PREEMER TRIAL -

Prophylactic mesh versus no mesh in midline emergency laparotomy closure for prevention of incisional hernia: a multicenter, double-blind, randomized controlled trial

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PREEMER TRIAL -

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1. Protocol Synopsis

Title	PREEMER TRIAL - Prophylactic mesh versus no mesh in midline emergency laparotomy closure for prevention of incisional hernia: a multicenter, double- blind, randomized controlled trial Light weight synthetic mesh for incisional hernia prevention after emergency laparotomy
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Study Population	Patients, who have an emergency midline laparotomy for any gastrointestinal reason, will be randomized in a 1:1 ratio either to mesh group with a retrorectal prophylactic self-gripping mesh or to control group with 4:1 small stitch closure by continuous monofilament suture.
Study Objective	Compare light weight synthetic prophylactic mesh to no mesh in midline emergency surgery laparotomy closure for prevention of incisional hernia
Study Design	Randomized, double-blinded, multi-center study
Study Endpoints	Primary Endpoint: Incidence of incisional hernia, either symptomatic or asymptomatic detected clinically and/or radiologically within 2 years from surgery. Secondary Endpoints: • Comprehensive Complication Index within 30 days from surgery • Surgical site infection (SSI) rate defined by CDC classification of surgical site infection within 30 days follow-up • Fascial rupture within 30 days from surgery • Incidence of Incisional hernia within 5 years follow-up

	• Incisional hernia repair rate within 2 and 5 years after surgery • Re-operations due to mesh- or hernia within 2 and 5 years from surgery • Quality of life (RAND-36, AAS, PROMIS) within 30 days, 2 and 5 years from surgery • Medico-economic explorative measures o Time to create the retrorectal space and insert the mesh o Length of stay o Costs of materials used to close the abdomen o Length of sick leave
	At least 244 subjects will be enrolled in this study (122 per group, including 20% off lost to follow-up during 2 years interval). All patients undergoing midline emergency laparotomy during the enrollment period will be screened for inclusion and exclusion criteria and recorded at study sites in order to identify any selection bias.
Randomization	Patients having emergency midline laparotomy for any gastrointestinal indication and fulfilling the inclusion criteria, will be randomized prior to surgery after giving informed consent to the study. Patients are randomly allocated (1:1 ratio) either to an intervention group or a control group according to a computer-generated list compiled by a biostatistician otherwise uninvolved in the clinical care of trial patients. Allocation will be stratified according to BMI (<30 and ≥30kg/m^2), history of previous midline laparotomy and age (<65 and ≥65- years) and-blocked within strata using random permuted blocks (block size 2, 4, 6 and 8). A separate randomization list will be created for each participating center.

Total Study Duration	Approximately 7-8 years: • Site start-up: 3 months • Study Enrollment: 24 months • Short term follow-up: Discharge, 30 days • Long term follow-up: 2 years and 5 years
Inclusion/ Exclusion Criteria	Study Inclusion: • Midline emergency laparotomy for any gastrointestinal indication Study Exclusion:

Number of Patients

	• Previous ventral hernia repair with mesh in the midline o Previous inguinal or femoral hernia repair by any technique with mesh is accepted • Previous WHO class of physical activity 3-4 (WHO 3 more than 50% of time at rest, WHO 4 stays at rest most of the time) • Relaparotomy • Indication for laparotomy is incarcerated hernia • Pregnant or suspected pregnancy • <18 years • Metastastic malignancy of any origin • Planned ostomy • Patients living geographically distant and/or unwilling to return for follow-ups • No informed consent • Subject participates in another RCT Intra-operative exclusion criteria applicable for both randomization 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 at the operation • >2 cm hernia in midline • Ostomy made at the operation

Human Subjects Protection	Full approval of Ethical Committee of Oulu University Hospital approved by Institutional revision board in each participating hospital, with all other specific approvals, must be obtained for the study prior to study initiation at the site. Subjects must sign an EC-approved Informed Consent Form (ICF) prior to enrollment into this study. As the previous research on synthetic mesh utilized as prophylaxis at emergency laparotomies is scarce, an analysis of the complications and risks will be evaluated for safety reasons after 30 patients have been randomized to both groups 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.
Data Collected	Data collected will include the following: • Demographics, Patient Characteristics, and Pre-operative History: Age, BMI, previous surgical history, comorbid conditions and medications, history of smoking, previous hernias and hernia related operations • Intra-Operative Assessment: Prophylactic antibiotics, ASA, presence of hernias in midline, rectus diastasis, operative time, blood loss, contamination class, surgical procedure, ostomy creation and its' location from midline, length of wound, length and type of suture materials used, drains, vacuum assisted closure, other temporary closure method used, skin closure. • Post-Operative Assessment through Discharge: Surgical site infections, complications, re-operations, pain score (VAS) at discharge, Quality of life questionnaire, seromas, burst abdomen, fascial dehiscence, length of stay, mesh removals, length of planned sick leave, place of discharge. • Follow-Up Assessments: complications, clinically and/or radiologically detected hernia rate, procedure- or incisional hernia-related readmissions, procedure- or incisional hernia related reoperations, QoL (RAND-36, AAS, PROMIS) and economic measures, pain of abdominal wall, long-term seromas. Data will be collected 2 and 5 years postoperatively.

Data collection	Primary data collection will be performed by participating surgeons using electronical database.
Statistical Analysis	All analyses will be performed by or under the guidance of professional statistician and following the CONSORT guidelines. The primary endpoint as well as other categorical data will analysed by χ^2- test or Fisher's exact test. Ninety-five % confidence intervals (95% CI) are presented for between group differences (effect sizes). The incidence of hernia will also be analyzed using Kaplan-Meier analysis. Student's t-test or

	Welch test will be used for continuous variable, the latter if assumption of homogenous variances does not hold. Linear mixed model (LMM) or generalized linear mixed model (GLMM) will be used for repeatedly measured data, the previous for continuous data and latter for categorical data.
Finance	Materials and visits are funded by hospital districts as part of treatment expenses. External funding will be applied to cover the costs caused by imaging.

2.

Introduction

2.1 Incisional hernia incidence

Incisional hernia (IH) is a common complication of abdominal wall surgery. Its' incidence varies greatly (2–30 %) among studies (1-3) . The incisional hernia incidence is influenced by several factors, such as closing technique (4,5) , follow-up time (6) and the modality of radiological investigations,(7,8) , patient characteristics and co-morbidities as well as indication and type for surgery(9).

2.2. Incisional hernia etiology

The etiology of incisional hernia is multimodal. The site and orientation of the incision has an influence on the IH rates. Non-midline incisions—both paramedian and transverse—carry a significantly reduced risk of IHs compared to midline incisions (10-11) . Suturing technique and the suture material used affect the hernia rate as well. Taking small bites of 5 mm with an intersuturing space of 5 mm with slowly absorbable monofilament suture results in a lower hernia incidence compared to large bite mass suturing (4-5, 12-14) .

There is lack of evidence of basic biological pathogenesis of incisional hernias (IH). Specific features of connective tissue and the quality of fibroblasts are proposed to have an influence on the risk for hernia formation (15). The inflammatory response after an incision results in the fibroproliferative phase. Incisional hernia may be a result of disturbation in the fibroblast proliferation in the laparotomy wound matrix (16).

Fascial ischemia is presumed to be one crucial factor in the development of an IH. The fascia is hypovascular and a wound experiences hypoxic stress immediately after surgical incision, which has been considered a major risk factor for wound failure. Hypoxia interferes with angiogenesis and the healing process (17). The revascularization at the wound site is critical to improve healing response (18). Good surgical skills and maintaining sufficient perfusion in the wound area are important issues to be noted (19).

Along with previously mentioned physiological alterations, patients' comorbidities and characteristics can predispose them to develop of a hernia (9) . Connective tissue disorders increase the risk for herniation among various other patient-related factors (20, 21). One of the most common risk factor, that increase the likelihood of development an IH is smoking (75 %) (22). As a result of an analysis of 14,618 patients, Bosanquet in his review and meta-regression determined the factors affecting midline IH rates: diabetes mellitus, obesity, cachexia, increasing age, male sex, chronic obstructive pulmonary disease (COPD), a history of or operation for an abdominal aortic aneurysm (AAA), anaemia, smoking, corticosteroids and surgical site infection (SSI). Summarising the results of 56 publications, the prevalence of IHs after midline laparotomy was 12.8 % (range: 0 to 35.6 %) with a mean follow-up time 23.7 months (21) .

2.3 Incisional hernia definition and evaluation

Most commonly, an IH is a bulge or a gap in the area of a postoperative scar. It can be asymptomatic but is often associated with symptoms, such as pain, cosmetic discomfort, bowel obstruction or even incarceration (23,24) . Valsalva's manoeuvre is used to make the hernia more apparent clinically: the increase in intra-abdominal pressure causes the hernia sac to enlarge and protrude through the anatomic defect. The clinical examination is recommended to be performed in both standing and supine positions.

The examination can be difficult in obese patients or in postoperative situations in which incisional hernia may be difficult to distinguish from a postoperative complication, such as a hematoma, abscess or seroma. The radiological imaging (ultrasound

(US), computed tomography (CT) or magnetic resonance (MRI)) is useful in specifying the diagnosis (8,25-27) .

A standardised dynamic abdominal sonography for hernias offers a safe and a low-cost diagnostic tool with great specificity and positive predictive value (28) . A CT scan can also be an option in some cases like when planning operative treatment, although it induces a radiation load for patients.

When evaluating the IH rate, the difference between physical examination and imaging modalities (ultrasound or computer tomography) is important in terms of accuracy (29,30) . A standardised examination and dynamic evaluation by ultrasound of the abdominal wall is recommended in evaluating a possible hernia (14,31). Incidence of IHs increases during a follow-up study time from 12.6 % at 12 months to 22.4 % at 36 months(6,32,33).

There is a great diversity of abdominal wall IHs. During the early years of 2000 the first proposals for the classification of incisional ventral hernias were published. Through 2009, there were several proposals for classifying IHs according to defect size, recurrence and topography to some extent, but none of these achieved wide recognition or routine use(34-36). In 2009, the European Hernia Society (EHS) published a formula to classify primary and incisional abdominal wall hernias (36).

2.4 Incisional hernia prevention

European Hernia Society (EHS) guideline strongly recommends to utilise a non-midline approach to a laparotomy whenever possible to decrease the incidence of incisional hernia (14). However, this is clearly not an option in an emergency laparotomy, as midline incision is the fastest and the best visualizing opening to explore the whole abdominal cavity in an emergency setting.

For elective midline incisions, evidence-based recommendation is to perform a continuous suturing technique with slowly absorbable monofilament suture when closing the incision (14) Suturation should be done performing a single layer aponeurotic closure technique without separate closure of the peritoneum. A small bites technique with a suture to wound length (SL/WL) ratio at least 4:1 is the current recommended method of fascial closure (12-14, 37,38).

Prophylactic mesh augmentation in a non-emergency setting appears effective and safe and

can be suggested for high-risk patients (39-40). However, no recommendations can be given on the optimal

technique to close emergency laparotomy incisions because of lack of evidence (14) . This problem should be emphasized on due to high rates of IH after emergency laparotomy (41,42). All this makes the use of prophylactic mesh in the emergency setting an interesting proposition, as it may decrease the rate of IHs. However, there are concerns over potential mesh related complications including infection, chronic pain, seromas and bowel fistulas especially in emergency situations like peritonitis and intestinal obstruction. There is preliminary evidence published about the safety and efficiency of the prevention of IHs using meshes in the emergency laparotomy closure even in contaminated conditions (43,44).

In the resent systematic review and meta-analysis, only results of 2 studies and altogether 299 patients were eligible for the analysis (42) . Swiss case-control study reported an IH rate of 3,2% (2/63) in the mesh group and 28,6% (20/70) in the control group (43) . Spanish study group had the same kind of results in their retrospective cohort; IH rate of 5,9% (3/50) in the mesh group and 33,3% (33/100) in the control group (44) . There was no statistically significant difference in the incidence of surgical site infection or other complications when prophylactic mesh group was compared to standard closure group. SSI rate in Swiss study was 60% and respectively only 17% in the Spanish study. This may reflect differences in the patient selection, therefore the safety profile of the prophylactic mesh in the emergency setting has not been adequately described. Neither of the studies included in meta-analysis were not randomized controlled trials. There were also many methodological differences including patient selection, used mesh, and mesh placement. Thus, the conclusion of the systematic review paper was that there are limited data to assess the effect or safety of the use of prophylactic mesh in the emergency laparotomy setting (42) . Randomized control trials are required to address this important clinical question. EHS guideline group resulted the same conclusion in their recommendation report (14).

There are about 1650 patients are operated in Finland because of IH every year. According to the European study, the estimated cost for IH surgery is 6450 euros (45). The corresponding costs in Sweden were even higher reaching 9060 euros per treatment (12). Extrapolated to Finland, this means that operative treatment of IHs cause more than 10 million expenses to the Finnish health care sector in a year. Some of these costs may be avoidable by using the prophylactic mesh during the

closure of midline emergency laparotomies in the patients with IH risk factors.

Therefore, our study group stands on the idea to design and carry out the PREEMER randomized controlled trial (RCT) comparing prophylactic mesh to best standard suturing technique in this challenging setting.

3. Study Objective

The objective of this study is to compare prospectively the feasibility and the potential benefits of retrorectus self-gripping mesh (Progrip™, Medtronic) to controls operated with no mesh by using the best standard 4:1 small stitch suturing technique.

4. Study Design

This study is a multicenter, double-blinded, randomized controlled trial. Parameters will be collected prospectively after randomization. All enrolled subjects will undergo assessments at the following intervals: pre-operative, operative, discharge, 30 days, 2- and 5-years post–surgery. A
description of the study visits and required study procedures is summarized in Section 12, Schedule of events.

All patients are evaluated both clinically and radiologically at 2 years after index procedure in
order to diagnose clinical and/or radiological incisional hernia. The follow up will continue until 5 years after the surgery to assess long-term results and safety.

Ultrasound with and without Valsalva maneuver will be performed to all patients 2 years after
surgery. The extent of the fascial defect and hernia sac volume (ie. the volume of incisional hernia) are measured and graded according to the European hernia society criteria. (46)

If there is a suspicion of symptomatic or asymptomatic incisional hernia according to clinical
assessment and ultrasound findings are inconclusive, CT scan is required to verify the diagnosis of IH. If a patient have had no imaging done for any reason, the result of clinical

evaluation is
recorded. In case of several imaging modalities accomplished, all results are recorded. All study

patients are guided to contact their study site in case of any suspicion of incisional hernia at any point during follow up.

Quality of life will be measured using RAND-36, Activities Assessment Scale (AAS) and PROMIS questionnaire at all follow-up visits at 1 months, 2 years and 5 years as well as when a hernia is diagnosed.

5. Cost analysis

Costs of the treatment

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

for both groups will be analyzed in detail.

6. Study Endpoints

6.1 Primary Endpoints

The primary endpoint of this study is the incidence of incisional hernia, either symptomatic or asymptomatic detected clinically and/or radiologically within 2 years after surgery.

In case of inconsistency between clinical and radiological evaluation exists or either one is missing for any reason, a following definition of 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 ultrasound and CT scan, the result of CT scan will be applied.

6.2 Secondary Endpoints

Secondary Endpoints:

- Comprehensive Complication Index within 30 days from surgery
- Surgical site infection (SSI) rate defined by CDC classification of surgical site infection
  within 30 days follow up
- Fascial rupture within 30 days from surgery
- Incidence of Incisional hernia within 5 years follow-up
- Incisional hernia repair rate within 2 and 5 years after surgery
- Re-operations due to mesh- or hernia within 2 and 5 years from surgery
- Quality of life (RAND-36, AAS, PROMIS) within 30 days, 2 and 5 years from surgery
- Medico-economic explorative measures
    - 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

7. Study Population

Eligible patients will be recruited at the approved participating sites. All patients who are eligible, meet the inclusion and none of the exclusion criteria of this study, will be offered enrolment into the study at each study site. A screening log of all gastrointestinal emergency midline
laparotomies during study period will be maintained for further assessment of selection biases.

The following patient inclusion/exclusion criteria will be required for the study.

7.1. Inclusion Criteria

- Midline emergency laparotomy for any gastrointestinal indication
    - Conversion from laparoscopy to laparotomy is considered as inclusion criteria from
      Study protocol version 3.0 onwards.

7.2 Exclusion Criteria

- Previous ventral hernia repair with mesh in the midline
    - Previous inguinal or femoral hernia repair by any technique with mesh is accepted
- Previous WHO class of physical activity 3-4 (WHO 3 more than 50% of time at rest, WHO 4
  stays at rest most of the time)
- Relaparotomy
- Indication for laparotomy is incarcerated hernia
- Pregnant or suspected pregnancy
- <18 years
- Metastastic malignancy of any origin
- Planned Ostomy
- Patients living geographically distant and/or unwilling to return for follow-ups
- No informed consent
- Subject participates in another RCT

Intra-operative exclusion criteria applicable for both randomization 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 at the operation
- >2 cm hernia in midline
- Ostomy made at the operation

8. Center and Surgeon Selection

Participating investigators are qualified surgeons experienced with surgical emergency management of patients with emergency midline laparotomy and centers have a patient population large enough fitting the study requirements. All surgeons considered for participation must be experienced in closing the abdomen by 4:1 small stitch technique and prophylactic self-gripping polyester mesh (Progrip ™) placement. A detailed brochure with step-by-step pictures of midline laparotomy closure and mesh application will be delivered to each participating hospital. Principal investigator may advice with mesh application technique if desired.

Hospitals located in Finland are considered for participation.

9. Risk Analysis

9.1. Potential Risks

Surgeons performing emergency laparotomies will be trained and guided for the mesh placement. Based on previous studies, the use of the mesh is both safe and effective. Study patients will be followed very closely postoperatively.

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.

9.2. Potential Benefits

There may be some benefit due to trial-related closer follow-up of patients. Patients with a prophylactic mesh might have a lower incisional hernia rate.

10. Study Methods

10.1. Ethics Committee Approval

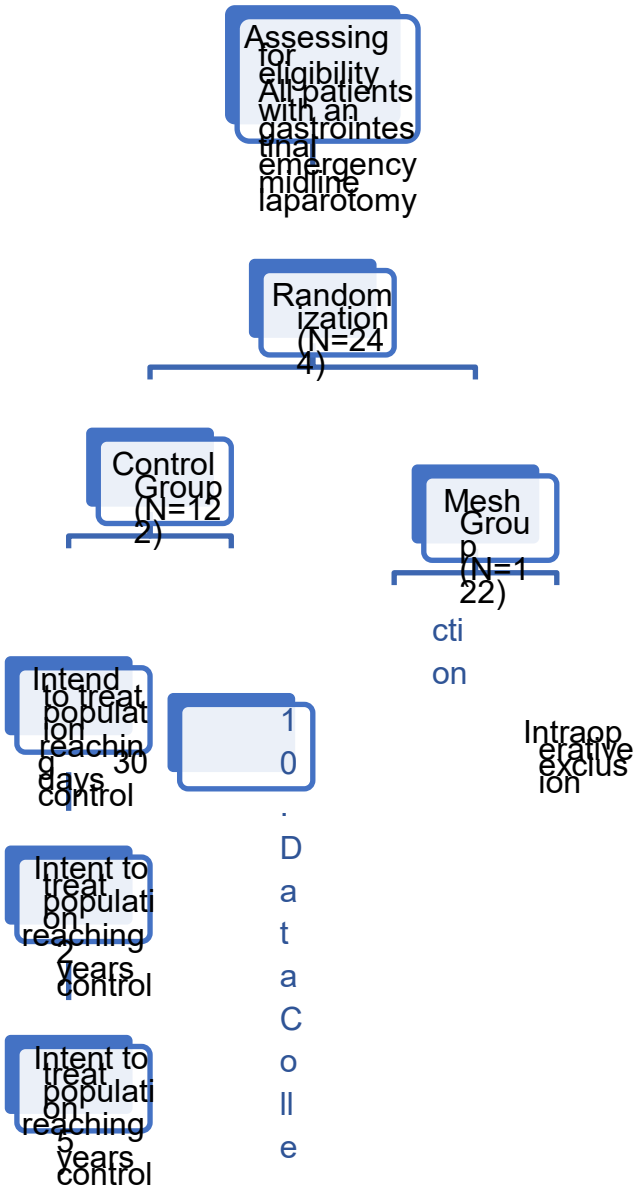
The study protocol, patient informed consent form and other required study documentation will be reviewed and approved by an ethics committee in Oulu University hospital and any other
required body, prior to study start-up.

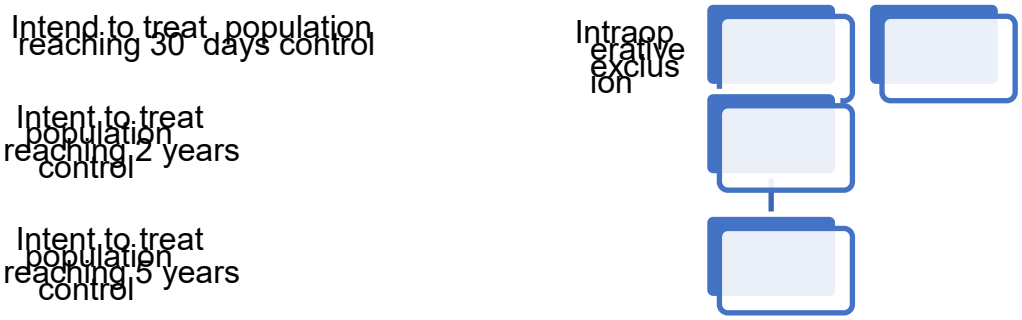
10.2. Study Duration and Enrollment

Study enrolment will take approximately 24 months. The enrolled patients will have a short-term follow-up at 30 days and, long-term follow-up at 2 and 5 years.

10.3. Study Plan

Figure 1 Flow Chart





Data will be collected at baseline, operative procedure, discharge, 30 days, 2 years and 5 years. Specific databases (Hoitoilmoitusrekisteri HILMO, Tilastokeskus) may be used to collect data of patients' survival and operations done to patient outside study sites. If there is any suspicion of

incisional hernia raised at any point of the follow-up, the patient is advised to contact the study site and additional clinical evaluation and ultrasonography if needed is arranged. The data will be collected using electronical CRFs and software designed for this study.

10.1 Patient Informed Consent

Using the study-specific, ethics committee approved, informed consent form, information pertinent to this study will be provided to the subjects and/or representative in writing and using non-technical language. The consent form will include a description of the study and its purpose,
potential benefits, potential risks, site contact information, and all other elements required of an informed consent.
Subjects are required to voluntarily sign the informed consent form before any study-specific
procedure is performed. The Investigator will conduct the informed consent process and will answer questions the subjects may have. If the subject agrees to participate, the informed-consent form must be signed and dated by the subject prior to enrolment in the study and separately signed and dated by the investigator taking consent. Only subjects who have signed the study informed consent will be included in the study.

10.2 Data Collection

Following information of patients will be collected using electronic database. The patient is pseudonymized for data collection and all data will be handled using study-ID.

Baseline

- Age
- 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
    - Immunosupressive medications
    - Biologics
- Creatinine
- INR

Operative Procedure

- Prophylactic antibiotics
- ASA
- Presence of hernias in midline
- Presence and width of rectus diastasis
- Contamination class
- Surgical procedure
- ICD-10
- Loss of blood
- Time to create the retrorectal 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 Comprehensive Complication Index
- Re-operations
- Burst abdomen
- Fascial dehiscence
- Length of stay (LoS)
- Mesh removals

- Place of discharge

Patients are guided to contact their study site in case of any problems with their recovery, any suspicion of hernia occurrence or wound complications.

30 days visit

The recovery of all patients is assessed at 30 days after the operation. All the patients are called
to. If there are any deviations in recovery, patient is invited to outpatient clinic for follow-up visit.

- Date of return to previous home unit
- Return to previous level of activity
- Return to work, length of sick leave
- Bulging
- Wound status
- Any complications of recovery
- Re-admissions
- Re-operations
- Removal of mesh
- Quality of life (RAND-36, AAS, PROMIS)
- Protocol deviations

2 years Visit

Patient related recovery outcomes and QoL questionnaires will be completed and any complications, clinical signs and/or abdominal ultrasound findings of incisional hernia or protocol deviations will be reported. Both the patient and the surgeon assessing the recovery and well-
being are blinded of the randomization group.

Ultrasound findings will all be analyzed by single independent radiologist in each study site,
blinded of the randomization group. Possible hernia opening, its size, location and

incisional
hernia sack volume will be defined both at rest and with Valsalva maneuver. If the findings are

inconclusive or there is discrepancy between the clinical assessment and imaging or a patient has a symptomatic incisional hernia and operative treatment is indicated, abdominal CT scan will be done to verify the hernia diagnosis or to plan operative technique.

5 years visit

Patient related functional outcome and QoL shall be completed and any complications, clinical signs of incisional hernia or protocol deviations are reported. Ultrasound scan will be done
following the same protocol as described at 2 years control if there is any suspicion of incisional hernia.

10.3 Blinding

Study patients will be blinded of the randomization group during the whole follow-up period. Both the surgeon evaluating the outcome at 30 days, 2- and 5- years control as well as radiologist will
be blinded of the randomization group. The method of fascial closure (i.e. the allocated procedure) will not be revealed in medical records. In both groups, the following sentence will be
written in the medical records: ”Fascial closure was performed according to randomization group”. Patients randomization number will be available in medical records. Envelopes marked with randomization number containing allocated group information are accessible at all times in
case of complications or other need to know the allocated group. A record of unsuccessful blinding will be maintained and published.

11. Definitions

11.1 Definition of Incisional hernia

Definition and classification by European Hernia Society of Incisional hernia will be used.
In the European Hernia Society (EHS) IH classification the abdomen is divided into a midline zone and a lateral zone. Borders for the midline area are cranially the xyphoid, caudally the pubic bone and laterally the lateral margin of the rectal sheath.

EHS Incisional Hernia Classification			
Midline	subxiphoidal	M1	
	epigastric	M2	
	umbilical	M3	
	infraumbilical	M4	
	suprapubic	M5	
Lateral	subcostal	L1	
	flank	L2	
	iliac	L3	
	lumbar	L4	
Recurrent incisional hernia?		Yes O	No O
length: cm		**width**: cm	
Width cm	**W1** <4cm O	**W2** ≥4-10cm O	**W3** ≥10cm O

EHS classification for incisional abdominal wall hernias. (46)

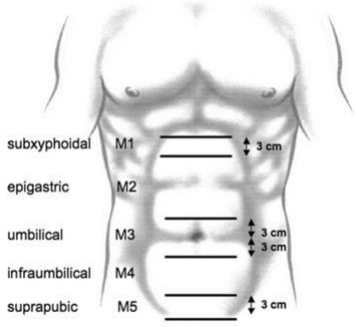
Midline Incisional Hernias are divided into the following subgroups M1–M5:

M1: subxiphoidal (from the xiphoid till 3 cm caudally)

M2: epigastric (from 3 cm below the xiphoid till 3 cm above the umbilicus),

M3: umbilical (from 3 cm above till 3 cm below the umbilicus),

M4: infraumbilical (from 3 cm below the umbilicus till 3 cm above the pubis) M5: suprapubic (from the pubic bone till 3 cm cranially).



EHS classification: zones of midline hernias.

11.2 Comprehensive Complication Index

All events should be classified according to the Comprehensive Complication Index.

11.3 Definition of Infection

CDC definition of surgical site infection for incisional site infection will be used.

Category	Criteria
Superficial incisional SSI	Infection occurs within 30 days after the operative procedure (where day 1= the procedure date) AND Involves only skin and subcutaneous tissue of the incision AND Patient has at least one of the following: a. purulent drainage from the superficial incision b. organisms isolated from an aseptically obtained culture from the superficial incision or subcutaneous tissue c. superficial incision that is deliberately opened by a surgeon, attending physician, or other designee and is culture positive or not cultured AND Patient has at least one of the following signs or symptoms: pain or tenderness; localized swelling; erythema; or heat. A culture negative finding does not meet this criterion d. diagnosis of a superficial incisional SSI by the surgeon or attending physician or other designee
Deep incisional SSI	Infection occurs within 30 or 90 days after the operative procedure (where day 1= the procedure date) AND Involves the deep soft tissues of the incision (eg, fascial and muscle layers) AND Patient has at least one of the following: a. purulent drainage from the deep incision b. a deep incision that spontaneously dehisces or is deliberately opened or aspirated by a surgeon, attending physician or other designee and is culture positive or not cultured AND Patient has at least one of the following signs or symptoms: fever (>38°C); localized pain or tenderness. A culture negative finding does not meet this criterion c. An abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histophathologic exam or imaging test
Organ/space SSI	Infection occurs within 30 or 90 days after the operative procedure (where day 1= the procedure date) AND Infection involves any part of the body deeper than the fascial/muscle layers, which is opened or manipulated during the operative procedure AND Patient has at least one of the following: a. purulent drainage from a drain that is placed into the organ/space (eg, closed suction drainage system, open drain, T-tube drain, CT-guided drainage) b. organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space c. an abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam, or imaging test AND Meets at least one criterion for a specific organ/space infection site

11.4 Activities Assessment Scale

A Finnish translation of Activities Assessment Scale will be used (47).

Kuinka vaikeiksi olet kokenut seuraavat toimet viimeisimmän vuorokauden (24h) aikana?	**Ei lainkaan vaikeaksi**	**Jonkin verran vaikeaksi**	**Melko vaikeaksi**	**Hyvin vaikeaksi**	**Mahdottomaksi**	**En ole tehnyt tätä viimeisen vuorokauden aikana muusta syystä**
Paikoillaan makaaminen	1	2	3	4	5	6
Istuminen	1	2	3	4	5	6

Asettuminen makuulle/istuallleen	1	2	3	4	5	6
Kurkottelu tai venyttely	1	2	3	4	5	6
1-2 kg nostaminen	1	2	3	4	5	6
Sisätiloissa liikkuminen	1	2	3	4	5	6
Portaiden kiipeämine	1	2	3	4	5	6
Liikkuminen ulkona tai töissä						
Paikoillaan olo, esimerkiksi televisiota tai tietokonetta katsoen, lukien tai puhelimessa puhuen	1	2	3	4	5	6
Kevyet askareet, esimerkiksi kevyet kotityöt, kyläily	1	2	3	4	5	6
Kohtalaisen raskaat askareet, esimerkiksi pihatyöt, lumityöt, reipas kävely, siivous	1	2	3	4	5	6
Raskas fyysinen aktiivisuus, kuten urheilu, kuntosaliharjoittelu, painavien taakkojen nostelu, raskas työ	1	2	3	4	5	6
Seksuaalinen kanssakäyminen	1	2	3	4	5	6

A Finnish translation of Promis-questionnaire will be used to evaluate the likelihood of incisional hernia(48).

PROMIS – kysely arpityräriskin arvioimiseksi

1. Uskotko, että Sinulla voi olla

   arpityrä?

   - ☐ Kyllä
   - ☐ Ei

2. Tunnetko kipua arvessa?

- ☐ Kyllä
- ☐ Ei

3. Onko arvessa pullotusta tai pattia?
   - ☐ Kyllä
   - ☐ Ei
4. Näkyykö arvessa pullostusta tai pattia?
   - ☐ Kyllä
   - ☐ Ei
5. Painosi?

   _____ kg
6. Pituutesi?

   _____ cm
7. Tupakoitko, tai oletko koskaan tupakoinut päivittäin?
   - ☐ Kyllä
   - ☐ Ei

12. Schedule of Events

Schedule of Events	Baseline	Procedure	Discharge	30 days + 7 days	2 year ± 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	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, consent withdrawal or subject has completed all study related visits.

13. Subject Withdrawal and Discontinuation

The subject's participation in any clinical trial is voluntary. The subject and/or the representative of subject has the right to withdraw at any time without penalty or loss of benefit. Study withdrawal means the subject is no longer participating in the study and no further study-related follow-ups will be performed. All subjects that withdraw after informed consent is signed will be evaluated at the time of withdrawal. Every effort will be made to document the subject outcome at the time of withdrawal. Data collected until withdrawal will be analyzed. The investigator has the right to discontinue subjects from the study at his/her discretion to ensure wellbeing of the subject. The reasons for withdrawal shall be documented (electronic Patient Withdrawal Request Form).

13.1 Subject lost to Follow-up

The investigator will attempt to contact the subject at least three times prior to designating them as lost to follow-up. The patient who may hesitate to come to follow-up visit, are asked to return the PROMIS questionnaire to estimate the risk of incisional hernia (48). The investigator will document the date and type of attempted communication. If a subject cannot be reached during the visit window, a missed visit will be recorded. Each patient in the trial will be invited for every follow-up visit according to schedule until he/she withdraws.

14 Procedures

14.1. Perioperative care

Perioperative care includes the assessment and optimization of medical risk factors and standard anesthesia. Antibiotic prophylaxis is accomplished according to the hospital protocol and routine practice.

Postoperative treatment at the surgical ward is accomplished according to the standard protocol.

14.2 Wound Closure technique

At the end of the operation, the abdomen will be closed according to patient's randomization group if applicable.

In the mesh group, the posterior layer of rectus sheath is opened as close to midline as possible without interrupting the midline. The space behind the rectus muscle is created mainly using blunt dissection. At each ends of the incision, opening of the retrorectus space is reached both cranial and caudal over the ends of the wound, if applicable. The posterior layer is closed using 0 or 2-0 slowly absorbable monofilament 4:1 small stitch techinique. The stitch bites are 5 mm with 5mm interstitch space. The length of the wound is measured, as well as the length of suturing material used. The aim is to close using suture material at least four times the length of the wound (4:1) by small stitch technique. After securing there will be no contact with the mesh and abdominal cavity, 8 cm wide self-gripping mesh (Progrip™, Medtronic) is applied on the posterior layer of the rectus sheath, reaching over the opening at each end. The anterior layer of rectus sheath is closed using slowly absorbable monofilament USP 2-0 or 0 suture by 4:1 small stitch technique. The length of the mesh and suture material used are measured. Subcutaneous layer will be left open if contamination class is 4. The subcutaneous layer may be left temporary with VAC or other wound dressing according to surgeons' preference. In contamination classes 1-3, the skin is closed

according to surgeons' preference.

In case the mesh cannot be safely kept outside the abdominal cavity, patient is intra-operatively excluded.

In the no mesh group, the rectus aponeurosis is closed in a single aponeurotic layer by using slowly absorbable monofilament USP 2-0 or 0 suture by 4:1 small stitch technique. Both the length of the wound and length of the suture material used is measured.

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

14.3 Postoperative treatment

Postoperative treatment will be accomplished according to standard protocol of each participating hospital.

14.4. Mesh (Progrip™, Medtronic)

A standard 8 cm self-gripping prophylactic mesh will be used in mesh group. The width of the mesh is standard. The length of the mesh is measured and reached over both ends of the
laparotomy opening.

15.General Reporting Requirements

Complications (Adverse events) reporting are an investigator's responsibility to assess and report. Adverse Events (AE) will be identified and captured on the electronic Complications eCRF
throughout the duration of the study as they occur and will be followed until they are adequately resolved or explained. Any Serious Mesh-Related Adverse Events with Clavien-Dindo Classification 3b or more should be reported to primary investigation site without delay after the site first learns of the event.

16. Investigator's Responsibilities and Qualifications

16.1 General Responsibilities

The role of the investigator is to implement and manage the day-to-day conduct of the clinical investigation and to ensure data integrity and the rights, safety and well-being of the subjects

involved in the clinical investigation. The participating institution shall appoint an appropriately qualified person to be the site principal investigator.
Prior to subject enrolment the investigational center must have Institutional review board approval for the study.

Investigators shall be qualified by education, training and experience to assume responsibility for the proper conduct of the clinical investigation. Investigators shall disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of the results. Investigators shall be knowledgeable with the method of obtaining informed consent.
The Investigator shall ensure compliance with the applicable regulatory requirements and ethical
principles for the process of obtaining informed consent. All protocol deviations should be recorded on the Protocol deviation form.

17 Data handling and record keeping

17.1 Confidentiality

Patient confidentiality will be strictly maintained. Patients will be assigned a Study ID. Access to patient records will be limited to the study group and the Investigator-delegated study
coordinator.

17.2 Data Management

Dedicated software and electronic database and the case report forms (eCRF) will be used to host the Clinical Trial data for this study. The database is developed and utilized in accordance with
international requirements and standards applicable to clinical investigations i.e. Good Clinical
Practice (GCP) and is a GCP compliant environment meeting applicable 21 CFR Part 11 requirements.

18. Case Report Forms

The electronical Case Report Forms (eCRF) and software are the primary data collection instruments for the study.

All data requested on the eCRFs will be recorded. All missing data will be explained.

19. Sample Size and Statistical Analysis

19.1 Sample size

To calculate a sample size needed to compare these two groups we estimated a 10 % rate of IH in mesh group and 25 % IH in control group on clinical assessment and ultrasound examination.
Assuming α = 0.05 and power = 80%, we would need 97 patients per group. Further, assuming a 2- year dropout rate of 20%, 122 patients per group are needed (totally 244 patients). The sample
size is calculated only for the primary outcome, the secondary outcomes will be interpreted as
hypothesis generating only. If the estimated 20% dropout rate exceeds, the sample size may be
recalculated.

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

19.2 Allocation

Patients having emergency midline laparotomy for any indication and fulfilling the inclusion criteria will be randomized prior to surgery after informed consent is signed. Patients are randomly
allocated (1:1 ratio) either to an intervention group or a control group according to a computer-
generated list compiled by a biostatistician otherwise uninvolved in the clinical care of trial patients. Allocation will be stratified according to BMI (<30 and ≥30kg/m^2), history of previous
laparotomy and age (<65 and ≥65- years) and-blocked within strata using random permuted blocks (block size 2, 4, 6 and 8). A separate randomization list will be created for each participating
center. All patients who have an emergency midline laparotomy during randomization period are assessed for eligibility.

19.3 Endpoint analysis

All analyses will be performed primarily according to modified intention to treat (ITT) principle.

Patients who fulfill exclusion criteria intraoperatively (after randomization) will not be included in the analyses. Per protocol analyses will be used as safeguard against the risk of falsely claiming

equality/superiority. The primary endpoint will be the incidence difference of IHs with 95% confidence interval between the study groups during 2-years follow up. Secondary outcomes are
listed previously. The primary endpoint as well as other categorical data will be analyzed by the χ^2- test or Fisher's exact test. Student's t-test or Welch test will be used for continuous variable, the
latter if assumption of homogenous variances does not hold. The incidence of hernia will also be
analyzed using Kaplan-Meier analysis.

The linear mixed model (LMM) or generalized linear mixed model (GLMM) will be used for repeatedly measured data, the previous for continuous data and latter for categorical data. Multiple imputations of missing outcome data will be used for sensitivity analyses. Prospectively
planned subgroup analyses are as follows: BMI>30, previous hernia and contamination class 4.
However, sample size calculation is done only for the primary end point and subgroup analyses are hypothesis generating only. 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.

20. Publication Policy

The trial will be registered with an authorized registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior to the start of recruitment. The success of the trial depends upon the collaboration of all participants. For this reason, credit
for the main results will be given to all those who have collaborated in the trial, through authorship and contributor-ship. Authorship decisions will be guided by standard requirements for authorship relating to submission of manuscripts to medical journals. These state that authorship credit should be based only on the following conditions being met (http://www.icmje.org):

• Substantial contribution to conception and design, or acquisition of data, or

analysis and interpretation of data
• Substantial contribution to drafting the article or revising it critically for important intellectual content
• Substantial contribution to final approval of the version to be published.

In light of this, the Principal Investigator and the main study group from Oulu and Helsinki University Hospitals and Dr Filip Muysoms will be named as authors in any publication, subject to

journal authorship restrictions. In addition, all collaborators (surgeons as well as biostatistician)
will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial. It is planned that the recruiting surgeons will also be named as authors, if the set target of the number of randomized patients is achieved.
To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the whole study group. In addition, individual collaborators
must not publish data concerning their patients, which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

20.1. Publication Plan

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.

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