CLINICAL INVESTIGATION PLAN

The COMPLY study– COMplications in inguinal PeniLe cancer surgerY

CIV-ID-24-09-049274

Version number: 1

Date: 2025-09-09

Sponsor: Region Skåne, 291 89 Kristianstad

Sponsor Representative and Coordinating Investigator:

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040-331888

Revision history

Document version	Date of Issue	Summary of Change
Version 1	2025-09-09	

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Signatures

Sponsor

I am responsible for ensuring that this CIP includes all essential information to be able to conduct this clinical investigation. I will submit the CIP and all other important clinical investigation-related information to the responsible investigator(s) so that they can conduct the clinical investigation correctly. I am aware that it is my responsibility to hold the staff members who work with this clinical investigation informed and trained.

2025-09-27

Sponsor's signature Date

Axel Gerdtsson

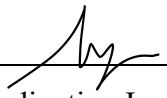
Printed name

Coordinating Investigator

I have read this CIP and agree that it includes all essential information to be able to conduct the clinical investigation. By signing my name below, I agree to conduct the clinical investigation in compliance with this Clinical investigation plan, the Declaration of Helsinki, SS-EN ISO14155:2020 (Good Clinical Practice), and the current national and international regulations governing the conduct of this clinical investigation.

I will submit this CIP and all other important clinical investigation-related information to the staff members and investigators who participate in this clinical investigation, so that they can conduct the clinical investigation correctly. I am aware of my responsibility to continuously keep the staff members and investigators who work with this clinical investigation informed and trained.

I am aware that quality control of this clinical investigation will be performed in the form of monitoring and possibly audits, and inspections.



250927

Coordinating Investigator's signature Date

Axel Gerdtsson

Printed name

Principal Investigator

I have read this CIP and agree that it includes all essential information to be able to conduct the clinical investigation. By signing my name below, I agree to conduct the clinical investigation in compliance with this Clinical investigation plan, the Declaration of Helsinki, SS-EN ISO14155:2020 (Good Clinical Practice), and the current national and international regulations governing the conduct of this clinical investigation.
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I am aware that quality control of this clinical investigation will be performed in the form of monitoring, audit, and possibly inspection.

Principal Investigator's signature Date

Printed name

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Funding and research agreement

This clinical trial is funded by the Gösta Jönssons foundation, the Hillevi Fries foundation, The foundation for urological research and Region Skåne (USVE). The study sponsor can finance part of the study sites expenses as stated in the agreement between the sponsor and the research sites.

List of used acronyms and abbreviations

Abbreviation	**Term/Explanation**
BMI	Body Mass Index
CE-mark	Conformité Européenne
CIP	Clinical Investigation Plan
CRF	Case Report Form
CT-scan	Computed Tomography scan
DMP	Data Management Plan
DSNB	Dynamic Sentinel Node Biopsy
EAU	European Association of Urology
EDC	Electronic Data Capture

EoS	End of Study
FDG-PET-CT	Fludeoxyglucose Positron Emission Tomography Computed Tomography
FNAC	Fine Needle Aspiration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HPV	Human Papilloma Virus
HrQoL	Health related quality of life
ICER	Incremental Costeffectioveness Ratio
IFU	Instructions for Use
ILND	Inguinal Lymph Node Dissection
ISF	Investigation Site File
ISRCTN	International Clinical Trials Registry Platform
LS	LigaSure Exact Dissector
LYMQOL	Lymph edema quality of life
LÖF	Landstingens Ömsesidiga Försäkringsbolag
MDCG	Medical Device Coordination Group
NPE	Norsk pasientskadeerstatning
PeCa	Penile Cancer
PeIN	Penile Intraepitelial Neoplasia
SOC	Standard of Care
SS-EN ISO	Swedish Standard - European standard International Organization for Standardization

1. Synopsis

ENGLISH	
Title:	The COMPLY study– COMplications in inguinal PeniLe cancer surgerY
Short title:	The COMPLY study
CIP number, version and date:	COMPLY Version 1, 2025-09-25
CIV-ID:	CIV-24-09-049274
Sponsor name and address:	Region Skåne, 291 89 Kristianstad
Participating Location(s) and country(ies):	Skåne university hospital, Malmö and Örebro university hospital, Örebro, Sweden Haukeland university hospital, Bergen, Oslo university hospital, Oslo and St Olavs university hospital, Trondheim, Norway Rigshospitalet, Copenhagen, Denmark
Name of investigational device:	LigaSure Exact Dissector
Background and rationale:	Subjects that are operated with inguinal lymph node dissection (ILND) for penile cancer (PeCa) are at risk of complications. This study will test if LigaSure Exact Dissector (LS), a vessel sealing device, will reduce time to drain removal and surgical site complications compared to standard of care (SOC).
Clinical development stage:	Post-market clinical investigation
Design of the clinical investigation:	Randomized controlled trial
Number of subjects:	116
Description of study population:	PeCa patients operated with inguinal lymph node dissection.
Inclusion criteria:	Diagnosis of PeCa Scheduled to be operated with ILND Able and willing to fill in forms electronically or in paper form at the clinic with the assistance of the study nurse. Written informed consent
Exclusion criteria:	<18 years Unable to understand the subject information according to the investigator's judgement. Pacemaker or other implanted devices as medically judged by the Investigator NOT to be applicable with LigaSure Exact Dissector use.

Study objectives:	Primary objective: To assess if time (days) until inguinal drain removal is shorter with LS compared to SOC. Secondary objectives: To assess if LS decrease the surgical site complications compared to SOC. To assess the complication rate according to Clavien-Dindo up to 90-days postoperatively. To assess if LS is superior to SOC in operating time (shorter operating time) and total drain volume (less volume). To investigate if LS is superior to SOC in proportion of study subjects with lower limb lymphedema at 3-5 and 10-14 months after ILND. To assess if LS is superior to SOC in proportion of study subjects with scrotal lymphedema at 3-5 and 10-14 months after ILND. To quantify and evaluate scrotal and lower limb lymphedema on CT-scan. To assess if scrotal volume measurement with caliper gauge and lower limb volume with V8-method are equivalent to scrotal volume and lower limb volume on computed tomography scan (CT-scan). To assess if LS affect Health related quality of life (HrQoL) less than SOC at 3-5 and 10-14 months after ILND compared to baseline. To assess if LS is cost-effective with the incremental costeffectioveness ratio (ICER) for LS at 3-5 and 10-14 months.
Study endpoints:	Primary endpoint: Time until inguinal drain removal after ILND Secondary endpoints: Surgical site complications (wound infection, lymphocele, lower limb lymphedema, wound dehiscence on the same side as the ILND performed) classified by Clavien-Dindo The 90-day complication rate (classified by the Clavien-Dindo) Operating time in minutes. Total drain volume in ml. Volume measurement of lower limbs with V8-method and CT-scan at 0, 3-5 and 10-14 months. Scrotal volume measured at 0, 3-5 and 10-14 months with caliper gauge and CT-scan.

	Lymphedema. Increment of 10% in excess volume (swollen limb/scrotum volume-normal limb/scrotum volume) of lower limbs or scrotum compared to baseline on either: -CT-scan of lower limb or scrotum. -scrotal volume measured with caliper gauge -lower limb volume measurement using V8 method -received treatment for lymphedema (compression stockings) Total HrQoL-score at 0, 3-5 and 10-14 months quantified with Lymph edema quality of life (LYMQOL). Calculation of ICER using EQ-5D-5L data at 0, 3-5 and 10-14 months.
Planned duration and follow up of the clinical investigation:	Q1 2026 – Q1 2031
Statistical considerations:	The difference in time until drain removal, operation time and total drain volume between the two groups will be assessed by the Mann-Whitney U test. The difference in complication rates and lymphedema between the two groups will be evaluated by Fishers exact test. The agreement between measurements by caliper gage V8 method and on CT-scan will be assessed by Bland-Altman method concerning scrotal volume and lower limb volume. LYMQOL will be assessed by linear mixed model. ICER will be calculated using the questionnaire EQ-5D-5L.

SVENSKA	
Titel	Comply studien. Komplikationer till inguinal lymfkörtelutrymning vid peniscancer.
Kortfattad titel	COMPLY studien
CIP nummer, version and datum:	COMPLY Version 1, 2025-09-25
CIV-ID:	CIV-24-09-049274
Sponsorns namn och adress:	Region Skåne, 291 89 Kristianstad

Deltagande sjukhus och länder:	Skåne universitetssjukhus, Malmö and Örebro universitetssjukhus, Örebro, Sweden Haukeland universitetssjukhus, Bergen, Oslo universitetssjukhus, Oslo and St Olavs universitetssjukhus, Trondheim, Norway Rigshospitalet, Copenhagen, Denmark
Namn på medicinteknisk produkt som ska undersökas:	LigaSure Exact Dissector
Bakgrund och anledning till studien:	Peniscancerpatienter som opereras med inguinal lymfkörtelutrymning (ILND) har stor risk att få en lokal komplikation efter kirurgin. Denna studie ska undersöka om LS, ett vävnadsförseglingsinstrument, kan minska tiden till dränavveckling och komplikationer efter ILND.
Kliniskt utvecklingsstadium:	Klinisk undersökning post-market
Design av klinisk studie:	Randomiserad kontrollerad studie
Antal individer:	116
Beskrivning av studiepopulationen:	Peniscancerpatienter som ska opereras med ILND
Inklusionskriterier:	Peniscancerdiagnos Ska opereras med ILND Vill och kan fylla i frågeformulär elektroniskt eller på papper med eller utan hjälp av en forskningssköterska. Skriftligt samtycke
Exklusionskriterier:	<18 år Oförmögen att förstå försökspersonsinformationen enligt undersökaren. Pacemaker eller annan inopererad utrustning som medicinskt anses vara kontraindicerad med LS enligt prövaren.
Mål:	Primärt mål: Att undersöka om tid till avveckling av inguinal drän är kortare med LS jämfört med SOC efter ILND Sekundära mål: Att undersöka om LS minskar risken för lokala komplikationer jämfört med SOC. Att undersöka komplikationsfrekvens enligt Clavien-Dindo upp till 90 dagar postoperativt. Att undersöka om LS är bättre än SOC avseende operationstid (kortare operationstid) och total dränvolym (mindre volym).

	Att undersöka om LS är bättre än SOC avseende andel av studiedeltagarna som har benlymfödem vid 3-5 och 10-14 månader efter ILND. Att undersöka om LS är bättre än SOC avseende andel med skrotalt lymfödem vid 3-5 och 10-14 månader efter ILND. Att kvantifiera och utvärdera skrotal och benlymfödem med CT. Att undersöka om mätning av pungvolym med skjutmått och benvolym med V8-metoden är lika bra som att mäta pung- och benvolym på CT. Att undersöka om LS påverkar HrQoL-värdet mindre än SOC vid 3-5, 10-14 månader efter ILND jämfört med baseline undersökningen. Att undersöka om LS är kostnadseffektivt med incremental costeffectioveness ratio (ICER) för LS vid 3-5 och 10-14 månader.
Endpoint:	Primär endpoint: Tid till avveckling av inguinaldrän. Sekundär endpoint (s): Lokala komplikationer i ljumsken (sårinfektion, lymfocele, lymfödem, sårruptur) klassificerade med Clavien-Dindo 90-dagar komplikationsfrekvens (klassificerad med Clavien-Dindo) Operationstid (min). Sammanlagd dränvolym (ml). Benlymfödem uppmätt med V8-metoden och CT vid 0, 3-5 och 10-14 månader. Skrotalvolym uppmätt med skjutmått och CT vid 0, 3-5 och 10-14 månader. Lymfödem. Ökning med 10% volym jämfört med utgångsvärdet innan operation (svullet ben/pungvolym-utgångsvärdet av ben/pungvolym) av ben eller pung på: -CT av ben eller pung -pungvolym uppmätt med skjutmått -benvolym uppmätt med V8 metoden -fått behandling för lymfödem (kompressionsstrumpor) Total HrQoL-värde vid 0, 3-5 och 10-14 månader uppmätt med LYMQOL. Mäta inkrementell kostnadseffektivitetskvot (ICER) utifrån EQ-5D-5L data vid 0, 3-5 och 10-14 månader.

Planerad tidsåtgång för studien:	Q1 2025 – Q1 2031
Statistiska beaktande:	Skillnaden i tid mellan dränavveckling, operationstid och total dränvolym mellan grupperna kommer att testas med Mann-Whitney U test. Skillnaden i komplikationsfrekvens och lymfödem mellan grupperna kommer att testas med Fishers exact test. Överensstämmelsen mellan mätningar med hjälp av skjutmått och och V8 metoden med CT-undersökning kommer att utvärderas med Bland-Altman avseende skrotalvolym och benvolym. LYMQOL kommer att utvärderas med linjär mixed model. ICER kommer att beräknas med hjälp av frågeformuläret EQ-5D-5L.

2. Identification and description of the investigational device

2.1. Description of the investigational device

LigaSure Exact Dissector (LS) is a Conformité Européenne (CE) -marked vessel sealing device used in surgery to seal vessels up to 7mm. LS uses the body's own collagen and elastin to create a permanent fusion zone. This technology can fuse blood vessels up to and including 7 mm, lymphatics, and tissue bundles, and has an average seal cycle of two to four seconds in most surgical situations with the Covidien Valleylab LS10 or FT10 electrical unit (1).

Figure 1. Picture of LigaSure Exact Dissector. (Downloaded from www.medtronic.com 2024-09-09)

2.2. Intended purpose

The intended purpose for the LS within this trial is to seal veins, arteries and lymphatic vessels up to 7mm while performing Inguinal Lymph Node Dissection (ILND) and consequently the device is used within its intended purpose its CE-marked for.

2.3. Manufacturer of the investigational device

Name: Medtronic AB
Adress: Gustav III:s Boulevard 42, 169 73, Solna, Sverige
Contact, phone number: 08-568 585 00

2.4. Model/type

LigaSure Exact Dissector (LS)

2.5. Target population

The LS is indicated for use in general surgery and in such surgical specialties as urologic, thoracic, plastic, and reconstructive surgery. Procedures may include, but are not limited to, bowel resections, gall bladder procedures, Nissen fundoplication, and adhesiolysis (1). In this study, the device will be used during ILND for subjects with penile cancer (PeCa).

2.6. Detailed description of the investigational device and materials coming into contact with the human body

The LS will be in contact with the human body during surgery. It will be used to seal and cut vessels and tissue. For more information please see Instructions for Use (1).

2.7. Traceability of investigational device

N/A. The investigational sites already have the device as it is used in hospital routine care. No additional traceability of the device is required outside hospital routine care.

2.8. Medical or surgical procedures

This device will be used in ILND.

2.9. Summary of required training/experience needed

The device is already in use in hospital routine care and no trial specific training is required.

3. Background and justification for the design of the clinical investigation

3.1. Background

PeCa is a rare condition, with an incidence rate of 2.3 per 100,000 men per year in Denmark, Norway, and Sweden in 2020 (2) The pre-invasive form of PeCa is known as penile intraepithelial neoplasia (PeIN) (3). In addition to PeIN, factors such as chronic inflammation, Human papilloma virus (HPV) infection, age, and smoking increase the

risk of developing PeCa (3, 4). The median age at diagnosis is 68 years, although approximately 7% of study subjects are diagnosed before the age of 40 (4).

PeCa spreads first to inguinal lymph nodes and then to the pelvic lymph nodes (5). Lymph node metastases are the most significant factor in predicting recurrence and mortality in penile cancer (6). Study subjects diagnosed with PeCa undergo metastatic screening, which includes thoracic, abdominal, and pelvic CT-scans, ultrasound of the groins and sometimes Fludeoxyglucose Positron Emission Tomography Computed Tomography (FDG-PET-CT). Fine needle aspiration (FNAC) is performed to confirm radiological suspicious lymph nodes. If the metastatic screening is negative, study subjects undergo a dynamic sentinel node biopsy (DSNB) of the inguinal lymph nodes. About 25% of study subjects have metastatic lymph nodes detected through this method (7, 8). In cases where inguinal metastases are detected through DSNB or FNAC, an inguinal lymph node dissection (ILND) is performed (4).

PeCa is treated with surgery and in advanced stages, additional therapy with chemotherapy and radiation therapy are required. Most study subjects with PeCa undergo lymph node surgery alongside the primary cancer surgery. Surgery for PeCa in Denmark are centralized to the university hospitals in Aarhus and Copenhagen, in Norway to university hospitals in Bergen, Trondheim, and Oslo, and in Sweden to university hospitals in Malmö and Örebro.

Study subjects undergoing ILND are at risk of complications, such as infection, lymphocele, and lymphedema (8-10). A preliminary report from the Swedish penile cancer registry indicates that up to 50% of the study subjects experience complications after ILND. LS is a tissue fusion and vessel sealing instrument that has shown promise in reducing complications compared to conventional surgery methods in ILND by sealing blood and lymphatic vessels up to 7 mm. In women operated with ILND for vulvar cancer, the LS reduced the surgical site complications (infection, lymphocele and lymphedema) from 70 to 29% (11).

To reduce post-operative complications, antibiotic prophylaxis, thrombosis prophylaxis and compression stockings are recommended (12, 13),. Additionally, a drain tube is inserted through the skin in the groin after ILND to drain lymphatic fluid from the wound. Volume-controlled removal of the inguinal drain helps decrease lymphocele formation (14). The drain is removed when there is less than 50 ml in the drain bag during two consecutive days. The study subjects usually have the drain two to three weeks postoperatively.

Risk factors for complications are the use of electrocautery compared to ligature or clips (15), a S-shaped or vertical incision (16, 17), sarcopenia and high body mass index (BMI) (18, 19). On the other hand the preservation of the fascia lata (20) and the saphenous vein reduce postoperative complications (21). Ultrasonic devices, however,

have not significantly reduced the incidence of lymphedema or the time required for drain removal compared to electrocautery (22).

The European Association of Urology (EAU) penile cancer guidelines suggest that tissue fusion and vessel sealing instruments like LS may lower complication rates in ILND and shortens the time with drain, although further studies are needed (23). This randomized trial will determine if the LS can reduce complications and time with drain compared to conventional surgery.

3.2. Evaluation of results of prior testing, assessments and clinical investigations

The LS is CE-marked and has an intended use in open surgical procedures where ligation and division of vessels, tissue bundles, and lymphatics is desired. The LS can be used on vessels (arteries, veins and lymphatics) up to and including 7mm. It is indicated for use in general surgery, urologic, thoracic, plastic, and reconstructive surgery (1).

3.3. Evaluation of clinical data

The following investigator-initiated studies have been performed with the LigaSure technique. A Spanish study involving eight subjects, that underwent ILND for PeCa, found that LigaSure technique decreased both complications and operative time (24). A study of 20 vulvar cancer subjects who underwent ILND using LigaSure small jaw demonstrated reduced postoperative complications and reduced time with drainage (11). LigaSure technique has also been evaluated in axillary lymph node dissection in 100 breast cancer subjects, where it was found to reduce operating time and the time to drain removal but did not impact the complication rate (25, 26).

The LS has been used in axillary lymph node dissection for breast cancer where it significantly reduced the time with drain, complication rate and total drain volume compared to SOC (27).

3.4. Description of the clinical development stage

This is a post-market clinical investigation (post-market stage).

4. Risks and clinical benefits of the investigational device and clinical investigation

4.1. Expected clinical benefits

The expected main clinical and health benefit from ILND performed using LS is that the post-operative complications such as lymphedema, infections and lymphocele might decrease, time with drain decreases due to improved sealing of lymphatic vessels and the operating time is expected to be shorter.

4.2. Risks

Subjects are included in the study based on the fact they will undergo ILND surgery as part of their treatment. Surgery is accompanied with inherent risks. The LS is already in use in clinical practice. The risk for the subject in this study is that the subject is randomized to either undergo ILND using the LS or not. If the subject is not participating in the study the surgeon can choose to use the LS or not.

The main known risk with the LS, as noted in the Instructions for Use (IFU) (1), is that the LS shall be used with caution in the presence of internal or external pacemakers or other implanted devices. The contact between an active instrument electrode and any metal objects (hemostats, staples, clips, retractors, etc.) may increase current flow and may result in unintended surgical effects, such as an effect at an unintended site or insufficient energy deposition. The LS shall not be used on vessels larger than 7 mm in diameter. The tissue or vessel can be divided after the seal cycle is complete otherwise this may result in improper sealing.

4.3. Steps to be taken to control or mitigate risks

To have surgery puts the subject at a major risk for complications, but the investigation does not add any steps that will add to this risk. The LS has been used for many years and the surgeons participating in investigation are all experienced in the procedure. The surgeons must follow the IFU to avoid potential risks that can be caused using the LS.

4.4. Rationale for benefit-risk ratio

The benefit of this study is to determine if LS can reduce time with drain and postoperative complications after ILND. The risk for the subjects in the study is low if the LS is used according to the IFU.

5. Objectives and hypotheses of the clinical investigation

5.1. The purpose of the clinical investigation

The study aims to determine whether LS reduces the time with inguinal drain and postoperative surgical site complications (wound infection, lymphocele, lymphedema, wound rupture) following ILND. If the study confirms that LS reduces these complications, compared to the use of standard of care (SOC) methods, it can be the recommended method in ILND procedure.

5.2. Objectives

5.2.1. Primary objective

To assess if time (days) until inguinal drain removal is shorter with LS compared to SOC.

5.2.2. Secondary objectives

1. To assess if vessel sealing with LS is superior to SOC in reducing surgical site complications (wound infection, lymphocele, lower limb lymphedema and wound dehiscence on the same side as the ILND performed) up to 90-days after ILND.
2. To assess the complication rate according to Clavien- Dindo up to 90-days postoperatively.
3. To assess if LS is superior to SOC in operating time (shorter operating time) and total drain volume (less volume).
4. To investigate if LS is superior to SOC in proportion of study subjects with lower limb lymphedema at 3-5 and 10-14 months after ILND.
5. To assess if LS is superior to SOC in proportion of study subjects with scrotal lymphedema at 3-5 and 10-14 months after ILND.
6. To quantify and evaluate scrotal and lower limb lymphedema on CT-scan.
7. To assess if scrotal volume measurement with caliper gauge and lower limb volume with V8-method are equivalent to scrotal volume and lower limb volume on computed tomography scan (CT-scan).
8. To assess if LS affect Health related quality of life (HrQoL) less than SOC at 3-5 and 10-14 months after ILND compared to baseline.
9. To assess if LS is cost-effective with the incremental costeffectioveness ratio (ICER) for LS at 3-5 and 10-14 months.

5.3. Hypotheses

5.3.1. Primary hypothesis

LS will reduce the time (with a median of 3 days) until inguinal drain removal compared to SOC.

5.3.2. Secondary hypothesis(es)

1. LS will reduce the proportion of surgical site complications (wound infection, lymphocele, lower limb lymphedema (on the same side as the ILND performed), wound dehiscence) from 50% to 25% compared to SOC.
2. LS will reduce the proportion of post-operative complications from 50% to 25% compared to SOC.

3. LS will reduce the operating time and reduce the total drain volume with 25% for ILND compared to SOC.
4. LS reduce the proportion of lower limb lymphedema at 3-5 and 10-14 months after ILND compared to SOC.
5. LS reduce the proportion of subjects with scrotal lymphedema at 3-5 and 10-14 months after ILND compared to SOC.
6. Clinical scrotal volume measurement and lower limb volume measurement using caliper gauge and V8-method are equivalent to scrotal volume and lower limb volume on CT-scan.
7. Subjects operated with LS will have a 5-point higher HrQoL-score at 3-5 and 10-14 months after ILND compared to SOC.
8. LS is cost-effective compared to SOC

6. Design of the clinical investigation

6.1. General information

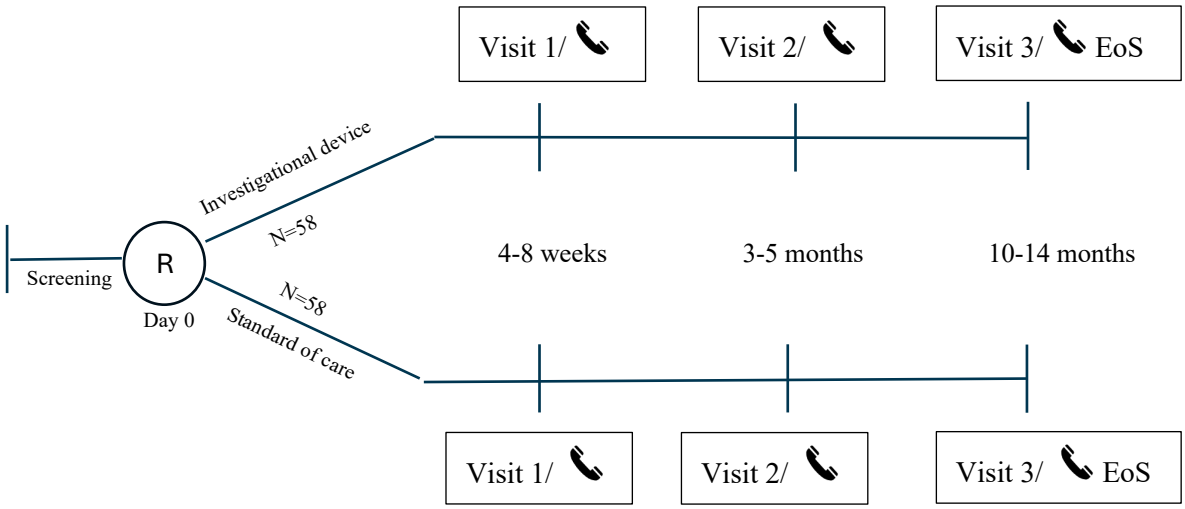
This is a prospective, multicenter randomized clinical trial on PeCa study subjects that are scheduled for ILND at university hospitals in Sweden, Norway, and Denmark. Subjects will be randomly assigned to either control group, that will undergo the standard of care or the intervention group that will be operated with LS. The study subjects will be followed one year after inclusion.

Study subjects that are diagnosed at the operating unit will have follow-up with an office visit and study subjects that are referred to the operating unit for surgery will have telephone follow-up.

6.2. Intervention

The study subjects will undergo ILND according to the randomization. Preservation of the fascia lata and saphenous vein will be done when possible. The wound will be closed according to local guidelines. The following situations are accepted for subjects randomized to LS, ligature/clips on vessels exceeding 7mm, dissection of the saphenous vein or femoral artery using bipolar scissor, electrocautery of bleeding not suitable or unavailable for the LS device.

Figure 2. ***Clinical investigation design***



6.3. Endpoints

6.2.1. Primary endpoint

Time (days) until inguinal drain removal after inguinal lymph node dissection. Study subject reported outcome. A copy of the chart with the date of drain removal will be used for confirmation of study subject reported outcomes.

6.2.2. Secondary endpoint (s)

1. Surgical site complication rate (wound infection, lymphocele, lower limb lymphedema on the same side as the ILND performed) classified by Clavien-Dindo. The complication must be confirmed by a visit to a doctor or a nurse. The visit doesn´t have to be to the operating unit. A copy of the chart describing the complication, needs to be stored at the operating unit. The complication needs to be classified using the Clavien-Dindo system for postoperative complications.

2. The 90-day complication rate (classified by the Clavien-Dindo). The complication must be confirmed by a visit to a doctor or a nurse. The visit doesn´t have to be to the operating unit. A copy of the chart describing the complication, needs to be stored at the operating unit. The complication needs to be classified using the Clavien-Dindo system for postoperative complications.
3. Operating time in minutes. Time from skin incision to start of skin closure.

4. Total drain volume in ml. Study subject reported outcome. The patient diary confirming the drain volumes must be collected and stored at the operating unit.
5. Volume measurement of lower limbs (cm^3) with V8-method and CT-scan at 0, 3-5 and 10-14 months.
6. Scrotal volume (cm^3) measured at 0, 3-5 and 10-14 months with caliper gauge and CT-scan.
7. Total HrQoL-score at 0, 3-5 and 10-14 months quantified with Lymph edema quality of life (LYMQOL).
8. Calculation of ICER using EQ-5D-5L data at 0, 3-5 and 10-14 months.
9. Lymphedema. Increment of 10% in excess volume (swollen limb/scrotum volume-normal limb/scrotum volume) of lower limbs or scrotum compared to baseline on either:
   -CT-scan of lower limb or scrotum.
   -scrotal volume measured with caliper gauge
   -lower limb volume measurement using V8 method
   -received treatment for lymphedema (compression stockings)

6.2.3. Safety endpoint(s)

No other safety outcomes than specified in primary and secondary outcome measures will be collected.

6.2.4. Description of the comparator

The LS will be compared to standard of care “SOC”, which comprises all methods for vessel sealing except LS. The method/s of use of in SOC is up to the surgeon’s preference.

6.4. Methods to minimize bias

Subjects will be stratified based on the hospital performing the ILND and randomized to ILND with LS or SOC. The stratification will be done since the different hospitals use different methods as SOC as well as antibiotic prophylaxis, thrombosis prophylaxis and wound closure. The subject will not be informed (blinded) of the randomized intervention until end of study. The blinding will not be done if the local hospital routine prohibits from it. Outcomes such as measurements of lower-limb volumes and scrotal volumes will be assessed by study personnel without knowledge of the intervention given. The study subject reported outcomes, EQ-5D-5L, LYMQOL and drain volume will be reported by subjects that do not have a knowledge of the intervention given (blinded). Study subject reported outcomes such as complications and drain removal will be controlled using chart review.

6.5. Description of the clinical procedures and diagnostic methods relating to the clinical investigation

Table 1 Flow chart of screening and follow-up visit

Procedure	Screening Inclusion Surgery (ILND -2weeks)	Visit 1/Telephone call (4-8 weeks)	Visit 2/Telephone call (3-5 months)	Visit 3/Telephone call (10-14 months) and End of Study
Incl/exclusion criteria	√			
Informed consent	√			
Medical history/ concomitant medications	√			
Randomization	√			
EQ-5D-5L and LYMQOL	√		√	√
Volume measurements of lower limb and scrotum [a, b]	√		√	√
CT-scan [a]	√		√	√
Intraoperative complications and information from the surgery		√		
Subject self-registration of drain volumes	√	√		
Registration of post-operative complications, time to drain removal, postoperative nights, pTN-stage		√	√	

a) Only for subjects with office visit follow-up at the investigational sites in Bergen, Copenhagen, Malmö, Oslo, Trondheim and Örebro.
b) Measurement instructions as described in Appendix 19.1. Lower limb lymphoedema and 19.2. Scrotal lymphoedema

6.5.1. Screening/Inclusion/Surgery

Surgery -2 weeks

For all study subjects
Study nurse / Investigator

- Inform subjects eligible for the study

- Study subjects eligible for the study that decline to participate in the study needs to be logged in the screening log with initials and year of birth.
- Collect informed consent and store it at the center.
- Provide the questionnaires (LYMQOL and EQ-5D-5L) if the study subject wishes to fill in the questionnaires in paper form. If the study subject wishes to use the Electronic Data Capture (EDC) system provided by Regions Skåne, collect the telephone number and email address and send the questionnaires to the study subject before surgery. The questionnaires need to be filled in before start of surgery.
- Collect information about use of anticoagulation, statin and immune modulating agents, smoking and previous radiation to the pelvis/groin.
- Determine the subject's frailty score (Ask about Congestive heart failure yes/no, History of chronic obstructive pulmonary disease yes/no, Hypertension requiring medication yes/no, Diabetes mellitus yes/no, Totally or partially dependent preoperative functional status vs independent)
- Measure length, weight
- Give the study subject thrombosis prophylaxis, compression stockings and antibiotic prophylaxis according to local guidelines.
- Register the subject electronically and enter the collected information. The study subject must be blinded to the randomization until end of study. The electronical system will provide the subjects study ID and randomize the study subject. From the chart collect and register the results from FDG-PET-CT, the cTNM-stage, age, date of diagnosis, preoperative chemotherapy, previous inguinal dynamic lymph node biopsy (DSNB).
- Operate the study subject, according to the randomization, with or without LS. Preserve the fascia latae and saphenous vein when possible. Close the wound according to local guidelines. The following situations are accepted for subjects randomized to LS, ligature/clips on vessels exceeding 7mm, dissection of the saphenous vein or femoral artery using bipolar scissor, electrocautery of bleeding not suitable or unavailable for the LS device.
- Electronically register the date of surgery, type of penile surgery, type of inguinal lymph node surgery, pelvic lymph node surgery, robot or laparoscopic surgery, vena saphena sparing surgery, fossa ovale dissection, intraoperative complications, operating time, type of surgery performed, bleeding,
- Instruct the study subject on how to fill in the study subject diary on drain volume.

The study subject

- The study subject fills in the EQ-5D-5L and LYMQOL electronically or in paper form.
- Starting the day after the surgery the study subject will record daily drain volume in ml that empties in the drain until drain removal (usually around 2-3 weeks postoperative). The study subject diary must be collected and stored at the center.

Only for study subjects with that will have an office visit follow-up at the operating unit
Study nurse / Investigator

- Refer the study subject for a CT-scan of the scrotum and both lower limbs. The CT must be done before surgery.
- Psuedonymize, using the study subject-id, the preoperative CT-scan of scrotum and lower limbs and send it electronically to a secure server at Region Skåne.
- Measure scrotal volume (both standing position and supine position) and volume of both lower limbs.

6.5.2. Visit 1 / Telephone call

Four to eight weeks after surgery

For all study subjects
The study nurse / Investigator

- Electronically register the number of postoperative nights, if the surgery was radical, total numbers of lymph nodes and metastatic lymph nodes and pTN. This can be done at any time after surgery up to 8 weeks postoperative.
- Register time to drain removal, daily drain volumes and complications from surgery until 30 days postoperative. The date of drain removal must be confirmed by chart record. A copy of the chart where the complication is defined and diagnosed and the date of drain removal shall be stored at the operating unit. The complication shall be classified using the Clavien-Dindo system for postoperative complications.

The study subject

- Report about complications from surgery until 30 days after surgery.

Only for study subjects with an office visit follow-up at the operating unit
The study nurse / Investigator

- Refer the study subject for a CT-scan of scrotum and lower limbs at 3-5 months postoperative.

6.5.3. Visit 2/ Telephone call

Three to five months after surgery

For all study subjects
The study nurse / Investigator

- Register electronically any post-operative complications (31 to 90-days following surgery)
- Register if the study subject wears compression stockings
- Send EQ-5D-5L and LYMQOL electronically or in paper form to the study subject. Register the questionnaires in the electronical system for study subjects that wishes to fill in the forms on paper.

The study subject

- Subjects fill in the EQ-5D-5L and LYMQOL electronically or in paper form.
- Report complications from 31 days until 90 days postoperatively.

Only for study subjects with that will have an office visit follow-up at the operating unit.

The study nurse / Investigator

- Collect CT-scans of lower limbs and scrotum performed 3-5 months after surgery, pseudonymize using the study subject's study-id and transmit it via secure electronic transfer to a protected server at Region Skåne.
- Measure weight, scrotal volume (both standing position and supine position) and volume of lower limbs.
- Refer the study subject for a CT-scan of scrotum and lower limbs at 10-14 months postoperative.

6.5.4. Visit 3/Telephone call/End of study

Ten to fourteen months after surgery

For all study subjects

The study nurse / Investigator

- Send EQ-5D-5L and LYMQOL electronically or in paper form to the study subject. Register the questionnaires in the electronical system for study subjects that wishes to fill in the forms on paper.
- Register if the study subject wears compression stockings
- Register if the study subject received treatment for lymphedema
- Register data on recurrence, if the study subject has received radiation therapy or inguinal surgery in the groin after the first surgery (at randomization).
- Register if the patient has completed the study. If no, describe the reason for discontinuation and if the patient is diseased.

Study subject

- Subjects fill in the EQ-5D-5L and LYMQOL electronically or on paper forms.

Only for study subjects with that will have an office visit follow-up at the operating unit.

- Collect the CT-scan of lower limb and scrotum performed 10-14 months after surgery and, pseudonymize it with the study-id and sent it electronically to a secure server at Region Skåne.
- Measure weight, scrotal volume (both standing position and supine position) and volume of lower limbs.

Study ends. Study subjects will receive the result of the randomization after they have filled in the questionnaires. Subjects will continue follow-up according to the national/regional recommendations.

6.5.5. Extra visit

During the study, if the patient needs an extra visit due to swelling of legs or scrotum, and the patient has office visit follow-up at the operating unit, the scrotal and lower limbs measurement needs to be registered in the database.

6.6. Timeline and End of the clinical investigation

The enrolment period will be 4 years to collect 116 subjects (30 subjects/year), and the study ends when the last subject has completed the last follow-up. Each subject will be in the clinical investigation for one year. Subjects will continue follow-up according to the national/regional recommendations.

The sponsor or by delegation, the National Coordinator, will notify the national competent/regulatory authority in all involved member states within 15 days after the clinical investigation has ended in all member states and will send the clinical investigation report within 1 year after the end of the clinical investigation including an easily understandable summary.

The subject will get an electronic notice after they have filled-in the LYMQOL at 1-year that the study has ended and receive the result of their randomization. For subjects that fill in their forms on paper, the study nurse/surgeon will call the subject after the subject have sent in their last questionnaire and inform that the study has ended and give the result of the randomization.
After study end, the study subjects will have follow-up according to the EAU / Swedish national penile cancer guidelines up to five years after diagnosis.

7. Subjects

7.1. Inclusion criteria

- Diagnosis of PeCa
- Scheduled to be operated with ILND
- Able and willing to fill in forms electronically or in paper form at the clinic with the assistance of the study nurse.
- Written informed consent

7.2. Exclusion criteria

- <18 years
- Unable to understand the subject information according to the investigator's judgement.
- Pacemaker or other implanted devices as medically judged by the Investigator NOT to be applicable with LigaSure Exact Dissector use.

7.3. Investigation population

The study will include 116 subjects. The study population are the target population. Immune-compromised subjects will be included since some of the subjects will be treated with neoadjuvant chemotherapy as part of the penile cancer treatment. Penile cancer is a disease diagnosed mostly in elderly subjects and most of the population is expected to be >60 years.

7.4. Criteria and procedures for subject withdrawal or discontinuation.

The subject will not be told the randomized intervention prior to surgery. Since the subject are under anesthesia, they cannot withdraw consent during the procedure.

A subject can withdraw their consent from the study at any time, and if possible, the investigator should ask what specifically the subject wishes to withdraw from. Already collected information will be used in the analyses as explained to the subject in the informed consent procedure. Subjects that withdraw their consent will have follow-up as part of the regular follow-up after penile cancer surgery.

During the surgery, if the surgeon considers it medically necessary, they can choose to discontinue the randomized intervention. In such case the subject will be excluded from further analyses regarding post-operative complications. The rationale for discontinuation must be noted in the CRF.

If the subject moves abroad, the follow-up will be discontinued, and the subjects will be lost to follow-up. The already collected data will be used in the analyses.

Subjects that do not come to the follow-up visit will be contacted by phone or mail. If the subject does not show/answer after three attempts, in three months, the subject is considered lost to follow-up.

8. Informed consent process

8.1. General process for informed consent

The principal investigator or delegated sub-investigator shall ensure that the subject is given full and adequate oral and written information about the clinical investigation, its purpose, any risks and benefits as well as inclusion and exclusion criteria. Subjects must also be informed that they are free to discontinue their participation in the clinical investigation at any time without having to provide a reason. Subjects will be given the opportunity to ask questions and be allowed time to consider the provided information and participation in the clinical investigation. If the subject chooses to participate, both the subject and the investigator shall sign the informed consent form. A copy of the subject information as well as a copy of the informed consent form shall be provided to the subject. The subject’s signed and dated informed consent must be obtained before performing any activity specific to the clinical investigation. The process shall be documented in the subject’s medical records, and the signed informed consents shall be maintained with the essential documents.
If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form. If new information is added to the clinical investigation, the subject has the right to reconsider whether he will continue his participation.

9. Statistical considerations

9.1. Analysis population

The clinical investigation will be analyzed according to intention-to-treat principle to avoid bias. Analyses will primarily be performed on the intention-to-treat population, i.e. all randomized.

9.2. Descriptive statistics

Depending on the distribution of the data mean (standard deviation) or median (interquartile range) will be given as summary statistics for continuous variables. Categorical variables will be presented as number (percent).

9.3. Analytical procedures

The analytical procedures will test differences between the standard and the intervention group.

The primary endpoint, time (days) until drain removal after inguinal lymph node dissection, will be assessed by the Mann-Whitney U test.

The proportion of surgical site complications; wound infection, lymphocele, lower limb lymphedema and wound dehiscence classified by Clavien-Dindo will be analyzed by Fisher's Exact test.

Fisher's Exact test will also be used to test the proportion of surgical site complication (Clavien-Dindo I or more) at 90 days and the proportion of lymphoedema between groups at 3-5 and 10-14 months.

Operation time in minutes and total drain volume in ml will be evaluated with the Mann-Whitney test.

Changes from baseline measures of lower limb volume and scrotal volume at 3-5 months and 10-14 months will be calculated. Lymphedema is defined as >10% increment in volume compared to baseline measurements. The proportion of lymphoedema will be tested by Fisher's Exact test.

The agreement between measurements by caliper gage V8 method and on CT-scan will be assessed by Bland-Altman method concerning scrotal volume and lower limb volume.

Quality of life will be measured using LYMQOL data for leg. The mean difference from baseline between the groups and time points (3-5 and 10-14 months) will be evaluated by linear mixed model. Group, time, their interaction and baseline LYMQOL measure will be considered as fixed effect.

The questionnaire EQ-5D-5L will be used to investigate cost-effectiveness at 3-5 and 10-14 months compare to baseline. Incremental Cost-Effectiveness Ratio (ICER) will be calculated and assessed.

Depending on the distribution of the data, the analysis method may be changed from non-parametric to parametric, or vice versa.

Deviations from the planned analyses will be presented and justified.

All statistics will be calculated using two-sided test and a p-value ≤0.05 will be considered significant.

9.4. Sample size calculation

A primary outcome measure is time until drain removal. To assess the difference between the two randomized groups Mann-Whitney U test will be performed.

The sample size needed to detect the difference was calculated by the function wmwpow in the package wmwpow in R. (28)

The distribution of the data is assumed to be double exponential with $\alpha=7$ and $\lambda=1$ with equal standard deviation. Information from previous research assuming equal standard deviation gives an effect size of 0.75 (11), but the effect size that we want to detect is lowered to 0.65 due to uncertainty of the standard. A total number of 116 evaluable study subjects (58 in each group) is needed to detect an effect size of 0.65 with a power of 0.808 and at a significance level of 0.05. We expect no loss of study subjects.

Around 110 study subjects are operated each year with lymph node surgery in Norway, Denmark and Sweden. Around 30 study subjects eligible for inguinal surgery are expected to be randomized in the study each year. The study inclusion will take around 4 years.

9.5. Number of procedures to be performed by a single user

Lymph node surgery in penile cancer subjects is performed by one to three surgeons at each center. No absolute number of surgeries by a single user will be given. Learning curve for usage of the LS is none since it is already in clinical use.

9.6. Pass/fail criteria

Pass criteria are considered if

- a reduction in 3 days with drain using LS
- a 50% reduction in surgical site complications (wound infection, lymphocele, lower limb lymphedema and wound dehiscence on the same side as the ILND performed)
- reduction in operating time of 20 minutes using LS
- subjects operated with LS will have a mean of 0.5 points higher in each domain on LYMQOL at 3-5 and 10-14 months after ILND compared to SOC.
- subjects operated with LS will have a mean of 1 point higher on the question on the quality-of-life question at 3-5 and 10-14 months after ILND compared to SOC.
- A difference of >0.5 QALY´s between SOC and LS
- LS is more cost-effective compared to SOC
- LS reduce the proportion of subjects with scrotal lymphedema at 3-5 and 10-14 months after ILND compared to SOC by 10%
- LS reduce the proportion of lower limb lymphedema at 3-5 and 10-14 months after ILND compared to SOC by 10%.
- considered if clinical scrotal volume measurement is equivalent to scrotal volume on CT-scan.

- LS reduce the post-operative complications by 50% compared to SOC.
- LS reduce the total drain volume with 25% after ILND compared to SOC.

9.7. Multiplicity control

There will be no adjustment for multiplicity, since there is only one primary endpoint for the primary objective.

9.8. Subgroup analysis

A subgroup analysis will be performed for the group of subjects that are being controlled with CT-scan at 3-5 and 10-14 months. For this subpopulation the difference in calculation of scrotal lymphedema using the caliper gauge and CT -scan. A subgroup analysis will also be performed in subjects that will measure lower limb volumes using the V8 method.

9.9. Missing data

Missing data will not be replaced.

9.10. Exploratory analysis and sensitivity analysis

If there are differences between groups regarding factors affecting outcomes, sensitivity analyses by models will be performed.

9.11. Reporting deviations

Deviations from the original statistical analysis plan will be reported in the publications.

9.12. Handling of imbalance of subjects per site

To counteract imbalance between the groups, separate block-randomized lists per site will be produced.

10. Data management and data protection

All data will be registered, managed, and stored in a manner that enables correct reporting, interpretation, and verification.

10.1. Case Report Form

Subject study data will be collected using a secure Electronic Data Capture (EDC) system provided by Regions Skåne. Descriptions of the methods for data entry and collection, including procedures for verification, validation will be specified in the study specific Data management plan.
The eCRF includes 2-factor authentication, access rights based on user roles, audit trail, query handling, and internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate. Authorized study site personnel designated by the Investigator will be entering information in the eCRF (complete data collection), as required by the CIP. The Investigator and designated site personnel will have read/write access to the eCRF. Other study roles, such as monitor and data manager will have read access, and as appropriate based on user role, write access for administrative data (e.g., queries and medical codes).

10.2. CT-scans

CT-scans will be transmitted from each investigational site to the sponsor for central measurement of scrotal volume and lymphedema. The CT-scans will be transferred pseudonymized with the study-id to a secure server at Region Skåne using Recomia (29). The cloud platform made available to RECOMIA and its research partners is delivered and maintained by Slicevault, a company dedicated to providing secure and compliant cloud-based solutions for managing medical images in clinical research.

10.3. Data cleaning and database lock

Procedures for data review, database cleaning, and issuing and resolving data queries will be specified in the study specific Data management plan. After data verification, validation and all queries are resolved for all subjects, the database will be closed. All access will be withdrawn except for data export. All handling of all detected errors after database lock will be documented.

10.4. Archiving

The principal investigator and sponsor will maintain the essential clinical investigation documents in the investigation site files archive and sponsor files archive, respectively. The sponsor shall keep all documentation and data for 10 years after the clinical investigation has ended. The pseudonymized study data will be stored on an internal storage unit within Region Skåne. The principal investigator will archive all local investigation documentation for at least 10 years after the clinical investigation has ended or longer if stipulated by local law.

10.5. Data protection

Data will be handled according to the General Data Protection Regulation (EU ordinance 2016/679, GDPR). If any part of the data is handled by any other organization, inside or outside the European Union, appropriate agreements and/or other documentation will be established, to ensure that the data processing is performed in accordance with the provisions of the General Data Protection Regulation (EU ordinance 2016/679, GDPR) and other relevant legislation, before any data transfer takes place.

In the subject information and the informed consent form, the subject will be given complete information about how collection, use and publication of their clinical investigation data will take place. The subject information and the informed consent form will explain how clinical investigation data are stored to maintain confidentiality in accordance with national data legislation. The informed consent form will also explain that for verification of the data, authorized representatives of the sponsor, as well as relevant authority, may require access to parts of medical records or study records that are relevant to the clinical investigation, including the subject's medical history.

Each included subject will receive a unique pseudonymized alphanumeric code to keep their identity confidential. This alphanumeric code will be the unique subject identifier (study ID) used in eCRF. The subject confidentiality is maintained in compliance with ISO

14155:2020, thereby ensuring that the study subject's identity remains unknown to unauthorized personnel. Study subject medical records and other source data will be kept in accordance with the organization's local guidelines at the site.
The PI at each investigational site must file a subject identification list (code list), which includes sufficient information to link records, i.e. the CRF and clinical records. This list should be preserved for possible future inspections/audits but should not be made available to the Sponsor except for monitoring or auditing purposes.

A data management plan (DMP) will outline the procedures for data collection, storage, sharing, and destruction, ensuring compliance with GDPR and ethical standards.
Only study personnel with relevant clearance will have access to identifiable data.
Pseudonymized data will be stored securely on encrypted servers within Sponsor Organization.

In case of a data security breach the following measures will be implemented to mitigate the possible adverse effects:

- the investigation site should notify the Sponsor of the discovery of the breach
- investigations by involved parties at the site of breach are conducted to determine the origin of the breach and apply corrective measures as needed. It will be handled according to each organizations data protection policy
- as required by the applicable regulations, involved study subjects are informed of data breaches (art 34 GDPR) after the Sponsor has become aware of the breach
- if needed and as required by the applicable regulations, Data Privacy Authorities are informed (art 33 GDPR) within 72 hours after sponsor has become aware of the breach. Reporting will be handled according to each organizations data protection policy
- as required by regulations, data breach records are maintained by the affected data processor/controller (art 30 GDPR) and according to each affected sites organizations data protection policy

11. Quality control

11.1. Monitoring

The clinical investigation will be monitored before the clinical investigation begins, during the clinical investigation conduct, and after the clinical investigation has been completed, to ensure that the clinical investigation is carried out according to the CIP and that data is collected, documented, and reported according to SS-EN ISO 14155:2020 and applicable ethical and regulatory requirements. The monitor is appointed by the sponsor and independent in relation to the principal investigator and site staff.

11.2. Monitoring plan

Monitoring will be risk-based, which means the extent of the monitoring is based on the sponsor's risk-assessment and is performed as per the investigation's monitoring plan. Monitoring is intended to ensure that the subject's rights, safety, and well-being are met as well as data in the CRF are complete, correct, and consistent with the source data.

Forum Söder is responsible for monitoring the study in Sweden.

In Denmark the study will be monitored by the Danish GCP unit.

In Norway the study will be monitored by Helse-Bergen.

11.3. Source data

The investigator must keep source documents for each subject in the investigation. A document describing what has been classified as source data in the investigation (source data reference document) should be included in the Investigation Site File (ISF). In this trial some source data is directly entered in the CRF.

The investigator must ensure that all source documents are accessible for monitoring and other quality control activities. Source data is defined before clinical investigation start at each individual site and can, in cases where source data is not registered in another document, consist of the CRF. This should be decided in consultation with the monitor and clearly stated in the source data reference document.
Access to investigation-related documentation, such as subjects' medical records, CRFs, other source data and other clinical investigation documentation will be provided for monitoring and auditing purposes. Access to subjects' medical records will require a confidentiality agreement to be signed by the person in charge of the medical records at the investigational site and by the monitor and auditor, if applicable. Access will also be granted in the context of regulatory inspections.

12. Amendments to the CIP

Amendments to the CIP will be decided upon by the Sponsors representative. Substantial modifications must be approved by the appropriate regulatory body/ies before implementation.

13. Deviations from the CIP

Investigator(s) are not allowed to deviate from the CIP except if it is for the protection of the subject´s rights, safety, or well-being under emergency circumstances.

All deviations shall be documented with an explanation and reported to the sponsor. Deviations will be reviewed by the sponsor and reported to the appropriate regulatory bodies as required and within set timeframes.

14. Statements of compliance

14.1. Compliance to the investigational plan, good clinical practice, and regulations

The clinical investigation will be conducted in accordance with the clinical investigation plan, the ethical principles of the Declaration of Helsinki, the principles of SS-EN ISO 14155:2020 and current national and international regulations governing this clinical investigation. This is to ensure the safety and integrity of the subjects as well as the quality of the data collected.

14.2. Ethical review of the clinical investigation

The clinical investigation will commence when written approval/favorable opinion from the Applicable National Regulatory Authority has been received.

The final version of the informed consent form and other information provided to subjects, must be approved or given a written positive opinion by the National Ethical Review Authority.

The Applicable National Regulatory Authority/ies must be informed of any changes in the CIP in accordance with the current requirements.

14.3. Insurance

Swedish Patient Insurance (Patientskadeförsäkring): The Swedish healthcare regions have signed a patient insurance with Landstingens Ömsesidiga Försäkringsbolag (LÖF).

Norwegian Patient Insurance, (Lov om erstatning ved pasientskader (pasientskadeloven). Norwegian study subjects can apply from Norsk pasientskadeerstatning (NPE).

Danish Patient Insurance, (Lov om patienterstatning): Danish study subjects can apply from Danish patienterstatningen.

15. Adverse events, adverse device effects and device deficiencies

The investigational device is CE-marked and used within the intended purpose and the investigation does not include any a(29)itional invasive or burdensome procedures. As such, no specific safety reporting is required in the context of the clinical investigation.

Vigilance reporting will be handled as per each Applicable National Regulatory Authority/ies requirements.
In Sweden this is done by healthcare institutions as part of their routine health-care reporting, as well as by manufacturers according to national regulations.

In Norway this is done by healthcare institutions as part of their routine health-care reporting, as well as by manufacturers according to national regulations.

In Denmark this is done by healthcare institutions as part of their routine health-care reporting, as well as by manufacturers according to national regulations.

16. Premature termination of the clinical investigation

The sponsor may suspend or prematurely terminate either the clinical investigation at an individual investigation site or the entire clinical investigation for significant and documented reasons.
The Swedish Medical Products Agency and/or another National Regulatory Authority may suspend or prematurely terminate the clinical investigation at the applicable investigation sites.
If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the Medical Products Agency, and/or another National Regulatory Authority, the sponsor will suspend the clinical investigation while the risk is assessed. The sponsor will terminate the clinical investigation if an unacceptable risk is confirmed. In such case, the sponsor will inform all investigators.

The sponsor shall consider terminating or suspending the participation of a particular investigation site or investigator in the clinical investigation if monitoring or auditing identifies serious or repeated deviations on the part of an investigator. If the suspension or premature termination was in the interest of safety, the sponsor shall inform all other principal investigators.

If, in the opinion of the investigator, the clinical observations in the clinical investigation suggest that it may be unsafe to continue the investigation at the site, the investigator may terminate participation in the investigation after consultation with the sponsor. A written statement fully documenting the reasons for such termination will be provided to the sponsor.

If the clinical investigation is prematurely terminated, the investigators shall promptly inform the subjects and take necessary steps to finalize their engagement in the clinical investigation. The study subjects that wish to discontinue the study will have regular follow-up according to the national penile cancer guidelines.

If the clinical investigation is interrupted or terminated prematurely the sponsor or Coordinating Investigators will report to the Medical Products Agency, and/or another National Regulatory Authority, as applicable, within 15 days together with a justification. If the sponsor has temporarily halted or prematurely terminated the clinical investigation on safety grounds, the Medical Products Agency, and/or another National Regulatory Authority, as applicable, will be informed within 24 hours. A clinical investigation report will be prepared within three months of the early termination or temporary halt, irrespective of the results. If the clinical investigation is restarted within three months of the temporary halt, the sponsor does not have to submit a clinical investigation report until the clinical investigation has been completed. The final clinical investigation report shall include detail with respect to the temporary halt.

17. Publication policy

The clinical investigation will be registered in International Clinical Trials Registry Platform (ISRCTN), a publicly accessible database, before the start of recruitment activities and the content will be updated throughout the conduct of the clinical investigation and the results entered at completion of the clinical investigation.

The results from the study will be published in a peer-reviewed scientific journal one to three years after the completion of the study.

The criteria for authorship are:

- Substantial contributions to the conception or design of the study; or the acquisition, analysis, or interpretation of data
- Drafting the work or revising it critically for important intellectual content
- Final approval of the version to be published
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

18. Appendix

18.1. Lower limb volume

Only for study subjects with an office visit follow-up at the operating unit. Volume measurements of lower limbs will be measured before surgery and at the first visit at 3-5 months postoperatively and at 10-14 months postoperatively. Both limbs need to be measured. The V8 method will be used for measuring the lower limb volume. The circumference for every 8 cm of the lower limb will be measured starting 10 cm above the heel and ending near the groin. (Figure 3) Volume will be calculated as the sum of each segment using the following formula: $V = 2/3\pi \times (C_1^2 + C_1 \times C_2 + C_2^2)$ where C_1 is the previous segment circumference and C_2 is the distal circumference of the next segment (30)

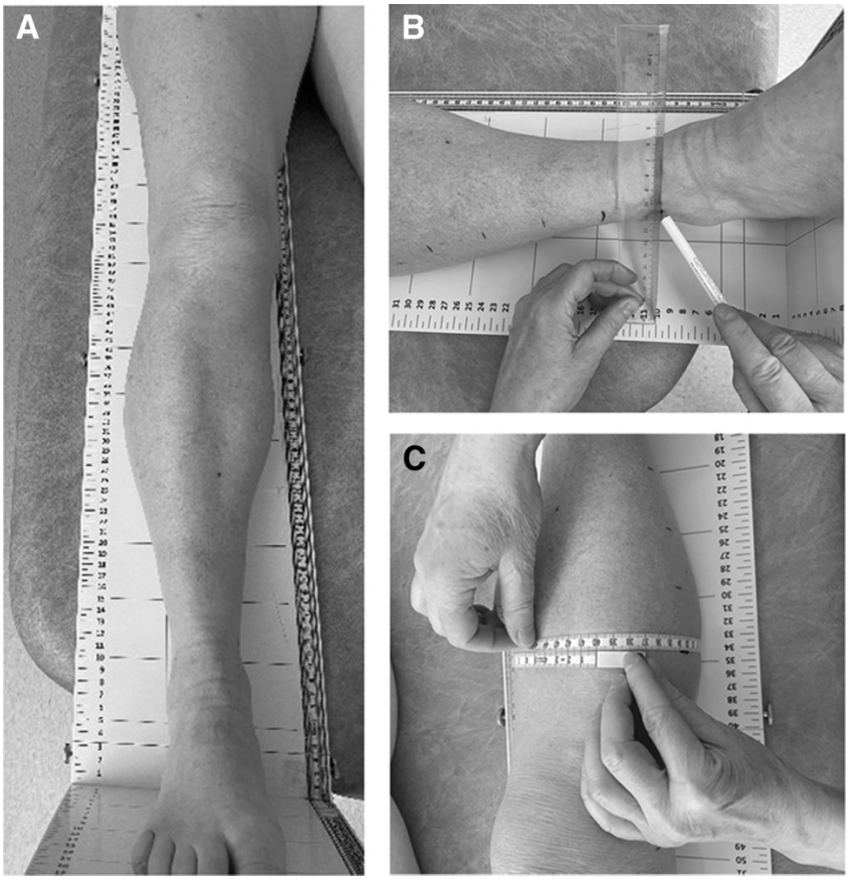


Figure 3. Lower limb measurement using the V8 method. (30)

18.2. Scrotal lymphoedema

Only for patients with an office visit follow-up at the operating unit. Measurement of scrotal volume will be performed before surgery and at the first visit at 3-5 months and 10-14 months postoperatively. The scrotal volume will be measured when the study subject is in a standing upright position and in a supine position. A caliper gage will be used to measure length (from symphysis pubis most distal part to scrotal base), width (transversal plane, largest diameter) and depth (sagittal plane, largest diameter) (Figure 4). Volume will be calculated using the formula V=length x depth x width x 0.52. (31)

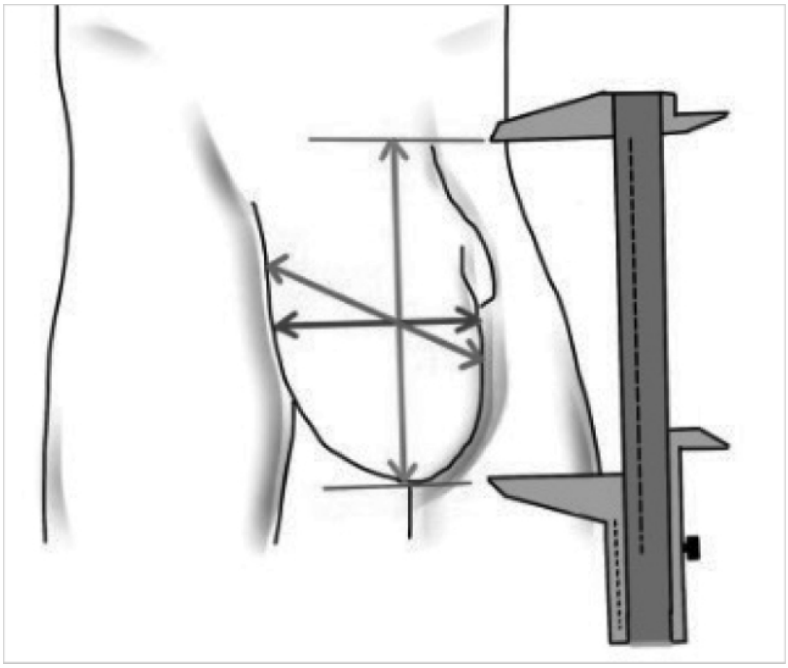


Figure 4. Volumetric measurement of scrotum using a caliper gage. (31)

18.3. European Association of Urology intraoperative adverse incidents grading

Intraoperative adverse incidents grading according to the European association of Urology (32)

Grade	Description
0	Event requiring no intervention or change in operative approach, no deviation from planned intraoperative steps, no consequence for the subject
1	Event requiring additional/alternative procedure in planned intraoperative steps, not life-threatening or involving part or full organ removal. The event was addressed in a controlled manner with no long-term side effects
2	Event requiring major additional/alternative procedure in operative approach but NOT immediately life-threatening. The event was addressed in a controlled manner, however, may have short- or long-term side effects
3	Event requiring major additional/alternative procedure in addition to planned intraoperative steps and incident becoming immediately life-threatening but NOT requiring part or full organ removal; may have short- or long-term side effects
4	Event requiring major additional/alternative procedure in addition to planned intraoperative steps becoming immediately life-threatening and with short- or long-term consequences to subject
	A. Requiring part or full organ removal
	B. Unable to complete planned procedure as planned due to a technical issue or surgical event and/or required unplanned stoma (change in body image, e.g. stoma, major skin flap)
5 A.	Wrong site or side for ablative surgery or removal of an organ or wrong subject or no consent
B.	Intraoperative death

18.4. Postoperative complications according to Clavien-Dindo (33)

Grades	Definition according to Clavien-Dindo
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anesthesia
- IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications) * requiring IC/ICU-management
- IVa	single organ dysfunction (including dialysis)
- IVb	multiorgandysfunction
Grade V	Death of a study subject

18.5. Data-points collected in the CRF

Written consent
Randomization to LS or SOC
Hospital (Bergen, Copenhagen, Malmö, Oslo, Trondheim, Örebro)
Antibiotic prophylaxis (cephalosporine, trimethoprim/sulfamethoxasole, quinolones, lincomycin, penicilline, other) and days (Single dose, one day, 10 days, other)
Trombosis prophylaxis with LMWH? 7 days, 30 days, other
Days with compression stockings (7 days, 30 days, 2 months, 6 months, other)
Class of compression stockings? I, II or III
Flat-knitted or round knitted?

Study subject ID
Age at diagnosis
Date of diagnosis of penile cancer
Congestive heart failure yes 1p/ no 0p
History of chronic obstructive pulmonary disease yes 1p no 0p.
Hypertension requiring medication yes 1p / no 0p
Diabetes mellitus yes 1p /no 0p
Totally or partially dependent preoperative functional status 1p vs independent 0p
Medications Immune modulating agents? Yes or no. if yes specify. Statins? Yes or no. if yes specify. Anticoagulation? Yes or no. if yes specify.
Smoking (number of cigarettes and years, previous smoker, never smoked)
How many years smoker, how many cigarettes per day.
ECOG 0-5
Weight, length at surgery and at every measurement of both lower limbs at 3-5 and 10-14 months postoperatively.
Pre-operative FDG-PET-CT performed (YES/NO), Number of positive inguinal lymph nodes detected by PET and inguinal side (RIGHT/LEFT)
cT-stage, cN-stage, cM-stage
Neoadjuvant chemotherapy (date start stop, number of cycles, type of chemotherapy)
Previous inguinal radiation therapy to the pelvis / groin (date, number of grey and fractions)
Previous sentinel node surgery in right groin? YES/NO
Previous sentinel node surgery in left groin? YES/NO
Follow up with office visits at the hospital in Bergen, Copenhagen, Malmö, Oslo, Trondheim or Örebro? Yes/No Preoperative
CT-scan of lower limbs and scrotum before surgery? Yes/no
If yes date YYYY/MM/DD
Scrotal volume measurements 0, 3-5, 10-14 months
Measurements of lower limbs at 0, 3-5, 10-14 months

Date of surgery
Operation time in minutes for right groin (skin incision to subcutaneous sutures, not for skin closure)
Operation time in minutes for left groin (skin incision to subcutaneous sutures, not for skin closure)
Type of penile surgery (local excision including circumcision, glansectomy, partial amputation, total amputation)

Type of inguinal lymph node dissection right side: sentinel node (sentinel node/ILND/sentinel node+ILND
Type of inguinal lymph node dissection left side: sentinel node (sentinel node/ILND/sentinel node+ILND
Pelvic LND right side?
Pelvic LND left side?
Robot assisted or laparoscopic surgery (yes/no) if yes location Inguinal DX/inguinal SIN/pelvic Dx/pelvic SIN)
Laparoscopic surgery (yes/no) if yes location Inguinal DX/inguinal SIN/pelvic Dx/pelvic SIN) Vena saphena magna ligated on the right side? (yes/no),
Vena saphena magna ligated on the left side? (yes/no),
Fossa ovale dissected on the right side? (yes/no)
Fossa ovale dissected on the left side? (yes/no),
Intraoperative bleeding in ml
Intraoperative complication classified using the EAUiaiC
Did you use any the following methods in ILND other than described on the right side?
clips yes/no if yes describe
electrocoagulation yes/no if yes describe
ligature yes/no if yes describe
other yes/no describe
Did you use any the following methods in ILND other than described on the left side?
clips yes/no if yes describe
electrocoagulation yes/no if yes describe
ligature yes/no if yes describe
other yes/no describe

Did you use LigaSure Exact Dissector in ILND on the right side?
Did you use LigaSure Exact Dissector in ILND on the left side?

What surgical equipment did you use in the right groin?
clips yes/no if yes please specify the name and manufacturer
electrocoagulation yes/no if yes please specify the name and manufacturer
ligature yes/no if yes please specify the name and manufacturer
other yes/no please specify the name and manufacturer

What surgical equipment did you use in the left groin?
clips yes/no if yes please specify the name and manufacturer
electrocoagulation yes/no if yes please specify the name and manufacturer
ligature yes/no if yes please specify the name and manufacturer
other yes/no please specify the name and manufacturer

Microscopical radical operation? (yes/no)
pTN
Number of postoperative nights at the hospital
Lymph node yield inguinal right side
Lymph node yield inguinal left side

Lymph node yield pelvic right side
Lymph node yield pelvic left side

Number of lymph nodes with cancer.
Postoperative complication 0-30 days? Yes/no
Post-operative complication according to Clavien-dindo (30 days)
Type of complication, date of complication, therapy for the complication and if the complication is related to the ILND surgery in the right groin or left groin

Post-operative complication according to Clavien-dindo (31-90 days)
Type of complication, date of complication, therapy for the complication and if the complication is related to the ILND surgery in the right groin or left groin
Daily measures of drain volume in ml
Drain removal right groin and left groin.

If the subject wears flat-knitted compression garments
If the subject wears round-knitted compression garments
Has the subject received treatment for lymphedema? Yes/no
If yes describe_____

Recurrence
Date of recurrence
Location of recurrence
Radiation therapy after surgery?
Inguinal surgery after first surgery (at randomization)?

EQ-5D-5L before surgery 3-5 and 10-14 months after surgery
LYMQOL before and at 3-5 and 10-14 months after surgery.
CT-scan of lower limbs and scrotum at 3-5 and 10-14 months postoperatively

End of study
Has the patient completed the study? Yes/no
If no: Discontinuation of the study (yes/no)
Reason for discontinuation?
Dead yes or no (date)

Extra visit
Date
Reason for patient contact?
Lower limb volume measurements
Scrotal volume measurement

Date of visit 1,2 and 3

18.6. Patient diary COMPLY

Patient diary COMPLY-study

Study-ID: _____

Drain fluid measurement

You have a drain in the groin after surgery. The drain removes drain fluid from the groin to a drain bag. Please empty the drain bag every morning and measure the amount of drain fluid that was in the bag. Please write in the list the amount of drain fluid for right and left groin. If you don´t have a drain on either left or right side you note 0 ml. Continue to measure every day until the drain is removed. Bring this form to the clinic where you were operated or send it in by mail.

Day 0 = day of surgery	Drain right side. Amount of drain fluid in ml.	Drain left side. Amount of drain fluid in ml.
Day 1		
Day 2		
Day 3		
Day 4		
Day 5		
Day 6		
Day 7		
Day 8		
Day 9		
Day 10		
Day 11		
Day 12		
Day 13		
Day 14		
Day 15		
Day 16		
Day 17		
Day 18		
Day 19		
Day 20		
Day 21		
Day 22		
Day 23		
Day 24		
Day 25		
Day 26		
Day 27		

Day 28		
Day 29		
Day 30		
Day 31		
Day 32		
Day 33		
Day 34		
Day 35		
Day 36		
Day 37		
Day 38		
Day 39		
Day 40		
Day 41		
Day 42		
Day 43		
Day 44		
Day 45		
Day 46		
Day 47		
Day 48		
Day 49		
Day 50		

Study-ID: _____

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