopy is low. To the best of our knowledge the risk of unknown pregnancy is low and the fetal risks are very low. Inclusion of women of childbearing potential requires use of a effective contraceptive which shall be maintained from day of informed consent until day after procedure. Women who are breastfeeding suspend breastfeeding during 24 hours after bronchoscopy.

Statistics
A total of 300 patients (100 patients in each group) with a power of 80% and we estimate to generate a statistical significant level of less than 0,05 for the primary endpoint. Interim analysis will be performed after 150 patients. We use the method according to Pocock, where the significance limit is p=0.0294 at the interim analysis and 0.0294 at the main analysis.
The primary endpoint, discharge within two hours, will be analysed using a Chi^2 test.
Secondary endpoints, the questionnaires (SOC, CSQ-SWE, HADS, S-PSR, QoR-23), patient satisfaction and bronchoscopists evaluation, both on a Likert type scale will be analysed with Mann-Whitney U-test.
Number of requests and total dose of propofol will be analysed with Student´s t-test.
All analyses above will be done with planned comparison, first we compare group MM with the combined MP+GP group, and thereafter the groups MP and GP will be compared.

The number of dose request from the PCS device and total dose of propofol/alfentanil/topical anaesthetics, respectively, will only be compared between groups GP and MP. To investigate if the total administered dose of propofol is associated with patient characteristics according to questionnaires (SOC, CSQ-SWE, HADS) we will use Pearson correlation analysis and linear regression with total dose as dependent variable to be able to analyse several questionnaires simultaneously.
Safety variables, vital parameters, level of sedation and number of interventions will be analysed with Students t-test or Mann-Whitney U-test.

Quality control and quality assurance

Department of Anesthesiology and surgical clinic, University hospital of Linköping is the coordinating center for the study with Lena Nilsson as sponsor and primary investigator. The study team consists of the study actively participating researchers (doctors and nurses). Concerned staff at the pulmonary clinic will be informed in detail about the study by the research team before the study start, and the research team will have regular contact with the staff during the study period. Once the study is completed results of the study are presented to all personnel involved.

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written standard operating procedures to ensure that trials are conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP, and Helsinki Declaration (2013).

Monitoring

The study will be monitored according to an agreement between sponsor/principal investigator and the independent monitor Forum Östergötland (University Hospital, SE-581 85 Linköping).

The investigator is obligated to give direct access to medical record for monitors, inspectors from the Medical Product Agency and any possible evaluator from the ethics committee.

The monitor will ensure that informed consent are obtained according to regulations, compliance with the study protocol, to correct the data collected for the study developed CRF and that adverse events reported according to LVFS 2011: 19. It is not planned for external control (audit) of the study. The study will be registered in accordance with "The International Committee of Medical Journal Editors (ICMJE) Initiative" to "Clinical Trials.gov" upon approval by the MPA and EPN.

At the initial meeting the monitor will review study protocol, clinical research form (CRF), study binder including all essential documents, the facility and equipment used within the study. Afterwards a written report is sent to the sponsor.

The first monitoring visit will take place when the first 2-5 patients are enrolled in the study. At each visit the monitor checks inclusion/exclusion criteria, signed consents, that source data conform to the information specified for the study efficacy/safety variables and SAEs but also other documents of importance. The monitor checks with the sponsor if significant changes have been made in study related documents and that permission for the changes have been obtained as well as that changes are traceable. A report will be sent by the monitor to the sponsor after each conducted visit.

Further visits during the study will be done according to the agreement.

The last monitoring visit at the clinic will be when the last participant has completed his last visit. The monitor verifies that study binder with essential documents including CRF is complete and ready for archiving. A written report of the visit is written by the monitor and sent to the sponsor.

Source data
Source data is defined as any information in original records and certified copies of original records of clinical findings, observations or other activities necessary for reconstruction and evaluation for the study (e.g. CRFs, medical records). For this study, a separate Source Data Identification List will be written defining the source data for this study.

Ethical considerations

The patients are supervised by experienced personnel during and after the procedure. The anaesthetic nurses and anaesthesiologist are trained to handle possible emergency situations that might occur in connection with sedation and recovery. Respiration and circulation is monitored continuously in accordance with clinical routine, and does not cause any discomfort or pain to the patient.

The study does not require any extra hospital visits for the patient. The questionnaires might by some be regarded as integrity violating. We stress that answering is voluntary and that all questions need not to be answered. Our experience is that patients in a phase of stress and sorrow after serious information about illness, often find it of value to express their thoughts and feelings.

Procedure for recruiting and obtaining informed consent

During the first visit (pre-procedural visit) at the clinic recruitment to the study will be done. The patient is given verbal and written information about the study objectives, purpose and approach and will be given the opportunity to ask questions to the investigator. Participation is entirely voluntary. If the patient accepts study participation it results in a signed informed consent by the patient and investigator. The information and subsequent consent informs the patient that an independent monitor and medical regulatory authorities are allowed to compare data from the medical record with CRF.

Handling and archiving data

Patients, who are selected to undergo bronchoscopy during the time for the study will be recorded in a screening log. Reason for exclusion shall be documented in the log. Patients' that fulfil the criteria for inclusion and have no exclusion criteria will be registered in a patient identification list with their personal identification number, full name and the assigned study number (consecutively). Information regarding the participation, including where the code list is stored (if necessary to break the code), will be recorded by the investigator in the patients' medical journal. The patient will receive a study number which can be tracked through the patient identification list. The patient identification list will be kept with the signed consent in a locked room at the clinic. Patients will not be given a "Study ID card" due to the drugs short

half-life. The envelopes for randomization are stored in a locked drug room at the clinic only accessible for pulmonary nurses at the clinic.

For this study, a study binder will be established that contains study protocol, patient information, informed consent from patients, patient registration form, form for the registration of adverse events (AE), form for recording serious adverse events (SAE), patient questionnaires' used in the study, screening and patient identification list, data source list, delegation list, application and approval of the study from the regional Ethics Committee in Linköping and Medical Proiduct Agency, and any amendments.

Codelist will be stored in locked room at the clinic. Relevant data from the patients' medical history is recorded in CRF. Relevant data is medical history and medication that affect the patient's cardiorespiratory stability and / or treatment of pain / anxiety. Other data collected will be written in the CRF at each visit. Data from PCS will manually be transferred from device to CRF. A delegation list will be established which identify all individuals involved and the primary investigator delegated tasks.
The CRF will be recorded both by pulmonary nurse, nurse anaesthetic, anaesthesiologist and pulmonary physician/bronchoscopist who individually will all have the right to make corrections of their individual records in the CRF. Deviations from the study protocol will be treated individually. Data will be analysed according to intention-to-treat (ITT). Deviations from the study protocol will be treated individually. Data will be analysed according to intention-to-treat (ITT). Data will be coded and entered into a computer database. The handling of data, including data quality control, will comply with regulatory guidelines (e.g., International Conference on Harmonization Good Clinical Practice [ICH GCP]).

All study-related data will be stored in rooms with limited access. Medical records will be archived in the County Archives under current regulations for archiving of patient medical records. The study documents are stored according to RA-FS 1999: 1 and rules for conservation and thinning of research documents at Linköping University of at least 10 years. Thereafter the documents will be destroyed. Privacy applies according to Hälso- och sjukvårdslagen for persons who take part of the medical record and study documents concerning patients in the study.

Insurance
Patients are insured by Läkemedelsförsäkringen and Patientförsäkringen.

Finance
The study is funded by grants from regional funds. The application is made by the Department of Anesthesiology and surgical clinic, University hospital of Linköping. The study has no sponsorship from industry.

Reporting and publishing
Study results will be summarized and submitted to the MPA within one year after end of study. Presentation of the results is planned in regional, national and international contexts, and the results will be sent for publication in an internationally recognized journal.

Substantial amendment of study and declaration of end of trial

Requests for a substantial amendment in the study protocol will be sent by sponsor to the MPA and Ethics Committee. When the study is closed an End-of-trial (EOT) report will be sent by sponsor to the MPA.

Discrepancies' and violations

If discrepancies or violations are made that affect, or with high probability could affect the patients' safety or the study's scientific value, sponsor will report immediately to the MPA.

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Agreement

I have read the protocol and will conduct the study according to the protocol, Good Clinical Practice and applicable regulations.
I will inform the employees who will be involved in the study and will assure me that they have sufficient knowledge to carry out the study.

Primary investigator and sponsor signature	Date

Printed name

Appendix 1 – Observer's assessment of alertness/sedation (OAA/S) scale

Observation	Score level
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1

Appendix 2 – Modified Post-discharge Surgical Recovery (S-PSR) scale

Enkäten fylls i samma dag på kvällen (kl 20) som Du genomförde undersökningen

Samtliga uppgifter kommer att behandlas konfidentiellt och vad du svarat kommer inte att kunna identifieras i resultatredovisningen.

Dagens datum är:_____

Tid du denna enkät fylls i? Klockan_____

Vilket datum gjorde Du undersökningen? Den_____

När ankom du till sjukhuset? Klockan____

När fick du åka hem? Datum_____Klockan_____

Nedanstående fråga handlar om hur du upplever din hälsa. Ringa in den siffra som bäst överensstämmer med hur du upplever din hälsa just nu, där 1 står för ”mycket dålig” och 10 för ”mycket god”.

Just nu upplever jag att min hälsa är:

Mycket dålig 1 2 3 4 5 6 7 8 9 10 Mycket god

Om du graderar din hälsa med 5 eller lägre vilka hälsoproblem/svårigheter har du idag?

_____

_____

V.g vänd på bladet

Följande påståenden handlar om hur du känner dig just nu. Varje påstående består av två ändpunkter med en gradering däremellan. Ringa in den siffra som bäst motsvarar hur du känner dig.

Just nu känner jag mig:

pigg	1	2	3	4	5	6	7	8	9	10	slö
smärtfri	1	2	3	4	5	6	7	8	9	10	mycket smärtpåverkad
mycket trött	1	2	3	4	5	6	7	8	9	10	full av energi
inte alls kapabel att göra det som jag brukar göra	1	2	3	4	5	6	7	8	9	10	helt kapabel att göra det som jag brukar göra
ha ett stort behov av vila på dagtid	1	2	3	4	5	6	7	8	9	10	inte alls i behov av vila på dagtid
inte alls lika rörlig som vanligt	1	2	3	4	5	6	7	8	9	10	precis lika rörlig som vanligt
i behov av att bara vara hemma i bostaden	1	2	3	4	5	6	7	8	9	10	helt redo för att lämna bostaden
har kraft/ork att fysiskt anstränga mig	1	2	3	4	5	6	7	8	9	10	helt utan kraft/ork att fysiskt anstränga mig
bättre än jag trodde att jag skulle göra	1	2	3	4	5	6	7	8	9	10	sämre än jag trodde att jag skulle göra

V.g vänd på bladet.

Just nu känner jag mig:

inte alls återhämtad efter undersökningen	1	2	3	4	5	6	7	8	9	10	helt återhämtad efter undersökningen
helt tillbaka till min vanliga livsföring	1	2	3	4	5	6	7	8	9	10	inte alls tillbaka till min vanliga livsföring
helt tillbaka till mitt vanliga själsliga tillstånd	1	2	3	4	5	6	7	8	9	10	inte alls tillbaka till mitt vanliga själsliga tillstånd

Appendix 3 –Post Anaesthetic Discharge Scoring System (PADSS) for Home readiness after Ambulatory Surgery

Category	Description	Score
Vital signs	< 20% of preoperative value 20-40% of preoperative value > 40% of preoperative value	2 1 0
Ambulation	Steady gait; no dizziness With assistance No ambulation; dizziness	2 1 0
Nausea or vomiting	Minimal Moderate Severe	2 1 0
Pain	Minimal Moderate Severe	2 1 0
Surgical bleeding	Minimal Moderate Severe	2 1 0

Appendix 4 – Modified Quality of Recovery (QoR-23)

Kryssa i det som stämmer bäst överensstämmer med hur du mått de senaste 24 timmarna.

Under de senaste 24 timmarna har jag;

	Instämmer inte alls				Instämmer helt
	1	2	3	4	5
1. Kunnat andas lätt	☐	☐	☐	☐	☐
2. Sovit gott	☐	☐	☐	☐	☐
3. Kunnat njuta av maten	☐	☐	☐	☐	☐
4. Känt mig utvilad	☐	☐	☐	☐	☐
5. Haft en känsla av allmänt välbefinnande	☐	☐	☐	☐	☐
6. Haft kontroll över min situation	☐	☐	☐	☐	☐
7. Känt mig avslappnad	☐	☐	☐	☐	☐
8. Haft en röst som varit som vanligt	☐	☐	☐	☐	☐
9. Kunnat borsta tänderna	☐	☐	☐	☐	☐
10. Kunnat sköta om mitt eget utseende	☐	☐	☐	☐	☐
11. Kunnat skriva som vanligt	☐	☐	☐	☐	☐
12. Kunnat återgå till arbetet eller sköta om vanliga bestyr i hemmet	☐	☐	☐	☐	☐

Har du upplevt något av följande **under de senaste 24 timmarna?**	**Inte alls**				**Hela tiden**
	5	4	3	2	1
13. Illamående	☐	☐	☐	☐	☐
14. Kräkningar	☐	☐	☐	☐	☐
15. Rastlöshet	☐	☐	☐	☐	☐
16. Skakningar eller ryckningar	☐	☐	☐	☐	☐
17. Frusenhet	☐	☐	☐	☐	☐
18. Yrsel	☐	☐	☐	☐	☐
19. Oro	☐	☐	☐	☐	☐
20. Nedstämdhet	☐	☐	☐	☐	☐
21. Ensamhet	☐	☐	☐	☐	☐
22. Insomningssvårigheter	☐	☐	☐	☐	☐
23. Mardrömmar	☐	☐	☐	☐	☐

Sedan du kom hem efter proceduren har du haft några besvär som du inte hade innan?

Nej o Ja o Om ja, vilket besvär har du haft?

_____

Om ja, har du behövt kontakta sjukvården?

_____

Appendix 5 – Sense of coherence (SOC)

Här är några frågor som berör skilda områden i livet. Varje fråga har 7 möjliga svar. Var snäll och markera den siffra som bäst passar in på ditt svar. Siffran 1 eller 7 är svarens yttervärden. Om du instämmer i det som står under 1, så ringa in 1:an; om du instämmer i det som står under 7, så ringa in 7:an. Om du känner annorlunda, ringa in den siffra som bäst överensstämmer med din känsla. Ge endast ett svar på varje fråga.

1. När du talar med människor, har du då en känsla av att de inte förstår dig?

1	2	3	4	5	6	7
har aldrig den känslan						har alltid den känslan

2. När du har varit tvungen att göra någonting som krävde samarbete med andra, hade du då en känsla av att det

1	2	3	4	5	6	7
kommer säkert inte att bli gjort						kommer säkert att bli gjort

3. Tänk på de människor du kommer i kontakt med dagligen, bortsett från dem som står dig närmast. Hur väl känner du de flesta av dem?

1	2	3	4	5	6	7
tycker att de är främlingar						känner dem mycket väl

4. Har du en känsla av att du inte riktigt bryr dig om vad som händer runt omkring dig?

1	2	3	4	5	6	7
mycket sällan eller aldrig						mycket ofta

5. Har det hänt att du blev överraskad av beteendet hos personer som du trodde du kände väl?

1	2	3	4	5	6	7
har aldrig hänt						har ofta hänt

6. Har det hänt att människor som du litade på har gjort dig besviken?

1	2	3	4	5	6	7
har aldrig hänt						har ofta hänt

7. Livet är:

1	2	3	4	5	6	7
alltigenom intressant						fullständigt enahanda

8. Hittills har ditt liv:

1	2	3	4	5	6	7
helt saknat mål och mening						genomgående haft haft mål och mening

9. Känner du dig orättvist behandlad?

1	2	3	4	5	6	7
mycket ofta						mycket sällan/aldrig

10. De senaste tio åren har ditt liv varit:

1	2	3	4	5	6	7
fullt av för-ändringar utan att du visste vad som skulle hända härnäst						helt förutsägbart utan överraskande förändringar

11. De flesta saker du gör i framtiden kommer troligtvis att vara:

1	2	3	4	5	6	7
helt fascinerande						fullkomligt urtråkiga

12. Har du en känsla av att du befinner dig i en obekant situation och inte vet vad du skall göra?

1	2	3	4	5	6	7
mycket ofta						mycket sällan/aldrig

13. Vilket påstående beskriver bäst hur du ser på livet?

1	2	3	4	5	6	7
det går alltid att finna en lösning på livets svårigheter						det finns ingen lösning på livets svårigheter

14. När du tänker på ditt liv, händer det mycket ofta att du:

1	2	3	4	5	6	7
känner hur härligt det är att leva						frågar dig själv varför du överhuvudtaget finns till

15. När du ställs inför ett svårt problem är lösningen:

1	2	3	4	5	6	7
alltid förvirrande och svår att finna						fullständigt solklart

16. Är dina dagliga sysslor en källa till:

1	2	3	4	5	6	7
glädje och djup tillfredsställelse						smärta och leda

17. I framtiden kommer ditt liv förmodligen att vara:

1	2	3	4	5	6	7
fullt av för-ändringar utan att du vet vad som händer härnäst						helt förutsägbart och utan överraskande förändringar

18. När något otrevligt hände tidigare brukade du:

1	2	3	4	5	6	7
älta det om och om igen						säga ”Det var det” och sedan gå vidare

19. Har du mycket motstridiga känslor och tankar?

1	2	3	4	5	6	7
mycket ofta						mycket sällan/aldrig

20. När du gör något som får dig att känna dig väl till mods:

1	2	3	4	5	6	7
kommer du säkert att fortsätta att känna dig väl till mods						kommer det säkert att hända något som förstör den goda känslan

21. Händer det att du har känslor inom dig som du helst inte vill känna?

1	2	3	4	5	6	7
mycket ofta						mycket sällan/aldrig

22. Du är inställd på att ditt personliga liv i framtiden kommer att vara:

1	2	3	4	5	6	7
helt utan mål och mening						fyllt av mål och mening

23. Tror du att det i framtiden alltid kommer att finnas människor som du kan räkna med?

1	2	3	4	5	6	7
det är du säker på						det tvivlar du på

24. Händer det att du har en känsla av att du inte exakt vet vad som håller på att hända?

1	2	3	4	5	6	7
mycket ofta						mycket sällan/aldrig

25. Även en människa med stark självkänsla kan ibland känna sig som en ”olycksfågel”. Hur ofta har du känt det så?

1	2	3	4	5	6	7
aldrig						mycket ofta

26. När något har hänt, har du vanligtvis funnit att:

1	2	3	4	5	6	7
du över- eller undervärderade dess betydelse						du såg saken i dess rätta perspektiv

27. När du tänker på svårigheter som du troligtvis kommer att möta inom viktiga områden av ditt liv, har du då en känsla av att:

1	2	3	4	5	6	7
du alltid kommer att lyckas övervinna svårigheterna						du inte kommer att lyckas övervinna svårigheterna

28. Hur ofta känner du att det inte är någon mening med de saker du gör i ditt dagliga liv?

1	2	3	4	5	6	7
mycket ofta						mycket sällan/aldrig

29. Hur ofta har du känslor som du inte är säker på att du kan kontrollera?

1	2	3	4	5	6	7
mycket ofta						mycket sällan/aldrig

Appendix 6 – Coping Strategies Questionnaire (CSQ-SWE)

Människor, som har haft ont länge, utvecklar olika sätt att hantera eller ta itu med sin smärta, t.ex. genom att tänka på annat än det onda eller göra något som leder bort tankarna från plågan. Här nedan kommer en rad påståenden på vad olika människor tänker och gör när de upplever smärta. Läs varje påstående, svara så gott Du kan och tänk inte för länge på varje fråga. Markera för varje påstående hur du tänker eller gör, när du får ont, med en siffra från 0 till 6. Skriv i rutan till vänster om påståendet. Du får använda vilken siffra som helst på skalan och samma siffra får användas flera gånger.

0	1	2	3	4	5	6
Aldrig			**Ibland**			**Alltid**

0 betyder att du aldrig tänker eller gör så.
3 betyder att du tänker eller gör så ibland.
6 betyder att du alltid tänker eller gör så.

	1 Jag försöker tänka att smärtan finns utanför mig, som om det vore någon annan som hade ont och inte jag.
	2 Jag går ut och hittar på något att göra, t.ex. går i affärer eller går på bio.
	3 Jag försöker tänka på något trevligt.
	4 Jag tänker inte på smärtan som smärta, utan som en dov känsla eller värmekänsla.
	5 Det är fruktansvärt, det känns som om det aldrig kommer att bli bättre.
	6 Jag intalar mig själv att jag måste härda ut och fortsätta som tidigare trots smärtan.
	7 Jag läser.
	8 Jag intalar mig att jag kan övervinna smärtan.
	9 Jag tar värktabletter.
	10 Jag räknar tyst för mig själv eller går igenom en sång eller ramsa i tanken.
	11 Jag tänker mig smärtan som en annan upplevelse, t.ex. som en domning.
	12 Det är hemskt och jag upplever att smärtan överväldigar mig.
	13 Jag knäcker tankenötter för att hålla tankarna borta från smärtan.

	14 Jag känner det som om livet inte är värt att leva.
	15 Jag vet att någon gång kommer någon att kunna hjälpa mig och då försvinner smärtan ett tag.
	16 Jag promenerar mycket.
	17 Jag ber till Gud att det snart måtte gå över.
	18 Jag försöker intala mig att det inte är min kropp som plågas, utan någonting annat som finns utanför mig.
	19 Jag slappnar/kopplar av.
	20 Jag tänker inte på smärtan.
	21 Jag försöker tänka åratals framåt i tiden på hur det kommer att bli när jag blivit av med det onda.
	22 Jag intalar mig att det inte gör ont.
	23 Jag intalar mig att jag inte kan låta smärtan hindra mig från att göra vad jag måste.
	24 Jag bryr mig inte om det.
	25 Jag tror att läkarna en dag ska finna bot för min plåga.
	26 Jag vet att jag klarar av smärtan hur illa det än blir.
	27 Jag låtsas inte om den.
	28 Jag oroar mig ständigt över om smärtan någonsin ska försvinna.
	29 Jag går och lägger mig.
	30 Jag tänker på trevliga minnen.
	31 Jag tänker på goda vänner som jag trevligt tillsammans med.
	32 Jag ber en bön att smärtan ska upphöra.
	33 Jag tar en dusch eller ett varmt bad.
	34 Jag föreställer mig att smärtan finns utanför min kropp.
	35 Jag fortsätter som om ingenting hade hänt.
	36 Jag tar det som en utmaning och bekymrar mig inte.
	37 Även om det gör ont, håller jag igång som vanligt.

Appendix 7 – Hospital Anxiety and Depression Scale (HADS)

Läs varje påstående nedan och sätt ett kryss i rutan till vänster om det svar, som kommer närmast hur du känner dig under den senaste veckan. Fundera inte alltför länge. Det första svar som dyker upp är antagligen riktigare än ett svar som du funderat på länge.
Svara på alla frågorna, kryssa bara i en ruta för varje påstående!

1.
Jag känner mig spänd eller ”uppskruvad”
- ☐ För det mesta
- ☐ Ofta
- ☐ Då och då
- ☐ Inte alls

2. Jag uppskattar fortfarande samma saker som förut.
- ☐ Precis lika mycket
- ☐ Inte riktigt lika mycket
- ☐ Bara lite
- ☐ Nästan inte alls

3. Jag känner mig rädd, som om något förfärligt håller på att hända.
- ☐ För det mesta
- ☐ Ofta
- ☐ Då och då
- ☐ Inte alls

4. Jag kan skratta och se saker från den humoristiska sidan.
- ☐ Lika mycket som jag alltid kunnat
- ☐ Inte riktigt lika mycket som förut
- ☐ Absolut inte så mycket som förut
- ☐ Inte alls

5. Oroande tankar kommer för mig.
- ☐ Mycket ofta
- ☐ Ofta
- ☐ Då och då
- ☐ Någon enstaka gång

6. Jag känner mig glad.
- ☐ Inte alls
- ☐ Inte så ofta
- ☐ Ibland
- ☐ För det mesta

7. Jag kan sitta i lugn och ro och känna mig avspänd.
- ☐ Absolut
- ☐ Oftast
- ☐ Inte ofta
- ☐ Inte alls

8. Jag känner mig som om allting går trögt.
- ☐ Nästan jämt
- ☐ Ofta
- ☐ Ibland
- ☐ Inte alls

9. Jag känner mig rädd, som om jag har ”fjärilar i magen”.
- ☐ Inte alls
- ☐ Någon gång
- ☐ Rätt ofta
- ☐ Mycket ofta

10. Jag har tappat intresset för mitt utseende.
- ☐ Helt och hållet
- ☐ Ganska mycket
- ☐ Lite grand
- ☐ Inte alls

11. Jag känner mig rastlös, som om jag måste vara på språng.
- ☐ Väldigt mycket
- ☐ En hel del
- ☐ Inte så mycket
- ☐ Inte alls

12. Jag ser fram emot saker och ting med glädje.
- ☐ Lika mycket som förut
- ☐ Något mindre än tidigare
- ☐ Klart mindre än tidigare
- ☐ Nästan inte alls

13. Jag får plötsliga panikkänslor.
- ☐ Mycket ofta
- ☐ Ganska ofta
- ☐ Inte så ofta
- ☐ Inte alls

14. Jag kan njuta av en bra bok, eller ett bra radio- eller TV – program.
- ☐ Ofta
- ☐ Ibland
- ☐ Inte så ofta
- ☐ Mycket sällan