Title page

Near Infrared Fluorescent Technique for Sentinel Lymph Node Mapping in Endometrial Cancer

Version 1.3 170215

The study consist of two subsets of patients

-High risk endometrial cancer (HREC) in whom a full pelvic lymphadenectomy is performed after removal of sentinel lymph nodes

-Low risk endometrial (LREC) cancer or comorbid HREC in whom no further lymphadenectomy is performed after removal of sentinel lymph nodes

Hence two study protocol with different sample size analyses

Sentinel lymph node detection in high risk endometrial cancer. A prospective non-randomized trial using an anatomically based surgical algorithm.

Protocol identification number: SLN-HREC Version 1.3

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1. List of Abbreviations

AJCC	American joint committee on cancer
CT	Computerized tomography
FIGO	Int. federation of Obstetrics& gynecology
ICG	Indocyanine Green
IPP	Infundibulopelvic pathway
ITC	Isolated tumor cells
LPP	Lower paracervical pathway
SAE	Serious adverse event
SLN	Sentinel lymph node
UPP	Upper paracervical pathway
WHO	World Health Organization

2. Synopsis

Protocol Title	**Sentinel lymph node detection in high risk endometrial cancer. A prospective non-randomized trial using an anatomically based surgical algorithm.**
Indication	Endometrial cancer presumed stage I-II with high risk features defined as: Endometrioid grade 3,Endometrioid grade 1 or 2 with >50% myometrial invasion or cervical stroma invasion, Non-endometrioid histology, Non-diploid cytometry (until February 14, 2017).
Primary objective	This study aims to evaluate sensitivity and false negative rates for a pelvic sentinel node concept based on a defined surgical algorithm and with a clear definition of SLN based on uterine lymphatic anatomy.
Secondary objectives	To evaluate technical success rated including reinjection of tracer in case of non-display of a pathway. To evaluate perioperative outcomes, adverse events, postoperative complications and proportion isolated paraaortic lymph node metastases when pelvic sentinel lymph node mapping is performed
Study Design	Non-randomized controlled trial
Planned sample size	250-550 women
Inclusion criteria (all fulfilled)	-Women of age 18 years and older at the time of informed consent. -Women with a pathologically proven endometrial carcinoma of any histologic subtype, clinically stage I-II planned for primary surgery. -Women with at least one of the following preoperative high risk criteria (endometrioid cancer FIGO grade III, a non endometrioid histology, >=50% myometrial tumor invasion, cervical stromal invasion or until February 14 2017 a non-diploid cytometry). -Women must be able to understand and sign an informed consent in Swedish language. -Absence of any exclusion criteria.
Exclusion criteria (none fulfilled)	-Non-consenting patients. -Pregnancy -Inability to understand written and/or oral study information. -WHO performance status III or more. -Age > 85 years and WHO performance status II or more. -Surgical contraindication to a laparoscopic approach or lymphadenectomy at surgeon's discretion. -Anesthesiologic contraindication to a laparoscopic approach at the anesthetist's discretion.

	-Preexisting lower limb lymphedema grade II or more. -Locally advanced disease or intraabdominal/distant metastases at preoperative CT, MRI or ultrasonography. -Allergy to Iodine. -Patients with a known liver disease. -Patients with a bleeding disorder or mandatory antithrombotic treatment.
Primary outcome	The sensitivity of the sentinel lymph node specimen in women with nodes mapped by ICG. The negative predictive value of the sentinel lymph node concept in women who are mapped
Secondary outcome	Bilateral and unilateral detection rate. Sensitivity of the overall SLN concept (Defined by ICG and/or SLN Macro) Intraoperative complications (SLN procedure as such and per sub-procedure) Postoperative complications until 30 days after surgery
Standard treatment	Hysterectomy, BSO, pelvic and paraaortic lymphadenectomy and infracolic omentectomy as per national guidelines
Experimental treatment	Separate removal of sentinel lymph nodes and upper paracervical tissue before standard treatment as of above.
Duration of study	3-7 years

3. Background

3.1 Endometrial cancer and surgical staging

Minimally invasive surgery confers similar survival with lower health care costs and less perioperative complications than laparotomy in the treatment of endometrial cancer (EC) MIS is the recommended treatment modality with robot-assisted laparoscopic surgery gaining ground over traditional laparoscopy (1-4).
In endometrial cancer, nodal involvement is a strong prognostic factor and also determines the addition of adjuvant treatment. Therefore, information on nodal metastases is important and in many countries a full pelvic and paraaortic lymphadenectomy is recommended despite an increased risk for lymphatic complications in form of lymphedema, lymphocysts and in rare cases lymphatic ascites (ESMO-ESGO-ESTRO, Swedish National Treatment protocol, NVP 2012).

3.2 The sentinel node biopsy concept in endometrial cancer

Preliminary data from the department of Obstetrics and Gynecology in Lund shows that robot assisted surgery with detection of sentinel lymph nodes with the use of ICG is feasible in 84% of unselected endometrial cancer patients selected for primary surgery using the inclusion criteria in this study.
The concept of identifying nodal metastases by detection of sentinel lymph nodes as a marker of nodal metastatic disease or not therefore is appealing. However, during later years many studies have been published, most of them retrospective, using a variety of tracers and with little or no information on used surgical algorithm, used definition of SLN and without reference to lymphatic anatomy.

The bilateral technical success rate of SLN identification is important to determine if this technique can be translated to clinical practice. A clear anatomically definition of what is a SLN and a strict surgical algorithm as described in this study is important. Based on pilot studies at our institution on cervical and endometrial cancer we expect that the bilateral pelvic SLN identification (defined as at least one SLN per hemi pelvis) will be 90% or more. We intend to separately study if reinjection of ICG will enhance the bilateral detection rate. A lower bilateral detection rate will lead to the need of full lymphadenectomy in a higher proportion of patients. In the present study, including only high risk endometrial cancer patients, this has no overall clinical significance as a complete lymphadenectomy is the alternative for this group of patients. A lower than expected detection rate will therefore not be an incentive for premature stop of accrual. Importantly, accreditation of surgeons will be performed as described and is likely important to achieve a similar success rate as in pilot studies.

4. Rationale for study

Technical success rate/ SLN mapping rate varies. A high technical success rate is crucial to avoid the need for a full hemi-pelvic or pathway-wise LND in case of failure. In pilot studies from Lund University we have shown that reinjection of tracer increases the technical success rates both defined per hemi-pelvis and pathway-wise, defined by detection of at least one SLN per hemi-pelvis to at least 90%. By the use of Indocyanine green, a fluorescent tracer, we have also identified two bilateral separate pelvic pathways, the upper para-cervical pathway (UPP) running along the upper lympho-vascular parametrium usually to external iliac and/ or obturator nodes and the further lateral to the common iliac artery to paraaortic nodes and the lower para-cervical pathway (LPP) running via the sacro-uterine ligament to nodes medial of the internal iliac artery and/ or presacral nodes then further medial to the common iliac artery to paraaortic nodes. Hence there are two bilateral pelvic pathways draining further to the paraaortic region below as well as above the inferior mesenteric artery (appendix 1). Therefore, we believe that lower paraaortic SLN can only be defined in the absence of pelvic SLN along the pelvic pathways but with clear filling of pelvic lymphatic channels up to the aorta. In pilot studies at our institution we have never observed this situation. Alternatively, lymph nodes cranial of the inferior mesenteric artery but caudal of the left renal vein (infrarenal, supra-mesenteric nodes) theoretically may be dyed via the infundibulo-pelvic ligament and may then be considered as true paraaortic SLN but only in the absence of dyed node more caudally. Neither this situation has been observed after a cervical injection of tracer rarely filling the infundibulo-pelvic ligament. Moreover, attempts to find paraaortic SLN would be a step away from decreasing surgery in endometrial cancer. Although detection of pelvic SLN may miss paraaortic skip metastases we hypothesize that ultra-sectioning of SLN and including a pre-sacral dissection of SLN may decrease the incidence of true paraaortic skip metastases.

Surgical competence and experience is necessary to achieve a high technical success rate and a low false negative rate for SLN. The study setting including only high volume surgeons at two tertiary high volume centers enables an evaluation of the true potential of the pelvic SLN concept in endometrial cancer. This study aims to include consecutive high-risk endometrial cancer patients fulfilling criteria to ensure the results are representative for the endometrial cancer population.

For site accreditation and surgeons' eligibility, see section 7.5

5. Study objective

5.1 Primary objective

This study aims to evaluate sensitivity and false negative rates of the pelvic sentinel node concept based on a defined surgical algorithm and with a clear definition of SLN based on described uterine lymphatic anatomy with the use of ICG as tracer.

5.2 Secondary objectives

To evaluate the overall SLN concept based on SLN identification by ICG and intraoperative find of macroscopically cancer suspect nodes.
To evaluate if reinjection of tracer increases the bilateral technical success rate.
To evaluate perioperative outcomes, adverse events, postoperative complications and the occurrence of "isolated" paraaortic lymph node metastases when pelvic sentinel lymph node mapping is performed.

6. Study plan and design

Prospective non-randomized controlled trial, where every included woman is her own control.

Overview study plan.

Consecutive high risk endometrial cancer planned for robotic surgery, clinically with the primary tumor confined to the uterus (uterine stage I-II).
High risk defined as at least either of deep (>=50%) myometrial invasion, cervical stromal invasion, endometrioid cancer FIGO grade 3, or a non-endometrioid histology or until February 14, 2017 a non-diploid tumor.

Cervical injection of ICG

Registration of adverse events during insufflation and placement of port including necessary adhesiolysis.

Pelvic SLN identification with near infrared technique for identification of Indocyanine green (ICG) in lymphatics and lymph nodes. Ipsilateral cervical reinjection of ICG in case of non-display of any lymphatic pathway. Separate removal of the upper lymphovascular parametria. Registration of SLN- associated intraoperative adverse events.

Surgery according to the preoperative assignment:
A= primarily a full pelvic and paraaortic lymphadenectomy to the level of the left renal vein after detection of pelvic SLN
B= Due to comorbidity secondly a full pelvic lymphadenectomy after detection of SLN.
Omentectomy in non-endometrioid cancers. Registration of associated intraoperative adverse events.

A Querleu-Morrow Type A to C1 hysterectomy and bilateral adnexectomy. Registration of associated intraoperative adverse events.

SLN's for ultrasectioning and immunohistochemistry. The remaining nodes
for standard pathological bisectioning and staining with hematoxylin/Eosine.

Registration of postoperative adverse events until 30 days after surgery using the Clavien Dindo classification.

Continuous data management. Interim analysis of sensitivity and false negative rates for SLN's after 50 ICG mapped pelvic node positive patients (see section 11).

7. Study treatment

7.1 Overview treatment

- Intraoperative cervical injection of ICG (immediately before onset of surgery)

- Intraoperative lymphatic mapping and sentinel node identification with robotic Near Infrared fluorescence imager will be used for an initial transperitoneal, then retroperitoneal evaluation of display of ICG fluorescence. The retroperitoneal dissection with opening of the avascular planes saving the lymphatic vessels will start pre-sacrally then further with the pelvic side walls. The upper lympho-vascular parametria will be kept intact by a careful opening of the para-rectal and para-vesical spaces.
- An ipsilateral reinjection of ICG will be performed in case of non-display of either of UPP or LPP. If the sentinel node cannot be identified in a particular pathway following a minimum of 10 minutes search, the case should be described as a ICG-negative mapping event for that pathway.
- The results of the lymphatic mapping will be marked on the anatomic plan and the specimens and labeling of those will be according to descriptions above.
- The complete SLN algorithm should be adhered to, i.e. in case of a ICG negative mapping (for **SLN type 1 and 2**) any macroscopic nodes suspicious for metastases should be removed and regard as **SLN macro**. All patients will be subject for at least a full pelvic lymphadenectomy after removal of SLN.
- The upper lympho-vascular parametrial tissue (the tissue medial of the obliterated umbilical artery, with the supra-vesical artery as distal/ventral border, the ureter as dorsal border and including tissue adjacent to the inner side of the broad ligament) will be removed and evaluated the same way as SLN's. This is to investigate the presence of lymph node in the upper parametria, theoretically the most juxtauterine nodes, hence the SLN. A separate dissection of potential nodes in the parametrial tissue is often difficult as most of the tissue is ICG positive.
- A full pelvic and paraaortic lymphadenectomy will be performed after identification of SLN's. To evaluate a potential occurrence of paraaortic SLN the infrarenal paraaortic lymphadenectomy will be performed with regards to definitions of potential paraaortic SLN's as of above.

- A Querleu-Morrow type B1 or C1 hysterectomy as appropriate with primarily a paraaortic lymphadenectomy to the level of the left renal vein or a full pelvic lymphadenectomy.
- All SLN and the upper parametrial tissue will be subject for ultra-sectioning and Immunohistochemistry at the histopathologic evaluation.

- Frozen section of the SLN will not be performed.

- Complications will be recorded and to enable association with parts of the procedure, most importantly, the SLN procedure as such and the lymphadenectomy, will be subdivided as described above. The classification described under the adverse events tables will be used.

- NOTE: Site accreditation and surgeon's skill and adherence to protocol will be verified as described. See section 7.5.

7.2 Standard treatment

7.2.1 Surgical Procedures

- Patients with endometrial cancer presumably stage I will undergo detection of pelvic SLN with fluorescent technique followed by a pelvic and paraaortic lymphadenectomy to the level of the left renal vein. A Querleu-Morrow type B1-CI hysterectomy with a bilateral salpingoophorectomy will be performed. An infracolic omentectomy will be performed in women with a non-endometrioid histology.
- Robot-assisted laparoscopy will be used.

7.2.2 Definition of anatomical boundaries for pelvic and paraaortic lymphadenectomy

Anatomical boundaries of lymph node compartments in the female pelvis				
Lymph node compartment	**Cephalad limit**	**Lateral limit**	**Caudad limit**	**Medial limit**
External iliac area	Bifurcation of external and internal iliac artery	Genitofemoral nerve	Cloquet's lymph node	External iliac vein
Obturator fossa	Internal iliac vein	Ileopsoas muscle	Os pubis, obturator nerve	Obliterated umbilical artery

Common iliac	Aortic bifurcation	Genitofemoral nerve	Bifurcation of external and internal iliac artery	Common iliac artery
Presacral	Aortic bifurcation	Common iliac artery	Lower promontory	Hypogastric nerve (as distinction between right and left)
Lower paraaortic	Inferior mesenteric artery	Ureter	Aortic bifurcation	
Higher paraaortic	Left renal vein	Ureter	Inferior mesenteric artery	

7.3 Intervention

7.3.1 Indocyanine green, dilution, dose and injection

7.3.1.1 Drug Information

Indocyanine Green solution (ICG) 2.5mg/mL.
Description: ICG (Pulsion medical system, PICG0025SE, Feldkirchen Germany) is a sterile, lyophilized green powder containing 25 mg of Indocyanine green with no more than 5% Sodium Iodide.
The ICG solution is prepared immediately before surgery and intended for single patient use. For preparation, 10mL of sterile water is injected directly into the lyophilized ICG in its glass vial. Invert the vial multiple times to ensure thorough mixing. Draw up 0,25 mL in six 1 mL syringes from the vial with ICG solution (2,5mg/mL) for the cervical injection. A 0.6x38mm 23Gx1 ½ needle. The content of four of the syringes are used for the initial injection and in case of non-display of any pathway one or two of the other are used for an ipsilateral re-injection.
The ICG solution is stored at room temperature. The solution is active for 6 hours, and should be discarded after that period of time.
Manufacturer: Pulsion medical system, Feldkirchen Germany
Availability: ICG will be provided by the manufacturer to each site.

Adverse Effects if ICG: All adverse effects are allergic in nature and occur in <1% of patients. Anaphylactic or urticarial reactions have been reported in patients with or without a history of allergy to iodides. If such reactions occur, treatment with the appropriate agents (e.g. adrenalin, antihistamines, corticosteroids) should be initiated.
Contraindications: Known hypersensitivity to iodine containing compounds. Known liver failure. Radioactive iodine uptake studies should not be performed for at least 1 week following the use of ICG.

Please refer to the current ICG package insert for complete prescribing information

7.3.1.2 Injection of Indocyanine Green (ICG)

- The ICG is prepared by thorough mixing of 10mL of sterile water with the lyophilized ICG in its vial creating a 2.5mg/mL concentration. The lot number, expiration date and dose injected (mg) will be recorded.
- Six separate sterile 1mL syringes is prepared with 0.25 mL ICG solution (0.625 mg ICG) in each syringe is prepared.
- A 0.6x38 mm 23G needle is attached to each syringe for the injection. A separate back table is used for the syringes.
- The ICG injection will be performed immediately before placement of surgical port and docking the robot.
- Half the ICG volume in each syringe is injected sub-mucosally and half the volume 3 cm into the cervical stroma at 2-4-8-and 10 O'clock respectively to a total dose of 2.5mg ICG and a total volume of 1 mL. Time for injection is recorded.
- After injection of dye, a fornix presenter without an intracervical device is placed
- A second ipsilateral injection of 0,25mL ICG is performed in case of non-display of either of the upper (UPP) or lower (LPP) paracervical pathways after a minimum of 10 minutes' observation time after ICG injection. The injection is done at 3 and 9 O'clock respectively, half the volume submucosally and half the volume 3 cm into the cervix.
- Display of the separate lymphatic pathways (UPP, LPP and IPP will be recorded after the first and if performed after the second injection).

7.3.2 Sentinel Node Identification

- Dissection for detection of SLN's will start with the cranially with pre-sacral area (along the LPP) to prevent disturbance from leaking ICG, thereafter, following opening of the avascular paravesical and pararectal planes to isolate the upper paracervical pathway.
- The described procedures in this protocol will be performed with robot-assisted laparoscopy.

The sentinel nodes are defined as the juxtauterine ICG positive node with an afferent ICG positive lymphatics in each of the UPP and LPP respectively on each pelvic side with the potential of parallel lymphatics in the UPP to the external and obturator areas. These SLN are defined as **SLN type 1.**
In case of a ICG positive lymph vessel where no nodes are ICG positive in that pathway, the node where the ICG positive lymphatic channel ends is defined as **SLN type 2**.
Nodes macroscopically suspect of metastatic disease will be defined as **SLN Macro** regardless of ICG uptake but be defined as ICG positive or negative as appropriate.
Importantly, to secure accuracy, the positions and types of SLN will be marked on an anatomical chart, recorded on a list with anatomical locations and placed in pre-labeled jars with corresponding anatomical positions and numbers. This list is used by the department of pathology for reporting the results to minimize the risk of errors in location of nodes and which nodes are SLN's and non-SLN's. A copy of the list is kept in the patients study file. Nodes defined as SLN will have red labels on the jars, other nodes will have black labels. (Appendix 2)
SLN's will be sent for final histological evaluation including ultrasectioning and immunohistochemistry as described. SLN's will not be sent for frozen section unless clinically motivated.

For the pelvic SLN concept, ideally one SLN should be identified per LPP and UPP per pelvic side wall.

The display of ICG in the respective pathways will be evaluated a minimum 10 minutes after the injection of ICG, first transperitoneally, and if not seen, after opening of the retroperitoneal avascular planes starting with the presacral plane, then the paravesical and pararectal planes leaving the lymphatics intact with the aid of switching between white light and the ICG mode (Firefly mode). In case of non-display of a pathway an ipsilateral injection of ICG as described will be performed. Another 10 minutes will be allowed for awaiting distribution of ICG in the respective pathways. To minimize disturbance by leaking ICG identification and removal of SLN's starts cranially, presacrally (along the LPP) and continues at the pelvic side walls along the UPP. After removal of SLN's the upper lymphovascular parametrial tissue is removed separately (defined as the tissue along the uterine artery, medial to the obliterated umbilical artery and caudal of the supravesical artery) as it may contain lymph nodes that may not be separated from the green lymphovascular tissue and hence be the juxtauterine lymph node.
After removal of sentinel nodes, a complete compartment-wise pelvic and paraaortic lymphadenectomy is performed followed by the hysterectomy.

7.3.2.1 Identification and definition of potential paraaortic SLN's.

During the paraaortic lymphadenectomy, situations where paraarotic SLN's theroretically can be defined are looked for. These situations are:
1. ICG positive supramesenteric lymph nodes without ICG positive nodes in the inframesenteric area, i.e nodes dyed directly and solely via lymphatics in the infundibulopelvic ligament.
2. In case no pelvic SLN's are identified and inframesenteric ICG positive nodes are present the most caudal of the inframesenteric ICG positive nodes on the right and left side will be considered paraaortic SLN's. See Appendix 2. Anatomic plan for localization of sentinel lymph nodes.

7.4 Treatment modifications

In case of no ICG uptake (including reinjection according to protocol) the SLN algorithm should be followed, i.e. removal of any macroscopically suspect nodes (marked as SLN macro) and as planned a full compartment-wise lymphadenectomy.
As the national protocol for high risk endometrial cancer recommends a full paraaortic and pelvic lymphadenectomy no patient will be subject for lymphadenectomy beyond the guidelines.

In case of conversion to open surgery before identification and removal of SLN's the patients should be included in evaluation of adverse events and feasibility on an intention to treat basis but not included in the calculation of sensitivity and negative predictive values for the sentinel node concept.

7.5 Participating surgeons

All included surgeons outside the primary investigating center must have had a case observation at the primary investigating center followed by an approved site visit by the principal investigating surgeon at their home center ensuring adherence to protocol. All included surgeons at the primary investigating center were approved by the principal investigating surgeon.
All included surgeons must have a previous experience of at least 100 robot assisted procedures.

8. Evaluation of histopathology

8. 1 Histopathologic evaluation of the sentinel nodes

All macroscopically identified SLN lymphoid tissue will be embedded and bisected if the minimum thickness exceeded 3 mm. If no macroscopically lymphoid tissue is identified in SLN or parametrial tissue the most suspicious find will be embedded and microscopically investigated. Ultrastaging using hematoxylin/ Eosin staining will be performed in five sections at three different levels, separated by 200 µm, if the maximum diameter of the SLN tissue exceeds one mm. From first and second level immunohistochemistry (pan-cytokeratin, MNF 116) will be performed. If no macroscopically lymphoid tissue is identified in SLN or parametrial tissue the most suspicious find will be embedded and microscopically investigated. ITC can be detected by Hematoxylin/Eosin or by Immunohistochemistry alone.

8.1.2 Classification of tumor size in SLN's

Sentinel nodes will be classified according to a modification of the AJCC staging for axillary nodes from breast cancer as follows:
Macro metastases = tumor greater than 2.0 mm in diameter.
Micro metastases = tumor cell aggregates between 0.2 and 2.0 mm in diameter.
Isolated tumor cells =individual tumor cells or aggregates that are less than 0.2mm in diameter, usually detected by immunohistochemistry.
Tumor absent – no tumor cells identified in H&E (or immunohistochemically, if applicable) stained sections.

8.2 Histopathologic evaluation of the non-sentinel nodes

Non- SLN nodes less than 3 mm in thickness will be embedded whole, and from nodes thicker than 3 mm at least half the node will be embedded. The slides will be evaluated after hematoxylin/Eosin staining.

Non-sentinel lymph nodes will be reported as positive or negative for metastases based upon routine sectioning and examination of a single H&E stained section.

9. Outcomes

9.1 Primary outcome

The sensitivity, negative predictive value and false negative rates of the sentinel lymph node procedure in women with SLN nodes mapped by ICG in at least one SLN (per patient analysis).

9.2 Secondary outcome

The sensitivity, negative predictive value and false negative rates of the sentinel lymph node concept in women SLN mapped by ICG and /or defined as SLN macro (the overall SLN concept, per patient analysis)
Sensitivity of SLN defined by ICG per lymphatic pathway.
Bilateral and unilateral detection rate including reinjection of ICG.
Intraoperative complications.
Postoperative complications until and including 30 postoperative days.
The occurrence of paraaortic skip metastases

10. Patient enrollment

Consecutive women with high risk endometrial cancer will be screened for eligibility. Both participating sites are tertiary referral centers within a public health care system.

10.1 Inclusion criteria

- Women of age 18 years and older at the time of informed consent.
- Women with a pathologically proven endometrial carcinoma of any histologic subtype, clinically stage I-II planned for primary surgery
- Women with at least one of the following preoperative high risk criteria (endometrioid cancer FIGO grade III, a non endometrioid histology, >=50% myometrial tumor invasion, cervical stromal invasion or until February 14 2017 a non-diploid cytometry)
- Women must be able to understand and sign an informed consent in Swedish language.
- Absence of any exclusion criteria

10.2 Exclusion criteria

- Non-consenting patients
- Pregnancy
- Inability to understand written and/or oral study information
- Who performance status III or more
- Age > 85 years and WHO performance status II or more
- Preexisting lower limb lymphedema grade II or more

- Surgical contraindication to a laparoscopic approach or lymphadenectomy at surgeon's discretion.
- Contraindication to a laparoscopic procedure at the anesthetist's discretion
- Locally advanced disease or intraabdominal/distant metastases at preoperative CT, MRI or ultrasonography
- Allergy to Iodine
- Patients with a known liver disease
- Patients with a bleeding disorder or mandatory antithrombotic treatment.

10.3 Schedule of events table/ checklist

Procedures	Screening	Enrollment/ Baseline	Surgery-ICG SN/postoperative parameters	Final histology Lgll/inner gen. 4 weeks postop
Medical History routine	**X**			
Gynecologic History routine	**X**			
Physical Exam routine	**X**			
CT abdomen/chest evaluation	**X**			
MRI/US evaluation	**X**			
"High risk endometrial cancer"	**X**			
Informed consent oral		**X**		
Informed consent written		**X**		
Enrollment		**X**		
Preop CRF		**X**		
Surgery with ICG			**X**	
Perop CRF			**X**	
Specimens from surgery sent and answered by pathologist as per protocol			**X**	**X**
Postop CRF/including 30 day morbidity			**X**	**X**

11. Evaluation criteria

- Patients with at least one SLN identified will be included for determining the sensitivity and the negative predictive value of the SLN ICG concept (SLN type 1-2) and the overall SLN concept (type 1-2 and macro)

- All patients who are injected with ICG and not converted to open surgery before detection and removal of SLN's will be included for evaluation of technical success rate (described per patient, per hemi pelvis and per separate pathway) after first and in case of non-display of any of the LPP and UPP after reinjection of ICG as described.

- All patients included, regardless of conversion to open surgery and mapping of ICG will be included in the overall evaluation of feasibility and safety.

- Intraoperative adverse associated with the detection and removal of SLN will be evaluated and reported separately as well as adverse events related other sub procedures during the operation on all patients who have at least one SLN removed regardless of type, i.e all patients in whom SLN were removed separately.

- Postoperative complications until 30 days after surgery will be reported using the Clavien Dindo classification.

12. Adverse events

The study protocol has been revised related principles for study monitoring and for reporting adverse events to the principal investigating centre after inclusion of the second centre.

12. 1 Definitions

An adverse event (AE) is any new medical problem or exacerbation of an existing problem experienced by a subject enrolled in the study, whether or not it is considered drug-related by the investigator. (Appendix 3)

This study will utilize the Adverse Events Logs (Tables 10.1-5). Any SAE will be reported to the study coordinator (Michele.bollino@med.lu.se) using the SAE log. (appendix 4).

Adverse events related to the study drug (ICG).
All adverse events occurring from the first dose of study drug until hospital discharge (whether or not attributed to the study drug) will be reported on the Adverse Event Log. In addition, any adverse event reported by the subject to the investigator after discharge and determined to be reasonably associated with the study drug should also be captured and followed until resolution.

Adverse events related to the sentinel node procedure as such (excluding AE related the study drug, ICG)
All intraoperative events related to the SLN procedure will be reported on the adverse events log.

Adverse events related the surgical procedure (excluding the SLN part) including AE until 30 postoperative days.
All adverse events will be reported on the adverse events log.

Serious adverse event (SAE):
An adverse event that results in one or more of the following:
-Any death occurring until and including 30 postoperative days
-Any life-threatening event until and including 30 postoperative days.
-Any medical event requiring inpatient hospitalization or prolongation of existing hospitalization beyond five postoperative days

NOTE: Hospitalizations that are not considered SAE are:
-Hospitalization planned prior to first administration of study drug
-Hospitalization for elective treatment of a pre-existing condition unrelated to the study medication
- Hospitalization due to social / practical reasons such as an untimely coordination with local community home care services.

Attribution: Attribution is the determination of whether an adverse event is related to a medical treatment or procedure. The categories of attribution are:

Definite: The adverse event is clearly related to the study drug/intervention
Probable: The adverse event is likely related to the study drug/intervention.
Possible: The adverse event may be related to the study drug/ intervention
Unlikely: The adverse event is doubtfully related to the study drug/ intervention
Unrelated: The adverse event is clearly NOT related to the study drug/intervention

Unexpected Adverse Event: An unexpected adverse event is an event not mentioned in the package insert/ manufacturer's instructions or the specificity or severity of which is not consistent with the package insert/ manufacturer's instructions.
The grading described beneath and the attribution described above will be used for cathegorization of unexpected adverse events.

Reporting to the IRB:
Each participating center will report adverse events to their IRB per local guidelines.

Coordinating Center Reporting Responsibilities

Reporting to the study coordinator, Lund University Hospital
Same criteria as above.

Reporting to the IRB:
Same criteria as above.

The Study Coordinator will distribute reports which are serious, unexpected and associated with the study intervention (possibly, probably or definitely) to all participating investigators. Copies of all serious adverse event reports will be kept on file the department of Obstetrics and Gynecology, Lund University Hospital.

The study coordinator will also report all individual SAE's related to study drug, the sentinel node procedure as such, are life threatening or resulting in death (defined above and in table 10.6) to the Safety Monitoring Committee (SMC) for clinical studies at the respective hospital (Skåne University Hospital and Karolinska University Hospital) for an independent evaluation.

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the SMC. Alternatively, the SMC may initiate suspension or early closure of the study based on its review of the investigator reports.

13. Study Monitoring / study accrual oversight

The study principal investigator, local principal investigator and study coordinator will conduct meetings (teleconferenced) every 6 months to discuss the protocol. The s-PI and l-PI can call a meeting to convene at additional times if deemed necessary, for example following statistical review at the interim period if stopping the study for either achieved goals or futility. Apart from the monitoring described below, the number of node positive patients and potential false negative SLN's will be monitored continuously by e-mail to the study coordinator by the use of the study number assigned to each patient.

In case of identified inconsistencies or missing data, additional source documents (identified only by unique patient number) will be requested from the site to resolve ongoing inconsistencies.

The principal investigator and/or the study coordinator will, if deemed necessary by the principal or second participating center perform audits of informed consents and subject eligibility.

13.2 Duration of study

The study was initiated at Lund university hospital (From June 2014) with a later inclusion of the second investigating center (Karolinska University Hospital, from February 2017) motivating a revision of the study protocol related estimated time for enrollment of patients and for accreditation of the second centre and its surgeons.

Assuming that the prevalence of lymph node metastases is 20% in high risk endometrial as defined above 250 patients will be needed to obtain 50 lymph node positive observations. Given a 95% bilateral detection rate of ICG positive SLN's approximately 15 patients more will need to be included. On the other hand, ultrasectioning and IHC of SLN's may increase the proportion of patients with nodal metastases by identifying micro metastases. As there will be a continuous report of ICG mapped pelvic node positive patients to the study coordinator an interim analysis will start after 50 such patients regardless of the total number of patients included (see 11, statistical considerations). Accrual will not be suspended during the interim analysis as the intervention is estimated to pose minimal risk to patients and the national treatment protocol, recommending a full lymphadenectomy, will be followed, even in the event of futility.
If the trial continues to stage 2, another 300 patients will be required. (see 15, statistical considerations)
Given an estimate that the accrual rate is five high risk patients per month per center (each of Lund University Hospital and Karolinska University Hospital) and the fact that the second center started inclusion later, a total of 46 months (calculated from June 2014) will be required to reach 250 high risk endometrial cancer and a total of 30 additional months to reach 550 high risk patients.

14. Data Management

Preoperative, intraoperative and postoperative data from each surgery will be recorded on standardized study sheets available to each study site. Each study site will be allocated a study number which will serve as the prefix to the case number. For example, Lund university Hospital will be allocated the prefix "Lu" and the first study patient will have the study number "Lu-001. Each investigating center will hold a record with the full identification of patients whereas data otherwise should only identify the patient by the study number (see above).
Staff at the individual centers will be responsible for completing the data collection sheet for each patient and all data will continuously and all be entered into a common secured web-based database (https://data.dynareg.se/slnicgec) using the designated study numbers. Upon interim analysis, the full data will be monitored by the study coordinator, the principal investigator, local principal investigator and study statistician.
Separate analysis of patient data from individual sites can only be performed with the written permission of the study principal investigator (Jan Persson).

14.1 Early Study Closure

Death will be reported according to section 10.1 above and per local IRB reporting guidelines. The SMC will review all reported deaths monthly. Early closure of the study will be based on judgement of the SMC.
The study will be stopped for futility reasons as described under the statistics section.

14.2 Protocol Deviations

Major protocol deviations shall be reported by mail to the study coordinator. Michele.bollino@med.lu.se and filed at Lund University Hospital using the designated study number. Major protocol deviations include, but are not limited to, violations to inclusion/ exclusion criteria, erroneous preparation of ICG or surgery by a non-accredited surgeon.

15. Statistical considerations

This study is designed to evaluate the application of the sentinel node (SLN) technique in determining the lymph node (LN) status in patients with high risk endometrial cancer
The main statistical endpoint will be sensitivity and false negative rates /negative predictive value. The sensitivity is the proportion of patients who test as SN (+) among the patients who have LN metastases (LN+). The patients will, according to the Swedish national guidelines for high risk endometrial cancer undergo a full infrarenal paraaortic and pelvic lymphadenectomy, however with separate removal of SLN as defined above, hence serve as their own controls. As lymph node status (lymph node metastases or no lymph node metastases) is a definite parameter (false positive result can by definition not occur) specificity and positive predictive values will not be reported in this study.
The final sample size analysis was performed after one year inclusion of patients as the bilateral detection rate of SLN (including reinjection of ICG if necessary) initially was not known. The time for accrual was revised after inclusion of the second participating center.

We used the Fleming two stage design for evaluation of study termination (Fleming, 1982).
The null hypothesis that the sensitivity is 85% will be tested against one-sided alternative.
The study is terminated after stage one if it is unlikely that the sensitivity is $\geq 92.5\%$ or if sensitivity is significantly higher than 85%. In the first stage, 50 LN+ patients with at least one pelvic SLN defined by ICG will be accrued. If there are 43 or fewer responses in these 50 patients, the study will be stopped for futility. If there are at least 48 responses in 50 patients, the study will be stopped and the null hypothesis rejected. Otherwise, 69 additional patients will be accrued for a total of 119 node positive patients. The null hypothesis will be rejected if 108 or more responses are observed in 119 patients. This design yields a type I error rate of 0.05 and power of 0.8 when the true sensitivity is 92.5%.
For the first stage, we estimated a total of 250 patients to be included taking into consideration a 95% bilateral SLN detection rate, and an estimated 23 % rate of node positivity including an increase in node positivity rates due to ultra-sectioning and immunohistochemistry. For the second

stage, another 300 patients have to be included. As the number of node positive patients will be reported continuously to the study coordinator this will be decisive of the number of patients that has to be included for each stage.

16. Ethical considerations

16.1 Informed consent

Before inclusion in the study, patients will be given oral and written information in Swedish of the study aims, all treatment procedures and expected and possible adverse events see. They will be informed as to the strict confidentiality of their patient data, and that their medical records will be reviewed by their treating physician and personnel only. The patient is at any time, with or without given reason to do so, free to withdraw their consent to study participation, and this choice will not affect their subsequent treatment options or care. A copy of the signed informed consent will kept in the study file.

16.2 Patient protection and Good Clinical Practice

The responsible investigator will ensure that the study is conducted in agreement with the declaration of Helsinki and/or Swedish laws and regulations; whichever provides the greatest protection for the patient. Participating women will be treated according to the international guidelines on GCP

16.3 Subject identification

Participating patients will be identified by a study specific code consisting of the patient's initials and the investigating site, followed by a three-digit number. This code will be used when transfer of data into the study database. The woman's national identification number will not be entered into the database. The key to the code will be available to the investigator only.

17. Trial sponsor and financing

This is an academic study sponsored by the investigator, Skåne County Council, Skåne University Hospital Donations fund, Sweden, and Radiumhemmets Research funds, Sweden, with no involvement of any external sponsor.

18. Publications

All study data belong to the investigators. It is the intention to publish the results in a scientific journal. Co-authorship and the listing of authors' names are determined by the investigators.

19. Approvals

The study, patient information and informed consent must be approved by each participating site's regional ethics committee before any patients are enrolled.

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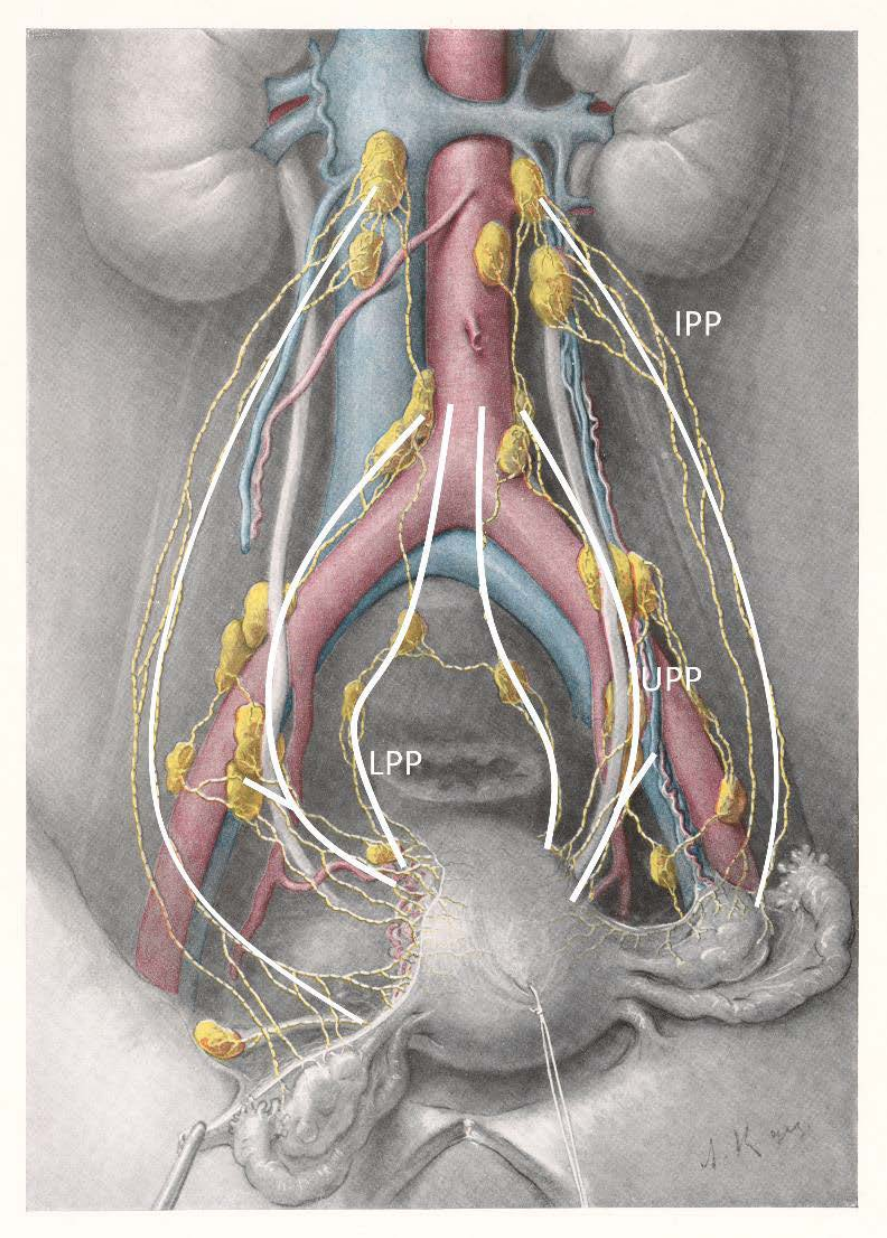
21. Appendices

Appendix 1. Anatomic description of lymphatic pathways draining the uterus



The upper paracervical pathway (UPP) follows the uterine artery to the pelvic side wall draining primarily to the external iliac and obturator nodal compartments, then running lateral to the common iliac artery further to the paraaortic area.

The lower paracervical pathway (LPP) follows the ventral rim of the sacrouterine ligament, primarily to internal iliac and presacral nodes, then running medial of the common iliac artery further to the paraaortic area.

The infundibulopelvic ligament pathway (IPP) runs via the Ip-ligament further to the supramesenteric paraaortic area.

Assuming that lymph runs from the uterus and then cranially, supramesenteric paraaortic true SLN's logically can only be defined when inframesenteric lymph are not ICG positive: Theoretically this may occur in situation when no pelvic nodes are dyed or when ICG have dyed pelvic nodes but not have been distributed further to the inframesenteric node, i.e that ICG goes directly to the supramestenteric nodes via the IP-ligament.
Alternatively, when inframesenteric paraaortic nodes are ICG positive via the UPP and /or the LPP but no pelvic nodes in these pathways are dyed.

For the pelvic SLN concept, ideally one SLN should be identified per LPP and UPP per pelvic side wall.

Appendix 2. Anatomical plan for localization of sentinel lymph nodes/ list of nodal specimens.

Injection site of ICG ☐ cervix

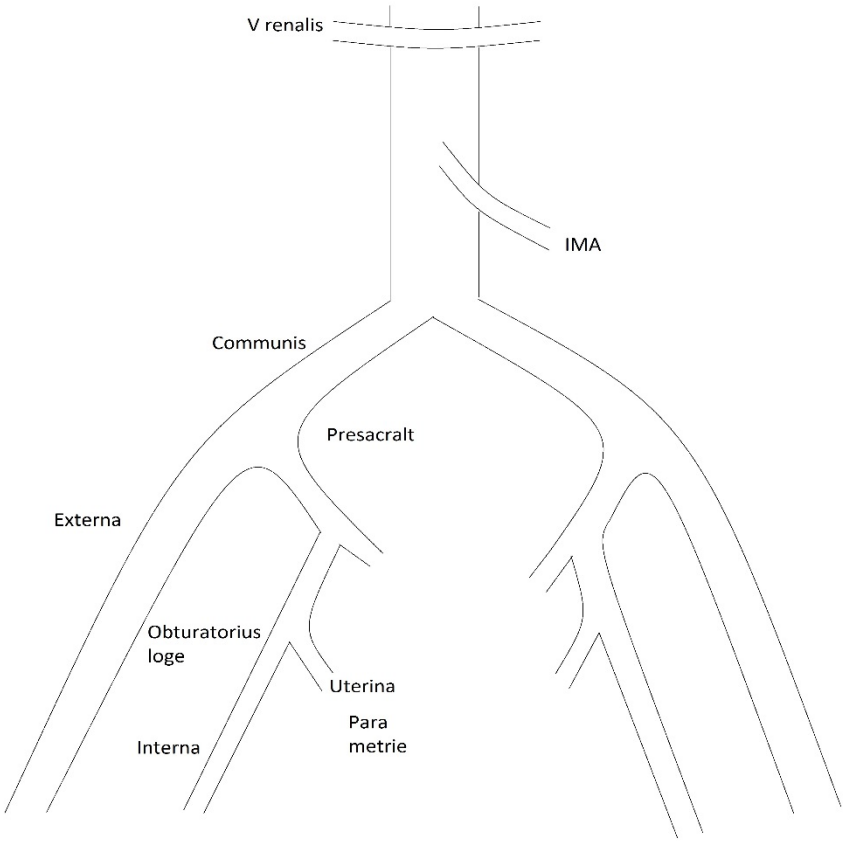
Reinjection cervix: ☐ yes ☐ no

Display after first injection

	UPP	LPP	IP-ligament
Right			
Left			

Display after second injection

	UPP	LPP	IP-ligament
Right			
Left			



Mark position and type of SLN on anatomical chart with number corresponding to position and number at list and on separate jars for each SLN.

O = ICG positive juxtauterine Sentinel node **(SLN1**)

☐= ICG neg juxtauterine lymph node with afferent lympahtic vessel **(SLN 2)**

X = Tumor suspect lymph nodes regardless of mapping **(SLN makro)** but with information on ICG positivity or not.

List of nodal specimens (swedish) Endometrial cancer pat-id date

m preparat saknas från station stryks raden i listan. Burknumrering behålls för övriga prep.

KK Burk nr	Körtelposition	Patol burk nr	Dosa nr	Antal bitar	Mikro Antal körtlar	Varav med metast
1	Uterus, höger ovarium & tuba, vänster ovarium & tuba					
2	Lgl Iliaca Externa höger ICG NEG					
3	Lgl Iliaca Externa höger ICG POS					
4	Lgl Obturatorius höger ICG NEG					
5	Lgl Obturatorius höger ICG POS					
6	Lgl Iliaca Communis höger ICG NEG					
7	Lgl Iliaca Communis höger ICG POS					
8	Lgl Presacralt höger ICG NEG					
9	Lgl Presacralt höger ICG POS					
10	Lgl Iliaca Externa vänster ICG NEG					
11	Lgl Iliaca Externa vänster ICG POS					
12	Lgl Obturatorius vänster ICG NEG					
13	Lgl Obturatorius vänster ICG POS					
14	Lgl Iliaca Communis vänster ICG NEG					
15	Lgl Iliaca Communis vänster ICG POS					
16	Lgl Presacralt vänster ICG NEG					
17	Lgl Presacralt vänster ICG POS					
18	Lgl Paraaortalt nedom IMA ICG NEG					
19	Lgl Paraaortal nedom IMA ICG POS					
20	Lgl Paraaortal ovan IMA ICG NEG					
21	Lgl Paraaortalt ovan IMA ICG POS					
22	SLN Parametrium höger					
23	SLN Parametrium vänster					
24	SLN typ 1 presacralt höger					
25	SLN typ 1 presacralt vänster					
26	SLN typ 1 iliaca externa höger					
27	SLN typ 1 obturatorius höger					

28	SLN typ 1 iliaca externa vänster					
29	SLN typ 1 iliaca obturatorius vänster					
30	SLN typ 1					
31	SLN typ 1					
32	SLN typ 2					
33	SLN makro					
34	SLN makro					
35						

Numbers 30-34 will be used for describing locations outside the most common sites and for SLN type 2 and SLN macro as appropriate. The locations will be written by hand on list and labels for jars.

Appendix 3. Adverse events details/ descriptions logs.

Intraoperative adverse events will be graded according to the following scale

Grade	Description
Grade 1	Mild; asymptomatic; not interfering with function.
Grade 2	Moderate; symptomatic; interfering with function but not ADL; medical intervention indicated.
Grade 3	Severe; symptomatic; interfering with ADL; operative intervention indicated; IV intervention indicated
Grade 4	Life-threatening; major urgent intervention indicated; disabling.
Grade 5	Death

Postoperative adverse events will be graded according to the Clavien Dindo classification

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 transfusionsand total parenteral nutritionare 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 patient

A. Adverse Events before docking the robot (during injection of ICG, insufflation, port placement and adhesiolysis) including conversions to open surgery.

STUDY NUMBER	AE/SAE	DESCRIPTION	Grade	Attribution
Example LU:019	AE	Converted, disseminated disea	1	No
Example KS :020	AE	Converted massive adhesions	1	

B. Adverse Events during sentinel node dissection

STUDY NUMBER	AE/SAE	DESCRIPTION	Grade	Attribution
LU019 examples	AE	Bleeding requiring suture	2	
KS020	AE	Obturator nerve damage	3	

C. Adverse events during completory pelvic/ pelvic + paraaortic lymphadenectomy

STUDY NUMBER	AE/SAE	DESCRIPTION	Grade	Attribution
LU019 examples	AE	Bleeding requiring suture or	2	
KS020	AE	Obturator nerve damage	3	

D. Adverse events during hysterectomy / omentectomy.

STUDY NUMBER	AE/SAE	DESCRIPTION	Grade	Attribution
LU019 examples	AE	Ureteral damage	3	
KS020	AE	Bowel damage	3	

E. Postoperative adverse events until 30 postoperative days (all events, also potentially unrelated)

STUDY NUMBER	AE/SAE	DESCRIPTION	Grade	Attribution
LU019 examples	AE	Port hernia	3	
KS020	AE	Fever of unknown origin	2	

Appendix 4. Serious adverse events log. (one per patient)

Mail to Michele.bollino@med.lu.se

Per definitions of SAE and attributions as outlined in protocol

Attribution: Attribution is the determination of whether an adverse event is related to a medical treatment or procedure. The categories of attribution are:

Definite: The adverse event is clearly related to the study drug/intervention
Probable: The adverse event is likely related to the study drug/intervention.
Possible: The adverse event may be related to the study drug/ intervention
Unlikely: The adverse event is doubtfully related to the study drug/ intervention
Unrelated: The adverse event is clearly NOT related to the study drug/intervention

Patients study number **Date for SAE**		
Type of SAE	**Yes /no**	**Attribution**
Death		
Life Threatening		
Drug /ICG related		
Intraoperative related the SLN procedure as such		
Intraoperative related the full LND/ hysterectomy		
Postoperative		
Unexpected AE		

Description / outcome of the SAE

Serious adverse event (SAE):
An adverse event that results in one or more of the following:
-Any death occurring prior to the postoperative outpatient evaluation 30 days postoperatively.
-Any life-threatening event until and including 30 postoperative days.
-Any medical event requiring inpatient hospitalization or prolongation of existing hospitalization beyond five postoperative days

NOTE: Hospitalizations that are not considered SAE are:
-Hospitalization planned prior to first administration of study drug
-Hospitalization for elective treatment of a pre-existing condition unrelated to the study medication
- Hospitalization due to social / practical reasons such as an untimely coordination with local community home care services.

Attribution: Attribution is the determination of whether an adverse event is related to a medical treatment or procedure. The categories of attribution are:

Definite: The adverse event is clearly related to the study drug
Probable: The adverse event is likely related to the study drug.
Possible: The adverse event may be related to the study drug.
Unlikely: The adverse event is doubtfully related to the study drug.
Unrelated: The adverse event is clearly NOT related to the study drug.

Unexpected Adverse Event: An unexpected adverse event is an event not mentioned in the package insert/ manufacturer's instructions or the specificity or severity of which is not consistent with the package insert/ manufacturer's instructions.

The grading described beneath and the attribution described above will be used for cathegorization of unexpected adverse events.