PREEMER trial: Study protocol for a randomized controlled trial

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Study protocol

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Abstract

Background: Despite the fact that, in itself, emergency midline laparotomy is a factor risk for an incisional hernia, active research on hernia prevention in emergency settings is lacking. Different kinds of meshes and mesh positions have been studied in elective abdominal surgery, but no randomized controlled trials in emergency settings have been published.

Methods: The PREEMER trial is a multicenter, double-blinded, randomized controlled trial to be conducted in seven hospitals in Finland (Oulu, Helsinki, Tampere, and Turku university hospitals and Jyväskylä, Lahti, and Seinäjoki non-university hospitals). A total of 244 patients will be randomized at a 1:1 ratio to either the retrorectus mesh group, featuring a self-gripping prophylactic mesh, or to the no mesh (control) group, both closed by small stitch 4:1 closure with continuous slowly absorbable monofilament suturing. The primary outcome of the PREEMER trial is the incisional hernia incidence two years after surgery, which will be detected clinically and/or radiologically. Secondary outcomes are the Comprehensive Complication Index score, incidence of surgical site infections and fascial dehiscence within 30 days of surgery; the incisional hernia repair rate and mesh- or hernia-related re-operations within the two- and five-year follow-ups; the incidence of incisional hernia within the five-year follow-up; and quality of life measured by RAND-36, the Activities Assessment Scale (AAS), and the PROMIS-questionnaire within 30 days and two and five years from surgery. Additionally, medico-economic explorative measures are analyzed.

Discussion: The PREEMER Trial will provide level 1 evidence on incisional hernia prevention in an emergency setting.

Trial registration: Clinical Trials NCT04311788

<https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?>

[sid=S0009MXF&selectaction=Edit&uid=U0003YIA&ts=2&cx=7ef75k](https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S0009MXF&selectaction=Edit&uid=U0003YIA&ts=2&cx=7ef75k). Registered March 7th, 2020

Introduction

Background and rationale {6a}

Emergency midline laparotomy is, in itself, a known risk factor of incisional hernia development with up to 33% incisional hernia incidence (1-4). However, no evidence-based recommendations have been given on the optimal technique for closing midline emergency laparotomy incisions (5,6). A small bite technique with a suture to wound length (SL/WL) ratio of at least 4:1 and a slowly absorbable monofilament suture is the current recommended technique for fascial closure in non-emergency settings (5). The same method can be utilized to close an emergency midline laparotomy as well as to avoid an incisional hernia or fascial dehiscence (4,7)

Prophylactic mesh augmentation in a non-emergency midline laparotomy appears both effective and safe in incisional hernia prevention (8). Additionally, there is emerging evidence and research suggesting that synthetic meshes are also safe in contaminated surgery and emergency surgery (9, 10).

However, there have only been a few studies on incisional hernia prophylaxis within an emergency setting. In a recent systematic review and meta-analysis, the results of two studies, and altogether 299 patients, were eligible to be analyzed (2). A case-control study from Switzerland reported an incisional hernia rate of 3.2% (2/63) in its intra-abdominal mesh group and 28.6% (20/70) in its sutured control group after emergency midline laparotomy for peritonitis (11). A Spanish group exhibited similar results in their retrospective cohort study including patients with emergency midline laparotomies: an incisional hernia rate of 5.9% (3/50) in the onlay mesh group and 33.3% (33/100) in the control group (12). There was no statistically significant difference in the incidence of surgical site infection or other complications when the prophylactic mesh group was compared to the standard closure group.

As an emergency laparotomy is a significant risk factor for incisional hernia, a mesh augmented closure should be considered. Therefore, our study group has designed a randomized controlled trial (RCT) comparing prophylactic mesh with the best standard suturing technique within this challenging setting.

Objectives {7}

The objective of this study is to evaluate whether the rectorectus placement of a self-gripping polypropylene mesh (ProgridTM, Medtronic) is safe and prevents an incisional hernia after emergency midline laparotomy. The results of mesh augmented closure are compared with controls operated with no mesh. In both groups, the fascia will be closed using the best standard 4:1 small stitch closing technique with a continuous slowly absorbable monofilament suture.

Trial design {8}

Enrolled subjects will undergo assessments at the following intervals: pre-operative, operative, discharge, and 30 days, two-, and five years post-surgery.

All study patients are evaluated both clinically and radiologically two years after their emergency midline laparotomies in order to detect clinical and radiological incisional hernias. The follow-up will continue until five years after surgery in order to assess the long-term results and safety.

Ultrasounds with and without the Valsalva maneuver will be performed on all patients two years after surgery. The extent of any fascial defect and the hernia sac volume (i.e., the volume of the incisional hernia) are measured and graded according to the European Hernia Society criteria of incisional hernias (13).

Quality of life will be measured using RAND-36, the Activities Assessment Scale (AAS), and the PROMIS questionnaire at all follow-up visits of 30 days, two years, and five years as well as when a hernia is diagnosed.

Methods

Participants, interventions and outcomes

Study setting {9}

This study is a multicenter, double-blinded, randomized controlled trial conducted in Oulu, Helsinki, Tampere, and Turku university hospitals and Jyväskylä, Lahti, and Seinäjoki non-university hospitals in Finland.

Eligibility criteria {10}

Inclusion Criteria

- Midline emergency laparotomy for any abdominal indication

Exclusion Criteria

- Previous ventral hernia repair with mesh in the midline
 - Previous inguinal or femoral hernia repair using any technique with mesh is accepted
- Previous WHO class of physical activity 3-4
- Relaparotomy within 30 days of previous abdominal surgery
- Indication for laparotomy is hernia-related
- Pregnant or suspected pregnancy
- Patient < 18 years old
- Metastatic malignancy of any origin
- Patients living geographically distant and/or unwilling to return for follow-ups
- No informed consent provided
- Patient participates in other RCT

Intra-operative exclusion criteria applicable for both randomized groups:

- Abdomen is left open
- Second-look laparotomy planned
- Inability to keep the mesh securely out of the peritoneal cavity or close the anterior fascia
- Intra-abdominal malignancy diagnosed during the operation
- > 2 cm hernia in midline

Who will take informed consent? {26a}

Patients fulfilling the inclusion criteria and not meeting the exclusion criteria will be offered the opportunity to participate by investigator when a decision of an emergency laparotomy is achieved. To control selection bias, a prospective database of patients not participating in the study will be maintained at each attending hospital during the study period.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable.

Interventions

Explanation for the choice of comparators {6b}

The fascia in the control group of the study will be closed using the best standard 4:1 small stitch suturing via continuous slowly absorbable monofilament suture beneficial also in the emergency setting (4). Self-gripping mesh (ProgridTM, Medtronic) in the rectorectus position was chosen to avoid need for separate attachment method of the mesh and to diminish the risk of seromas associated with onlay mesh (10,15).

Intervention description {11a}

At the end of the operation, the abdomen will be closed according to the patients' randomized group, if applicable.

In the mesh group, the posterior layer of the rectus sheath is opened as close to the midline as possible without interrupting the midline. The space behind the rectus muscle is created mainly using a blunt dissection. At each ends of the incision, opening of the retrorectus space is achieved both cranially and caudally over the ends of the wound, if applicable. The posterior layer is closed using USP 0 or 2-0 slowly absorbable monofilament 4:1 small stitch technique. The stitch bites are 5 mm with a 5. mm inter-stitch space. The length of the wound is measured as well as the length of the suturing material used. The aim is to close the fascia using a suture material at least four times the length of the wound (4:1) using the small stitch technique. After securing that there will be no contact with the mesh and abdominal cavity, an 8 cm-wide self-gripping mesh (ProgridTM, Medtronic) is applied on the posterior layer of the rectus sheath, extending over the opening at each end. The anterior layer of the rectus sheath is closed using slowly absorbable monofilament USP 2-0 or 0 sutures via the 4:1 small stitch technique. The length of the mesh and suture material used are measured. The subcutaneous layer will be left open if the contamination level is IV. The subcutaneous layer may be left temporarily open with vacuum assisted closure or another wound dressing according to surgeons' preference. In contamination levels I-III, the skin is closed according to the surgeons' preference.

In the control group, the rectus aponeurosis is closed in a single aponeurotic layer using slowly absorbable monofilament USP 2-0 or 0 sutures via the 4:1 small stitch technique. Both the length of the wound and the length of the suture material used are measured.

Cataloguing of the operative technique will be sent to all participating surgeons to standardize the procedure.

Criteria for discontinuing or modifying allocated interventions {11b}

If the mesh cannot be safely kept outside of the abdominal cavity, or the fascia cannot be securely closed in either randomization group, the patient is intra-operatively excluded.

Strategies to improve adherence to interventions {11c}

Not applicable.

Relevant concomitant care permitted or prohibited during the trial {11d}

Not applicable. Study patients will be treated according to standard of care.

Provisions for post-trial care {30}

Not applicable. Study patients will be treated according to standard of care.

Outcomes {12}

Primary Outcomes

The primary endpoint of this study is the incidence of incisional hernia, either symptomatic or asymptomatic, detected clinically and/or radiologically within two years after surgery.

The definition and classification of an incisional hernia provided by the European Hernia Society will be used to classify the primary outcome (13) .

In the case of inconsistencies between the clinical and radiological evaluations, or either clinical evaluation or imaging is missing for any reason, the following definitions of the primary endpoint will be used:

Clinical exam result	Imaging result	Primary endpoint
Hernia	Hernia	Hernia
No hernia	Hernia	Hernia
Hernia	No hernia	No hernia
No hernia	No hernia	No hernia
Hernia	Missing	Hernia
No hernia	Missing	No hernia
Missing	Hernia	Hernia
Missing	No hernia	No hernia

If there is inconsistency between the ultrasound and computer tomography (CT) scan, the result of the CT scan will be applied.

Secondary Outcomes

- Comprehensive Complication Index within 30 days from surgery
- Surgical site infection (SSI) rate defined via the CDC classification of surgical site infection within 30 days of follow-up
- Fascial dehiscence within 30 days from surgery
- Incidence of incisional hernia within five years of follow-up
- Incisional hernia repair rate within two and five years from surgery
- Re-operations due to mesh- or hernia within two and five years from surgery
- Quality of life (RAND-36, AAS, PROMIS) within 30 days and two and five years from surgery
- Medico-economic explorative measures
 - Amount of time to create the retrorectal space and insert the mesh
 - Length of stay
 - Costs of materials used to close the abdomen
 - Length of sick leave of a patient

A surgical site infection (SSI) is defined and recorded per the Centers for Diseases Control and Prevention (CDC) SSI definition.

All related costs are analyzed in detail. The direct costs, such as the meshes, resources, and hospital stay costs, are monitored, and the indirect costs from productivity losses of a patient are estimated.

The following costs of treatment for both groups will be analyzed in detail:

- Mesh and other materials used to close the abdomen
- Need for further surgery and medical treatment
 - All complications related to primary surgery
 - Mesh-related need for surgery or other treatment
 - Hernia-related need for surgery or any help from the medical system
 - Length of sick leave
 - Need for rehabilitation before returning home
 - Length of stay at hospital

Participant timeline {13}

The following data will be recorded prospectively using specific electronic case report forms (eCRF).

Baseline

- Age
- Body mass index (BMI)
- Charlson Comorbidity Index
- Previous surgical history of abdomen
- History of smoking
- Previous hernias
- Previous hernia-related operations
- Previous WHO scale
- Medications affecting healing
 - Corticosteroids
 - Immunosuppressive medications
 - Biologics
- Creatinine
- INR
- Albumine
- Informed consent and patient information
- Randomization

Intervention data

- Prophylactic antibiotics
- ASA
- Presence of hernias in midline
- Presence and width of rectus diastasis
- Contamination class
- Surgical procedure
- ICD-10
- Loss of blood
- Amount of time to create the retrorectus space and insert the mesh
- Length of wound
- Suture material and needle used
- Drains left
- Vacuum-assisted closure/other temporary closure/skin left open
- Skin closure

Primary hospital stay and discharge

- Surgical site infection (SSI) rate
- All complications during hospital stay measured by Comprehensive Complication Index
- Re-operations
- Fascial dehiscence
- Length of stay (LoS)
- Mesh removals
- Place of discharge

30-day follow-up

All patients are contacted by telephone 30 days after surgery. If there are any deviations from the recovery, the patient will be invited to the outpatient clinic for a follow-up visit.

- Date of return
- Return to previous level of activity
- Return to work, length of sick leave
- Bulging
- Wound status
- Any complications in recovery

- Re-admissions
- Re-operations
- Removal of mesh
- Quality of life (RAND-36, AAS, PROMIS)
- Protocol deviations

Two-year follow-up

Patient-related recovery outcomes and QoL questionnaires (RAND-36, AAS, PROMIS) will be completed, and any complications, clinical signs, and abdominal ultrasound findings of an incisional hernia or protocol deviations will be reported. Both the patient and surgeon assessing recovery and well-being of the patient will be blinded to the randomized groups.

The ultrasound findings will all be analyzed by a single independent radiologist at each study site who will be blinded to the randomized groups. Possible hernia opening, size, location, and incisional sack volume will be defined both at rest and with the Valsalva maneuver. If the findings are inconclusive or there is a discrepancy between the clinical assessment and imaging, or a patient has a symptomatic incisional hernia and operative treatment is indicated, an abdominal CT scan will be done to verify the hernia diagnosis or plan an operative technique.

Five-year follow-up

Patient-related functional outcomes and QoL will be completed and any complications, clinical signs of an incisional hernia, or protocol deviations will be reported. Additionally, ultrasound scans will be done following the same protocol as described for the two-year control if there is any suspicion of incisional hernia.

All exceptions to the protocol are recorded and explained in detail at each point of follow-up schedule.

Participant timeline

Schedule of Events	Baseline	Procedure	Discharge	30 days + 7 days	2 years ± 30 days	5 years ± 30 days	Unscheduled Visit
Informed Consent	X						
Demographics and medical history	X						
Risk analysis for hernia	X						
QoL (RAND-36, AAS, PROMIS)	X	X	X				
Procedure details	X						
Clinical evaluation	X	X	X	X	X	X	
Ultrasound findings	X	(X*)	(X)				
Protocol Deviation	X*	X*	X*	X*	X*	X*	X*
Complications	X*	X*	X*	X*	X*	X*	
Study Closure Form	X**						

*Complete if applicable

**Complete when lost to follow-up, if there is consent withdrawal, or the subject completed all study-related visits.

Sample size {14}

To calculate the sample size required to compare these two groups, we estimated a 10 % rate of incisional hernia in the mesh group and a 25% incisional hernia incidence in the control group upon clinical assessment and ultrasound examination. Assuming $\alpha = 0.05$ and power = 90%, we would need 97 patients per group. Furthermore, assuming a two-year dropout rate of 20%, 122 patients per group are needed (244 patients in total). The sample size is calculated only for the primary outcome, and the secondary outcomes will be interpreted for hypothesis-generating only. If the estimated 20% dropout rate is exceeded, the sample size may be recalculated.

All analyses will be performed by or under the guidance of a professional statistician and following the CONSORT guidelines (14).

Recruitment {15}

Eligible patients will be recruited at the approved participating sites. All patients who are eligible, will be offered enrolment in the study at each study site. A screening log of all abdominal emergency midline laparotomies throughout the study period will be maintained for the further assessment of selection biases.

After receiving the proper information on the possible advantages and disadvantages of the intervention as well as signing the voluntarily informed consent form, the subject will be enrolled in the PREEMER trial. Participating centers and investigators are qualified colorectal or general surgeons experienced in the surgical management of patients with abdominal emergencies and emergency midline laparotomies. Each hospital's contribution to the study will be limited to no less than 20 cases per hospital.

Assignment of interventions: allocation

Sequence generation {16a}

The allocation will be stratified according to patient BMI (< 30 and $\geq 30\text{kg/m}^2$), previous laparotomy history, and age (< 65 and ≥ 65 years). A separate randomization list will be created for each participating center.

Concealment mechanism {16b}

A dedicated electronic database and randomization software will be used to host the clinical trial data for this study.

Implementation {16c}

Patients are randomly assigned (1:1 ratio) to either an intervention group or control group according to a computer-generated list compiled by a biostatistician otherwise uninvolved in the clinical care of the trial patients. Patients undergoing emergency midline laparotomy for any abdominal indication and fulfilling the inclusion criteria will be randomized by investigator into the groups prior to surgery after the decision to perform a midline laparotomy is made and the informed consent form is signed. Participating centers and investigators are qualified colorectal or general surgeons experienced in the surgical management of patients with abdominal emergencies and emergency midline laparotomies. Each hospital's contribution to the study will be limited to no less than 20 cases per hospital.

Assignment of interventions: Blinding

Who will be blinded {17a}

Study patients will be blinded of the randomized group during the whole follow-up period. Both the surgeon evaluating the outcome at 30 days, two years, and five years follow-ups as well as the radiologist will be blinded to the randomized groups. In both groups, the following sentence will be written in the

medical records instead of revealing the randomized group: “Fascial closure was performed according to randomized group”.

Procedure for unblinding if needed {17b}

Patients’ randomization number will be available in the medical records. Envelopes marked with the randomization numbers and containing the allocated group information will be accessible at all times in the case of complications etc. A record of unsuccessful blinding will be maintained and published.

Data collection and management

Plans for assessment and collection of outcomes {18a}

A dedicated electronic database and randomization software will be used to host the clinical trial data for this study. All eCRFs are handled with a special trial ID and date of birth. Access to the database is limited to the main investigators, and all data requested on the eCRFs will be recorded. Any missing data will be explained. The data collection will be the responsibility of the principal investigator at each study site and will be reviewed by the study group.

Plans to promote participant retention and complete follow-up {18b}

The reasons for withdrawal are documented carefully. The investigator attempts to contact the subjects at least three times prior to designating them as lost to follow-up. The investigator documents the date and type of attempted communication. If a subject cannot be reached during the visit window, a missed visit is recorded; after three (3) consecutive missed visits, a subject will be considered lost to follow-up and a study exit form will be completed on the electronic database. Any data on a subject’s participation and procedures prior to withdrawal will be analyzed within the research.

Data management {19}

A dedicated electronic database and randomization software will be used to host the clinical trial data for this study. All eCRFs are handled with a special trial ID and date of birth of the patient. Access to the database is limited to the main investigators, and all data requested on the eCRFs will be recorded. Any missing data will be explained.

The data collection will be the responsibility of the principal investigator at each study site and will be reviewed by the study group.

Confidentiality {27}

Patient confidentiality will be strictly maintained. Patients will be assigned a study ID, and all data will be managed without names or personal social security numbers. Access to patient records is limited to the study group and the investigator-delegated study coordinator.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The linear mixed model (LMM) or generalized linear mixed model (GLMM) will be used for repeatedly measured data, the previous for continuous data and the latter for categorical data.

The statistical programs SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp) and SAS (version 9.4, SAS Institute Inc., Cary, NC, USA) will be used for the analyses.

Interim analyses {21b}

As the previous research on synthetic mesh utilized as prophylaxis at emergency midline laparotomy is scarce, an analysis of the complications and risks is done and evaluated for safety reasons after 30 patients have been randomized to each group and reached 30 days follow-up. For the same reason, there will be further analysis on the complications of the mesh after 30 patients randomized to each group have reached the 2 years follow-up.

If there are significantly more serious complications in either group compared to other at 30 days or 2 years control, the trial will be discontinued.

Methods for additional analyses (e.g. subgroup analyses) {20b}

The prospectively planned subgroup analyses are as follows: BMI > 30 and previous hernia and contamination class 4. However, sample size calculation will be done only for the primary end point, and subgroup analyses are hypothesis-generating only.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Multiple imputations of missing outcome data will be used for sensitivity analyses.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

There will be no public access to the full protocol, participant-level dataset, and statistical code.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

Not applicable.

Composition of the data monitoring committee, its role and reporting structure {21a}

There will be no data monitoring committee. If there are significantly more serious complications in either group compared to other at 30 days or 2 years control, the trial will be discontinued.

Adverse event reporting and harms {22}

All adverse events are reported by eCRF and published. A separate electronic Complication form will be filled for any complication Clavien-Dindo 3B or more serious. Interim analysis of adverse events will be accomplished once 30 patients in both groups have reached both 1 month and 2 years follow-ups.

Frequency and plans for auditing trial conduct {23}

Not applicable.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Important protocol modifications are communicated with the Oulu University Hospital Ethics Committee by amendments. All modifications are also registered at Clinical Trials.

Dissemination plans {31a}

The protocol of the trial will be published at the beginning of the trial. The results concerning the primary end point and results of secondary endpoints within 2 years follow up will be published once included patients have reached 2 years follow-up. The results of 5 years follow up will be published.

Discussion

The aim of this study is to, in a randomized, double-blinded, multicenter setting, assess the safety and efficiency of preventive self-gripping mesh in incisional hernia prevention for emergency abdominal midline laparotomies. The mesh closure group is compared to a control group without a mesh closed via a standard small stitch closure with a continuous slowly absorbable monofilament suture. The hypothesis is that a significant number of symptomatic incisional hernias and further operations due to the incisional hernia can be prevented with a prophylactic mesh. Quality of life is measured throughout the study in both groups to analyze the effect of the prophylactic mesh.

Prophylactic meshes significantly reduce the incidence of incisional hernia in high-risk patient groups (5,15). As the risk of incisional hernia after abdominal midline laparotomy increases to above 30% (12), a significant number of hernias could be prevented using a prophylactic mesh in the emergency setting. Onlay mesh has been associated with an increased risk of seroma (10, 15). As an emergency laparotomy, especially one at a contaminated surgical site, is prone to infections and seromas (12), a retrorectus

position was chosen for this study. This position also enables the skin to be left open in the cases of contamination level IV.

The use of synthetic materials in contaminated surgical sites has been increasing. However, there are concerns over its potential mesh-related complications, such as infection, chronic pain, seromas, and bowel fistulas, especially in emergency situations like peritonitis and intestinal obstruction (10). Therefore, it is crucial to evaluate the potential benefits, hernia risk groups, costs, quality of life, and long-term results in a randomized setting before adapting preventive meshes on a large scale.

If a significant number of incisional hernias can be safely prevented by using a mesh, not only will patients benefit from a better quality of life, but major health care cost savings can be achieved. Each year, there are about 1,650 patients operated upon in Finland due to symptomatic incisional hernias. According to a French study, the estimated cost for an incisional hernia surgery is 6,450 euros (16). The corresponding costs in Sweden are even higher, reaching 9,060 euros per treatment (17). Extrapolating this to Finland, this means that the operative treatment of incisional hernias cause more than 10 million Euros in expenses for the Finnish health care sector in a year. A majority of these costs may be avoided by using the prophylactic mesh during the closure of midline emergency laparotomies in patients presenting with incisional hernia risk factors.

In the two previous studies on this topic, the SSI rate in a Swiss study was 60% and, respectively, only 17% in a Spanish study (11,12). This reflects differences in their patient selection, as there were only subjects with peritonitis in the first study, while all kinds of emergency laparotomies were included in the latter. Neither of the studies included in the only meta-analysis on the topic were randomized controlled trials (2). There were also many methodological differences in both the mesh itself and the mesh placement in these two studies. Thus, the conclusion of the only systematic review paper published on the topic was that there is a limited amount of data available for assessing the effect and safety of the use of prophylactic mesh in an emergency laparotomy setting (2). Thus, randomized control trials are required to address this important clinical question. Moreover, the EHS guideline group came to the same conclusion in their recommendation report for preventing incisional hernias (13).

Trial Status

Ethics Committee approval in Oulu University Hospital was received February 25th 2020 for protocol version 1.0 dated January 2nd 2020. The recruitment will begin in April 2020 and is anticipated to be complete in 2022.

Abbreviations

AAS Activities assessment scale

SL/WL Suture length to wound length ratio

RCT Randomized controlled trial

WHO World Health Organization

USP United States Pharmacopeia

CT Computer tomography

SSI Surgical site infection

CDC Centers of Disease Control and Prevention

eCRF Electronic Case Report form

BMI Body mass index

INR International normalized ratio

ASA American Society of Anesthesiologists

ICD-10 International Classification of Diseases

LoS Length of stay

QoL Quality of life

ITT Intention to treat

LLM Linear mixed model

GLMM Generalized linear mixed model

Declarations

Acknowledgements

Not applicable.

Authors' contributions

The study was designed by the following contributors: EMU, MT, VS, PM, AR, MAS, PO, FM, TR

EMU was the major contributor to writing the manuscript.

PO designed the statistical methods of the study.

All authors read and approved the final manuscript.

Funding

There is no external funding granted to the Preemer Trial. The materials used within this study are funded by the hospital district.

Availability of data and material

The datasets generated and/or analyzed during the current study are not publicly available due to Finnish laws on privacy protection but are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The Ethical Committee at Oulu University Hospital has approved the PREEMER Trial February 25th 2020 (3/2020) and its consent to participate.

Consent for publication

Not applicable.

Competing interests

VM reports reports grants from Academy of Finland, Syöpäsäätiö (Cancer Foundation), Vatsatautien Tutkimussäätiö Foundation, Mary and Georg Ehrnrooth's Foundation, Helsinki University Hospital research funds, Finnish Gastroenterological Society, and Finska Läkaresällskapet; personal fees from City of Vantaa, and University of Helsinki, non-financial support from Astellas, all outside the submitted work.

FM reports grants and personal fees (consultancy, speaker, grants) from Medtronic, CMR Surgical, Intuitive Surgical, Dynamesh, Bard Davol, all outside the submitted work.

Other authors have nothing to declare.

Acknowledgements

Not applicable.

Authors' contributions {31b}

The study was designed by the following contributors: EMU, MT, VS, PM, AR, MAS, PO, FM, TR

EMU was the major contributor to writing the manuscript.

PO designed the statistical methods of the study.

All authors read and approved the final manuscript.

Funding {4}

PREEMER Study has received no funding. The materials used within this study are funded by the hospital district.

Availability of data and materials {29}

The datasets generated and/or analyzed during the current study are not publicly available due to Finnish laws on privacy protection but are available from the corresponding author upon reasonable request.

Access to final dataset will be limited for investigators of PREEMER study.

Ethics approval and consent to participate {24}

The Ethical Committee at Oulu University Hospital has approved the PREEMER Trial (Application number 3/2020) and its consent to participate. Written, informed consent to participate will be obtained from all participants.

Consent for publication {32}

Not applicable.

Competing interests {28}

VM reports reports grants from Academy of Finland, Syöpäsäätiö (Cancer Foundation), Vatsatautien Tutkimussäätiö Foundation, Mary and Georg Ehrnrooth's Foundation, Helsinki University Hospital research funds, Finnish Gastroenterological Society, and Finska Läkaresällskapet; personal fees from City of Vantaa, and University of Helsinki, non-financial support from Astellas, all outside the submitted work.

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Other authors have nothing to declare.

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