Title Page

Protocol Title: Validation of a risk matrix for severe postdischarge pain after ambulatory gynaecological laparoscopy

Protocol Version: 1

Brief Title: Predicting pain after ambulatory gynaecological laparoscopies

A study to investigate the validity of a pain prediction tool, developed for patients with gynaecological laparoscopic surgeries.

Institution responsible for the trial: Oslo University Hospital

Legal Registered Address: Postboks 4950 Nydalen, 0424 Oslo

Approval Date:

Sponsor Signatory: Leiv Arne Rosseland

Leiv Arne Rosseland	Dec 19, 2025
Name	**Date**

Sponsor functions including Medical Monitors, Coordinating Investigator, and Principal Investigator Names and Contact Information can be found in Appendix 10

The Protocol Amendment Summary of Changes Table

Date	Protocol version	Section # and Name	Description of Change	Brief Rationale
291025	1.5	8.6.3. Recruitment Strategy	Written study information will be distributed digitally to patients scheduled for ambulatory surgery, together with their surgical appointment letter.	To ensure that patients have the opportunity to review the study details prior to surgery and make an informed decision regarding participation.
291025	1.5	8.6.5. Data Quality Assurance	Signed consent and Nettskjema registrations will be stored for 5 years after end of study (e.g. 31.12.30).	Not necessary to store data for more than 5 years according to REK.
291025	1.5	1. Protocol summary (1.1.-1.2.), 4. Study Design, 7. Study Assessments and Procedures.	Added assessing postoperative pain in the PACU.	Same as in previous study.
291025	1.5	8.3.1. General Considerations	Introduction of Clonidine intraoperatively for pain prophylaxis changes n needed to be included in the study.	May affect pain perception postoperatively.
291025	1.5	8.3.2.2. Main Analytical Approach	Including the variable “Treated with Clonidine, Yes/No”	Inclusion of patients receiving Clonidine intraoperatively.

291025	1.5	8.3.2.3. Sensitivity Analysis	Evaluation of original prediction model.	Changes in inclusion criteria due to changes in clinical practise.
291025	1.5	8.5. Sample size Determination	Increase in sample size from 165 to 207.	Change in number of variables in the logistic regression model.
291025	1.5	2.2. Background	Definition of the four risk factors for severe postdischarge pain.	Specifying which risk factors to be studied.

Table of Contents

List of Abbreviations

NRS	*Numeric Rating Scale*
PACU	*Post Anaesthesia Care Unit*
POD1	*Postoperative day 1*
ASA	*American Society of Anesthesiologists*
OUS	*Oslo universitetssykehus*
UiO	*Universitetet i Oslo*
PVO	*Personvernombud*
REK	*Regional Ethics Committee*
ICF	*Informed consent form*

1. Protocol Summary

1.1. Synopsis

Protocol Title: Validation of a risk matrix for severe postdischarge pain after ambulatory gynaecological laparoscopy

Brief Title: Predicting pain after ambulatory gynaecological laparoscopies

Rationale:

Objectives, Endpoints, Assessments:

Objectives	Endpoints	Assessments
Primary		
• To validate a prediction tool for severe postdischarge pain (NRS 7-10) after gynaecological laparoscopic surgeries	• Worst pain since discharge from hospital within 24 h after surgery	• Pain assessment using the Verbal Numeric Rating Scale 0-10, on POD1

Study design: Prospective observational cohort study

This study design includes no masking.

Brief Summary:

The purpose of this study is to test and validate a newly developed risk matrix in a new sample of patients. The risk matrix will be a useful tool to preoperatively predict who is at risk for experiencing severe postoperative pain after discharge from ambulatory gynaecological surgery. When validated, the prediction tool will be implemented in everyday clinical practice with ambulatory gynaecological patients.

Study details include:

- The study duration will be up to 6-7 months.
- Data will be collected at three occasions, on the day of surgery, during PACU stay and on POD1.

Number of Participants:

Approximately 207 participants (minimum) will be enrolled in the study.

Schema

Procedure	Day of surgery	PACU	POD1	Notes
Written informed consent	x			
Inclusion/exclusion criteria	x			
Demography/Baseline data	x			Questionnaire
Postoperative pain		x		
Postdischarge pain			x	Postdischarge pain data collected by telephone follow-up
Intraoperative data collection			x	Patients' medical records (Dips and MetaVision)

1.3. Schedule of Activities (SoA)

2025

Activity	July	August	September	October	November	December	Spring 2026	Autumn 2026
Study applications OUS	x							

PVO/REK/Clinical Trials.com	x	x	x	x				
Data collection					x	x	x	
Analysis/writing article manuscript							x	
Publication								x

2. Introduction

Based on data from our previous study, "Preoperative factors associated with severe postdischarge pain after ambulatory gynaecological laparoscopy: a prospective cohort study", we have developed a risk matrix to predict who will suffer from severe pain after surgery. The risk matrix needs to be validated in a new gynaecological patient sample and may become a useful tool for clinicians.

2.1. Study Rationale

As day surgery is increasingly preferred over in-hospital treatment due to feasibility and reduced economic costs, it is important to evaluate patient related outcomes such as comfort and safety after discharge. Most previous studies on predictors for postoperative pain have not been focused on postdischarge pain.

Early identification of patients at high risk for severe pain can contribute to better and more targeted individual pain prevention and management, thereby reducing the incidence of unnecessary pain and discomfort after surgery. By identifying and treating patients who are particularly vulnerable to severe postoperative pain, we can also reduce hospital stays, prevent unplanned admissions due to pain, decrease the number of outpatient inquiries related to pain, and expedite recovery and return to normal activities. This will contribute to reduced resource use, improved patient care, and hopefully increased patient satisfaction.

The risk matrix for severe postoperative pain has the potential to improve clinical practice by providing clinicians with a simple, evidence-based tool that can identify high-risk patients before surgery. The scoring takes less than one minute. Today, we do not have such instrument at hand. The results from this project could influence current routines and treatments at OUS and may also be applicable to other patient populations and other hospitals.

2.2. Background

Despite the gynaecological laparoscopic procedure being considered less invasive compared to laparotomy (Brown 2019), 20-40% of patients report severe pain postoperatively (Gerbershagen 2013, Cruz 2021), which can negatively impact quality of life, recovery, patient satisfaction, and healthcare resource utilisation. Most of these women undergo ambulatory surgery, meaning they arrive for the operation and return home the same day. Since they have limited access to stronger pain medication upon returning home and lack direct access to medical expertise, unlike inpatients, severe postoperative pain can be both uncomfortable and problematic.

In our previous study, we found that over 42% of the patients experienced severe postdischarge pain within the first 24 h after surgery, that is a pain score of 7-10 on the NRS. We identified 4 preoperative risk factors independently associated with severe postdischarge pain: younger age, presence of preoperative pain, pain expectation and preoperative use of opioids. Our findings may contribute to clinicians' awareness of clinically relevant risk factors for severe postoperative pain in this patient population. Moreover, knowledge

on females-specific validated predictive factors for pain is important for successful treatment in gynaecological laparoscopic surgery which is one of the most common ambulatory surgical procedures (Joo, 2019).

2.3. Benefit/Risk Assessment

There is no risk connected to participation in the study. All patients will receive standard medical and surgical treatment throughout the study.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints	Assessments
Primary		
To validate a prediction tool for severe postdischarge pain (NRS 7-10) after gynaecological laparoscopic surgeries	Worst pain since discharge from hospital within 24 h after surgery	Pain assessment using the Verbal Numeric Rating Scale 0-10, on POD1

The primary clinical question of interest is to validate if the risk matrix developed previously using a different data set (i.e., a new population with similar patient and surgical characteristics) can predict severe pain after ambulatory gynaecological laparoscopy.

4. Study Design

Prospective observational cohort study

In this study, we will collect data necessary to validate a previously developed risk matrix, at two different time points: T1) preoperatively on the day of surgery, T2) during a follow-up call on POD1, to collect postdischarge pain data. In addition, patients' postoperative pain will be assessed using the NRS, during PACU stay.

Data to be collected:

- T1: Age, height, weight, living arrangement, education, employment status, financial concerns, smoking status, previous abdominal surgery, dysmenorrhea severity, preoperative pain, preoperative non-opioid analgesics/opioids, postoperative pain-expectation, preoperative anxiety related to surgery, insomnia, previous treatment for anxiety, depression or other psychological disorder.
- T2: Postdischarge pain on POD1: at rest, during activity, average pain, and worst pain since discharge. Non-opioid and opioids consumption after discharge will also be recorded. Any case of unplanned admission or health care contact.
- PACU: worst pain during PACU stay.
- Patients' medical records (Perioperative data): ASA classification, type of surgery, surgery duration, anaesthesia duration, intra- and postoperative medication.

Data will be registered in Nettskjema/TSD.

End-of-Study Definition

The end of the study is defined as having a complete data set for at least 207 patients.

A participant is considered to have completed the study if she has completed all questions including the follow-up call on POD1.

5. Study Population

Women scheduled for ambulatory gynaecological laparoscopy in general anaesthesia.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

Participants who are scheduled for ambulatory gynaecological laparoscopy, e.g. ovarian cyst removal, excision of endometriosis, salpingo-oophorectomy, salpingectomy, chromopertubation, ovarian drilling for polycystic ovary syndrome, adhesion removal, diagnostic laparoscopy, oophorectomy, removal of migrated intrauterine device, sterilisation/tubal ligation.

Informed Consent

2. Capable of giving written informed consent.

Other Inclusion Criteria

3. Must speak and read Norwegian.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Severe psychiatric disorder, severe cognitive dysfunction.

Prior/Concomitant Therapy

2. Intraoperative ketamine or lidocaine infusion or regional anaesthesia.

Other Exclusion Criteria

3. Does not speak or read Norwegian.

5.3. Screen Failures

Examples of screen failure patients would be no time to fill out the questionnaire due to time constraints, loss to follow-up, loss of data recordings.

6. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

- The right to request data deletion does not apply if the information is de-identified, included in analyses, or published.

6.2. Lost to Follow up

A participant will be considered lost to follow-up if the participant is unable to be contacted by the study site on POD1.

The following actions must be taken before the participant is considered lost to follow-up:

- Before a participant is deemed lost to follow-up, the investigator or designee must try to regain contact with the participant on postoperative day 1 (by SMS or at least 2 telephone calls)
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

7. Study Assessments and Procedures

Study assessment will be done by using a preoperative questionnaire, assessment of postoperative pain during the PACU stay and a postoperative telephone call on POD1. Data will also be collected from the patient's medical journal.

All screening evaluations must be completed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record all participants screened and to confirm eligibility or record screening failure, as applicable.

7.1. Safety Assessments

The patients will adhere to standard procedures for ambulatory gynaecological laparoscopic surgery patients.

8. Statistical Considerations

The statistical analysis plan will be finalized prior to start of data collection and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

8.1. Statistical Hypothesis

The primary objective is to demonstrate that the risk matrix for prediction of postdischarge pain performs well also in newly collected data. i.e. the objective is to validate a previously developed risk matrix in new data sampled from an equivalent patient population.

8.1.1. Multiplicity Adjustment

Not relevant.

8.2. Analysis Sets

All enrolled patients, e.g. those who fulfilled inclusion criteria will be included in the full analysis set (FAS).

8.3. Statistical Analyses

8.3.1. General Considerations

We will compare the collected sample with the previously collected sample on selected baseline variables to assess possible selection bias and generalisability of our results. Due to changes in clinical practise, a majority of patients is now treated with Clonidine, which was not the case when the matrix was developed. To avoid unnecessary delays in recruiting and to ensure that the results will be relevant for todays' patients, we will include patients treated with Clonidine. The previously developed risk matrix will be applied on the data and the predicted and observed outcomes will be compared. In case of under- or over-estimation, the risk matrix will be calibrated.

8.3.2. Primary Endpoint Analysis

The primary endpoint is severe postoperative/postdischarge pain (NRS ≥7).

8.3.2.1. Definition of endpoint(s)

This variable is dichotomized as follows: 0=0-6 and 1=7-10.

8.3.2.2. Main Analytical Approach

We will validate the performance of a newly developed risk matrix. We will compare the pr edicted probabilities of worse postdischarge pain using the risk model with the recorded values. Further, we will performed comprehensive validation. The observed and predicted outcomes will be arranged in a confusion matrix. Further, we will investigate discrimination ability of the model by computing AUC (area under the curve) and c-statistics. Overfitting will be assessed by computing a calibration slope. Finaly, we will refit the prediction model and preform tuning of the model parameters. Due to changes in clinical practise, we will include both patients treated and not treated with Clonidine. To investigate the effect of being treated with Clonidine, we will include this variable as a possible confounder.

8.3.2.3. Sensitivity Analysis

Due to changes in clinical practise, we will evaluate our original model on patients treated and not treated with Clonidine.

8.3.2.4. Supplementary Analysis

Not relevant

8.3.3. Secondary Endpoint Analysis

Only main outcome, postdischarge pain will be analysed.

8.3.4. Tertiary/Exploratory/Other Endpoint(s)/Estimand(s) Analysis

Not relevant

8.3.5. Other Safety Analyses

Not relevant

8.3.6. Other Analyses

Not relevant

Interim Analysis

Will not be performed. All data will be collected in estimated 6 months and data analysis will be performed shortly after all patients are included.

8.5. Sample Size Determination

The logistic regression model which will be validated includes 4 variables and one additional variable to adjust for the possible confounding effect of being treated with Clonidine, thus will require at least 75 patients who report severe post-discharge pain. Based on our

previous research, we anticipate that 40% will report severe postdischarge pain, therefore we aim to include at least 188 patients. Allowing for 10% drop-outs/loss to follow up we aim to include 207 patients. We anticipate including approximately 40 patients monthly, thus we will be able to include 207 patients in 5 to 6 months. This sample size will enable us to perform all pre-planned analyses with sufficient statistical power and provide estimates with sufficient precision.

Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

8.6.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
    - Applicable ICH Good Clinical Practice (GCP) guidelines
    - Applicable laws and regulations
- Any amendments to the protocol will require PVO/REK approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

8.6.2. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and answer all questions regarding the study.

- Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the PVO/REK or study centre. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF during their participation in the study, if relevant.
- A copy of the ICF must be provided to the participant.
- In the event of cancelled operation with rescheduling of the same surgery within 2 months a participant who is rescreened is not required to sign another ICF, but the patient will be asked to confirm their participation on the day of surgery.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained.

8.6.3. Recruitment Strategy

Written information on the study will be distributed digitally to patients scheduled for ambulatory surgery, together with their surgical appointment letter. This ensures that patients have the opportunity to review the study details prior to surgery and be prepared to make an informed decision regarding participation. On the day of surgery, patient recruitment will take place and written informed consent will be obtained by a member of the research team after the patient has confirmed their willingness to participate.

For patients scheduled on short notice, who may not have received the digital information letter in advance, the study information will be provided upon arrival by administrative staff or a nurse not affiliated with the research team. After the patient has read the information, the research team may approach the patient to discuss participation.

Data Protection

- Participants will be assigned a unique identifier in consecutive order. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- Data will be recorded in Nettskjema and stored in Tjenester for Sensitive Data (TSD) (UiO).

8.6.5. Data Quality Assurance

On the day of surgery, patients self-reported data will be directly recorded in Nettskjema, using a mobile phone or an Ipad. On POD1, a member of the research team or a research nurse will record data in Nettskjema during the follow-up call. In case paper solutions of the questionnaires are used, all data manually recorded will be double-checked by a member of the research team or a research nurse.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Signed consent and Nettskjema registrations will be stored for 5 years after end of study (e.g. 311232) or as long as recommended by REK.

8.6.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigators site and in TSD (UiO).

- Definition of what constitutes source data: signed consent, Nettskjema registrations and medical records (Dips/MetaVision).
- No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

8.6.7. Study and Site Start and Closure

First Act of Recruitment

Anticipated start date of the study is November 2025.

Study/Site Termination

According to the sample size calculation (n=188) + at least 10%, we will include at least 207 patients.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

8.6.8. Publication Policy

The study will be submitted for publication in a peer-reviewed international journal. Additionally, the study could be presented at relevant scientific meetings and congresses.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

8.6.9. Funding

No funding.

8.7. Appendix 10: Contact details

Project leader:	**Marlin Comelon, Anaesthesiologist, PhD** Address: Oslo universitetssykehus, Postboks 4950 Nydalen, 0424 Oslo Tel: 95705758 E-mail: mcomel@ous-hf.no
PhD candidate:	**Mi Stjernberg** Address: Oslo universitetssykehus, Postboks 4950 Nydalen, 0424 Oslo Tel: 91919812 E-mail: uxmier@ous-hf.no
Investigator:	**Milada Hagen** Address: Oslo Metropolitan University, Postboks 4, St. Olavs plass, 0130 Oslo Tel: 93003186 E-mail: milasm@oslomet.no
Investigator:	**Johan Ræder** Address: Det medisinske fakultet, Postboks 1078 Blindern, 0316 Oslo. Tel: 92249669 E-mail: j.c.rader@medisin.uio.no

9. References

Brown K., Chien PFW., Tang B. Laparoscopic gynaecological surgery. Obstet. Gynaecol. Reprod. Med. 2019; 29(8):213-18

Gerbershagen HJ, Pogatzki-Zahn E, Aduckathil S, Peelen LM, Kappen TH, van Wijck AJ, et al. Procedure-specific risk factor analysis for the development of severe postoperative pain. Anesthesiology. 2014;120(5):1237–45

Cruz JJ, Kather A, Nicolaus K, Rengsberger M, Mothes AR, Schleussner E, et al. Acute postoperative pain in 23 procedures of gynaecological surgery analysed in a prospective open registry study on risk factors and consequences for the patient. Sci Rep. 2021;11(1):22148

Joo J, Moon HK, Moon YE. Identification of predictors for acute postoperative pain after gynecological laparoscopy (STROBE-compliant article). Medicine. 2019;98(42):e17621

Signature: Leiv Arne Rosseland
Leiv Arne Rosseland (Dec 19, 2025 10:10:51 GMT+1)

Email: l.a.rosseland@medisin.uio.no

Protokoll Validation study 2025 v1.5 10.11.25 Clinicaltrials

Final Audit Report 2025-12-19

Created:	2025-12-19
By:	Marlin Comelon (marlin.comelon@gmail.com)
Status:	Signed
Transaction ID:	CBJCHBCAABAAdhmhFSta5VRmFor3jdFCO2UzAD-S_I7R

"Protokoll Validation study 2025 v1.5 10.11.25 Clinicaltrials" History

Document created by Marlin Comelon (marlin.comelon@gmail.com)
2025-12-19 - 7:28:55 AM GMT

Document emailed to l.a.rosseland@medisin.uio.no for signature
2025-12-19 - 7:30:41 AM GMT

Email viewed by l.a.rosseland@medisin.uio.no
2025-12-19 - 9:09:38 AM GMT

Signer l.a.rosseland@medisin.uio.no entered name at signing as Leiv Arne Rosseland
2025-12-19 - 9:10:49 AM GMT

Document e-signed by Leiv Arne Rosseland (l.a.rosseland@medisin.uio.no)
Signature Date: 2025-12-19 - 9:10:51 AM GMT - Time Source: server

Agreement completed.
2025-12-19 - 9:10:51 AM GMT