

CONFIDENTIAL

ROSE

A Phase III **R**andomized trial **O**f **S**ystematic Lymphadenectomy in Patients with
Apparent Early Stage High-grade Epithelial Ovarian Cancer (ROSE trial)

Protocol version 5.0

Trial registration: Intended to be registered with (Clinical Trial Registry of India) CTRI and
ClinicalTrial.gov after IRB approval



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By signing this protocol, the Investigator(s) acknowledge that it contains all necessary details for conducting the study and agree to follow it as written, in agreement with the Declaration of Helsinki adhering to ICH guidelines on Good Clinical Practice (ICH-GCP) and the applicable regulatory requirements.

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PROTOCOL SUMMARY

Study Synopsis

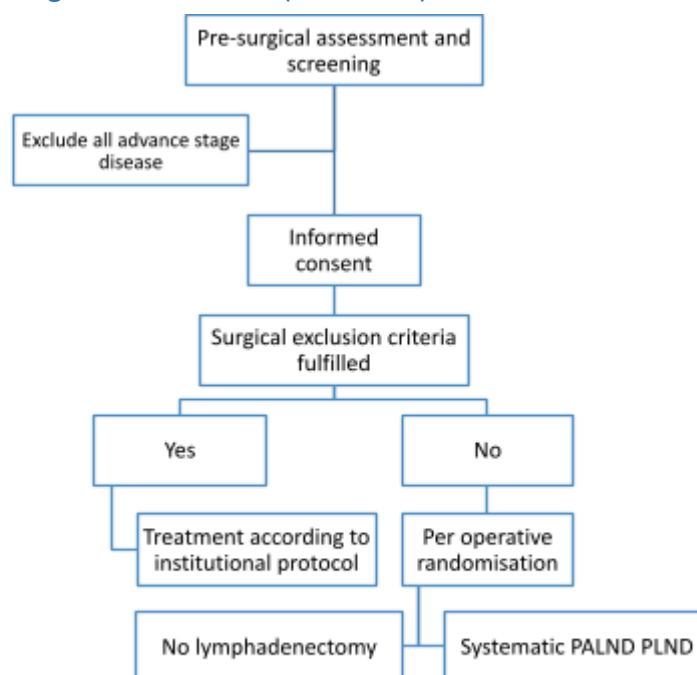
Study Title	A Phase III <u>R</u> andomized trial <u>O</u> f <u>S</u> ystematic Lymphadenectomy in Patients with Apparent <u>E</u> arly Stage High-grade Epithelial Ovarian Cancer (ROSE trial)
Abbreviated Title	ROSE
Protocol version	Version 5.0, 10/08/2026
Developmental phase	Non inferiority, Phase III
Study design	A phase 3, open label, multicentre, randomised clinical trial
Indication	Adult patients with apparent early stage but high grade epithelial ovarian cancer
Objectives	<u>Primary:</u> To assess the efficacy of omitting systematic pelvic and para-aortic lymphadenectomy, compared to systematic lymphadenectomy, in maintaining disease-free survival (DFS) in patients with apparent early-stage but high grade epithelial ovarian cancer. <u>Secondary:</u> 1. To compare overall survival (OS) between the two study groups. 2. To evaluate the pattern and site of disease recurrence. 3. To compare perioperative outcomes, including: a. Duration of surgery b. Intraoperative blood loss c. Length of hospital stay 4. To compare the incidence of intraoperative and postoperative adverse events occurring within 30 days from surgery 5. To compare Health-Related Quality of Life (HRQoL) at 30 days and 12 months after surgery. 6. To compare Patient-Reported Outcome Measures (PROMs) between the two groups at 30 days and 12 months after surgery.

Intervention	<u>Interventional</u> – Peritoneal washings + Total Hysterectomy, Bilateral Salpingo-Oophorectomy (TH BSO) + omentectomy + Random peritoneal biopsy <u>Control</u> – Peritoneal washings + Total Hysterectomy, Bilateral Salpingo-Oophorectomy (TH BSO) + omentectomy + Random peritoneal biopsy + Systematic pelvic and para aortic lymphadenectomy
Inclusion criteria	1. Age $\geq$ 18 years 2. Clinically and radiologically confirmed pelvic mass arising from single or both adnexa 3. No extra pelvic peritoneal tumour implants on radiology (CT/MR/PET scan) 4. No enlarged lymph nodes in the radiology (CT/MR/PET scan) 5. Serum CA 125/CEA ratio >25, if the serum CA125/CEA ratio is < 25, a colonoscopy and gastroscopy or radiological examination of the stomach should be negative for the presence of a primary tumour of the digestive tract (< 6 weeks before registration) 6. Frozen section analysis confirms high grade epithelial ovarian cancer 7. Patients who have given their signed and written informed consent 8. Good performance status (ECOG 0-2)
Exclusion criteria	1. Non epithelial and low grade ovarian malignancies, and borderline tumours 2. Intraoperative clinically suspicious lymph nodes (bulky nodes) 3. Synchronous other malignancies 4. Prior diagnosis of diseases of the lymph system (including lymph oedema of unknown origin) 5. Prior retroperitoneal lymph node dissection (systematic or sampling) 6. Pregnancy
Outcome	Primary efficacy endpoint: Disease free survival (DFS) Secondary: 1. Overall survival (OS) 2. Pattern and site of recurrence 3. Morbidity: Intraoperative and post-operative within 30 days

	4. Compare perioperative outcomes (duration of surgery, intraoperative blood loss, blood transfusion requirements, length of hospital stay) 5. Compare Health Related Quality of Life (HRQL) at 30 days and 12 months after surgery as measured by FACT-O 6. Compare Patient Reported Outcomes (PROMS) between the groups at 30 days and 12 months from surgery
Randomisation	Eligible patients with apparent early-stage epithelial ovarian cancer, confirmed intraoperatively by frozen section, will be randomized in a 1:1 allocation ratio to one of the following treatment arms: Arm A (Control arm): Standard surgical staging including systematic pelvic and para-aortic lymphadenectomy Arm B (Experimental arm): Standard surgical staging without systematic pelvic and para-aortic lymphadenectomy Randomization will be performed intraoperatively, immediately after frozen section confirmation of high-grade epithelial ovarian cancer and visual confirmation of apparent early-stage disease. A centralized, web-based randomization system will be used to ensure allocation concealment. Randomization will be conducted using permuted block randomization with variable block sizes, which will not be disclosed to participating coinvestigators.
Statistical analysis	The primary endpoint disease free survival (DFS) will be compared between treatment groups by a time-to-event analysis appropriate for the non-inferiority design, with a one-sided significance level of 0.025. Participants will be stratified by stage, histological cell type, participating centre and planned adjuvant chemotherapy. The primary analysis will be done in the intent-to-treat population and losses to follow-up will be regarded as censored observations.
Sample size	The sample size calculation assumes a 5-year disease-free survival (DFS) of 78% in the systematic lymphadenectomy arm. Non-inferiority of omission of systematic lymphadenectomy will be concluded if the absolute difference in 5-year DFS does not exceed 7%, a margin considered clinically acceptable in view of the substantial reduction in surgical morbidity associated with lymphadenectomy and the lack of proven overall survival benefit.

	Assuming a one-sided α of 0.025, 80% power, 1:1 randomization, uniform accrual over 3 years, a minimum follow-up of 5 years, and exponentially distributed survival times, approximately 330 events are required. To observe this number of events, 940 evaluable patients are required. Accounting for an anticipated 5% drop-out rate, a total of 1,000 patients (500 per arm) will be randomized.
Trial duration	Accrual period 3 years with a planned follow up for 5 years

1. Study design and flow chart (ROSE trial)



1. Background and Rationale

Epithelial ovarian cancer remains one of the leading causes of gynaecological cancer-related mortality worldwide.¹ While the majority of patients present with advanced disease, approximately 20–30% are diagnosed at an apparent early stage, often following surgery for an adnexal mass where malignancy is confirmed intra-operatively on the frozen section.² Accurate surgical staging is considered critical in this subgroup, as it guides adjuvant treatment decisions and prognostication. Comprehensive surgical staging traditionally includes peritoneal washings, total hysterectomy with bilateral salpingo-oophorectomy (TH BSO), omentectomy, peritoneal biopsies, and systematic pelvic and para-aortic lymphadenectomy.³⁻⁵ Among these components, lymphadenectomy has been

advocated primarily for staging purposes, based on the reported incidence of occult nodal metastases in early-stage epithelial ovarian cancer, particularly in high-grade tumours.⁶

However, despite its widespread acceptance, the therapeutic value of systematic lymphadenectomy in apparent early-stage high-grade ovarian cancer remains uncertain. Although most patients with high-grade disease receive platinum-based adjuvant chemotherapy irrespective of nodal status, the extent to which removal of clinically negative lymph nodes contributes independently to improved survival remains unclear.⁷⁻¹⁰ Systematic pelvic and para-aortic lymphadenectomy is associated with significant surgical morbidity, including increased operative time, blood loss, risk of vascular and nerve injury, lymphocele formation, lower-limb lymphedema, and prolonged hospital stay.¹¹ These complications are particularly relevant in patients with early-stage disease, many of whom may already have an excellent prognosis. In such a context, exposing patients to potentially avoidable morbidity without proven survival benefit raises important ethical and clinical concerns. Preliminary retrospective data from our institution involving 246 patients with epithelial ovarian cancer treated between 2013 and 2018 demonstrated no significant improvement in disease-free or overall survival associated with systematic pelvic and para-aortic lymphadenectomy after adjustment for known prognostic factors.

Over the past decade, the surgical management of other gynaecological malignancies has evolved toward less radical nodal assessment strategies. Sentinel lymph node mapping has largely replaced systematic lymphadenectomy in endometrial and cervical cancers, offering accurate staging with substantially reduced morbidity and no apparent compromise in oncologic outcomes.^{12,13} Furthermore, evidence from advanced ovarian cancer has demonstrated that removal of clinically and radiologically normal lymph nodes does not confer a survival advantage, reinforcing the concept that nodal involvement may be more prognostic than therapeutic in certain disease contexts.¹⁴ This paradigm shift underscores the need to critically re-evaluate the role of extensive lymphadenectomy in ovarian cancer, particularly in the early-stage setting.

While early-stage ovarian cancer is biologically distinct, these findings highlight the importance of questioning long-standing surgical practices in the absence of high-level evidence.

Current guidelines continue to recommend systematic lymphadenectomy as part of comprehensive staging, despite the absence of high-level evidence demonstrating a therapeutic benefit.¹⁵ Existing data are predominantly retrospective or derived from subgroup analyses, and no adequately powered randomized Phase III trial has specifically evaluated the role of systematic pelvic and para-aortic lymphadenectomy in apparent early-stage high-grade epithelial ovarian cancer.

The ROSE trial has been designed as a multicentre Phase III non-inferiority randomized controlled trial to address this important evidence gap. By evaluating whether omission of systematic pelvic and para-aortic lymphadenectomy results in non-inferior oncological outcomes while reducing surgical morbidity and improving quality of life, the ROSE trial seeks to generate high-level evidence to inform future surgical standards of care in early-stage high-grade epithelial ovarian cancer.

2. Study design

A phase 3, open label, multicentre, non-inferiority, randomised clinical trial

3. Key Research question(s):

The ROSE trial seeks to determine whether omission of systematic pelvic and para-aortic lymphadenectomy compromises oncological outcomes in patients with apparent early-stage high-grade epithelial ovarian cancer undergoing primary surgical staging. Although systematic lymphadenectomy has traditionally been incorporated into comprehensive staging surgery, its therapeutic value in clinically and radiologically node-negative disease remains uncertain, while it is associated with significant surgical morbidity and potential adverse effects on quality of life.

3.1 Primary Research Question

In patients with apparent early-stage high-grade epithelial ovarian cancer and no clinically, radiologically, or intraoperatively suspicious lymph nodes, is surgical staging without systematic pelvic and para-aortic lymphadenectomy non-inferior to conventional staging with systematic lymphadenectomy with respect to 5-year disease-free survival (DFS)?

3.2 Secondary Research Questions

- Does omission of systematic lymphadenectomy affect overall survival (OS)?
- Does omission of systematic lymphadenectomy influence the pattern and site of disease recurrence?
- Does omission of systematic lymphadenectomy reduce perioperative morbidity, postoperative complications, operative time, blood loss, and length of hospital stay?
- Does omission of systematic lymphadenectomy improve patient-reported outcomes and health-related quality of life?
- Can a less radical staging strategy achieve equivalent oncological outcomes while reducing treatment-related morbidity and surgical burden?

4. Study objectives

Primary:

To assess the efficacy of omitting systematic pelvic and para-aortic lymphadenectomy, compared to systematic lymphadenectomy, in maintaining

disease-free survival (DFS) at 5 years in patients with apparent early-stage epithelial ovarian cancer.

Secondary:

- To compare overall survival (OS) between the two study groups.
- To evaluate the pattern and site of disease recurrence.
- To compare perioperative outcomes, including:
 - Duration of surgery
 - Intraoperative blood loss
 - Blood transfusion requirements
 - Length of hospital stay
 - Readmission
- To compare the incidence of intraoperative and postoperative adverse events occurring within 30 days from surgery
- To compare Health-Related Quality of Life (HRQoL) at 30 days and 12 months after surgery.
- To compare Patient-Reported Outcome Measures (PROMs) between the two groups at 30 days and 12 months after surgery.

5. Outcome measures

5.1 Primary efficacy endpoint: The primary outcome is 5 year disease free survival (DFS)

Disease-Free Survival (DFS) is defined as the time from the date of randomization to the first occurrence of any of the following events: documented disease recurrence, or death from any cause, whichever occurs first.

Patients who are alive and disease-free at the time of last follow-up will be censored at the date of last contact.

Definition of Disease Recurrence: Disease recurrence will be defined in accordance with the GCIg criteria, based on one or more of the following.¹⁶⁻¹⁹

- Appearance of new disease-related symptoms consistent with recurrence along with rising serum CA-125 levels meeting GCIg criteria
- All patients with suspected recurrence will have a radiological documented evidence of recurrence/progression on imaging (CT/MRI/PET-CT)
- Histopathological confirmation will be obtained where clinically feasible but is not mandatory.

Primary Time Point for Analysis: DFS will be assessed at 5 years, which constitutes the primary time point for the non-inferiority analysis.

5.2 Secondary endpoints:

- Overall survival (OS) will be calculated from the date of randomization until the date of death from any cause or date of last contact (censored observation).
- Pattern or site of recurrence, defined as location of recurrence as per the radiological imaging recurrence which will be subdivided as follows:
 - Extra abdominal
 - Intra-abdominal: Peritoneal or nodal or both
 - Both intra-abdominal and extra abdominal

Safety analysis will assess the duration of surgery, intraoperative blood loss, blood transfusion requirements, length of hospital stay between the two groups along with Postoperative complications graded using Clavien–Dindo classification (Appendix A)^{20, 21}

Specific complications of interest include:

- Lymphocele formation.
- Lower-limb lymphedema.
- Surgical site infection.
- Vascular injury.
- Nerve injury.
- Urinary tract injury.
- Bowel injury.
- Reoperation.
- Readmission within 30 days.

Health Related Quality of Life will be assessed by FACT-O (Appendix B) and Patient Reported Outcomes (PROMS) (Appendix C) between the groups at 30 days and 12 months from surgery using standard questionnaires

Health-related quality of life will be assessed using the Functional Assessment of Cancer Therapy–Ovarian (FACT-O) questionnaires.²²

Assessments will be performed:

- Preoperatively (baseline).
- At 30 days after surgery.
- At 12 months after surgery.

Pathological outcome:

The study will document the following histopathological parameters

- Final FIGO stage.
- Histological subtype.
- Tumour grade.
- Number of lymph nodes removed (control arm).
- Number of positive lymph nodes identified.
- Frequency of occult nodal metastases.

These outcomes will provide additional information regarding staging accuracy and disease distribution.

6. Study enrolment

6.1 Inclusion Criteria

Potentially eligible patients will be screened during preoperative assessment clinics. All patients will undergo standard clinical evaluation, laboratory investigations, serum tumour marker assessment, and radiological imaging according to institutional practice. Written informed consent for study participation and intraoperative randomization will be obtained before surgery. Following intraoperative frozen-section confirmation of eligibility and verification of the absence of suspicious lymph nodes, patients will undergo randomization according to the study protocol.

Patients must meet all of the following criteria to be eligible for enrolment:

1. Age ≥ 18 years
2. Intraoperative frozen section diagnosis suggestive of high-grade epithelial ovarian carcinoma, including:
 - High-grade serous carcinoma
 - High-grade endometrioid carcinoma
 - Clear cell carcinoma
 - Mucinous carcinoma (infiltrative pattern)
3. Apparent early-stage disease at the time of surgery, defined as:
 - Disease apparently confined to the ovaries and/or adnexa
 - No macroscopic evidence of extra adnexal disease
 - No clinically, radiologically or intra-operatively enlarged pelvic or para-aortic lymph nodes
4. Primary surgery planned with intent of complete surgical staging, including:
 - Total hysterectomy
 - Bilateral salpingo-oophorectomy
 - Infra-colic or total omentectomy
 - Peritoneal washings and biopsies as per protocol
5. Serum CA 125/CEA ratio >25 ,
 - If the serum CA125/CEA ratio is < 25 , a colonoscopy and gastroscopy and/or radiological examination of the stomach should be negative for the presence of a primary tumour of the digestive tract (< 6 weeks before registration)

6. ECOG performance status 0–2
7. Adequate organ function, as assessed by standard preoperative laboratory parameters
8. Ability to provide written informed consent, including consent for intraoperative randomization

6.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded:

1. Low-grade epithelial ovarian carcinoma on frozen section
2. Borderline ovarian tumours
3. Non-epithelial ovarian malignancies, including:
 - Germ cell tumours
 - Sex cord–stromal tumours
4. Evidence of advanced disease, including:
 - Extra-pelvic peritoneal disease
 - Omental disease
 - Clinically or radiologically enlarged lymph nodes
5. Previous retroperitoneal lymphadenectomy
6. Concurrent malignancy or history of another malignancy within the past 5 years
7. Pregnancy or lactation
8. Serious medical comorbidities precluding major surgery
9. Inability to comply with study protocol or follow-up requirements

7. Sample size estimation

The ROSE trial is designed as a multicentre, open-label, randomized, controlled, Phase III non-inferiority trial with 5-year Disease-Free Survival (DFS) as the primary endpoint.

A non-inferiority design was selected because omission of systematic pelvic and para-aortic lymphadenectomy is anticipated to reduce operative morbidity, lymphatic complications, postoperative recovery time, and treatment burden while potentially preserving equivalent oncological outcomes.²³ The objective of the study is therefore to determine whether omission of systematic lymphadenectomy results in DFS outcomes that are not clinically inferior to those achieved with the current standard surgical approach.

Based on published literature and institutional data, the expected 5-year DFS in patients undergoing standard surgical staging with systematic lymphadenectomy is estimated to be approximately 78%⁷. A non-inferiority margin of 7% was selected following discussions among gynaecological oncologists and biostatisticians and represents the largest clinically acceptable difference in DFS that would be considered acceptable in view of the anticipated reduction in treatment-related morbidity and improvement in quality of life associated with omission of lymphadenectomy.

The sample size calculation is based on the following assumptions:

Expected 5-year DFS in the control arm: 78%

Absolute non-inferiority margin: 7%

One-sided significance level (α): 0.025

Statistical power: 80%

Allocation ratio: 1:1

Under these assumptions, approximately 330 events are required to adequately test the primary non-inferiority hypothesis.

Assuming an accrual period of 3 years, a minimum follow-up period of 5 years after completion of recruitment, and an anticipated loss to follow-up rate of approximately 5%, the total sample size required is 1,000 patients, comprising 500 patients in each treatment arm.

The primary analysis will be conducted according to the intention-to-treat (ITT) principle. Given the non-inferiority design, a complementary per-protocol (PP) analysis will also be performed. Non-inferiority will be concluded only if findings are consistent across both analytical populations. Time-to-event outcomes will be analysed using Kaplan–Meier survival estimates and Cox proportional hazards regression models adjusted for predefined stratification factors.

8. Sampling strategy, Randomization and Stratification

8.1 Sampling strategy

The study will employ a consecutive sampling strategy across all participating centres. All potentially eligible patients presenting during the recruitment period will be screened for participation.

Patients undergoing surgery for an adnexal mass suspected to be epithelial ovarian cancer will undergo standard preoperative evaluation, including clinical assessment, imaging investigations, serum tumour marker evaluation, and routine laboratory testing as per each individual institutional protocol requirements. Eligible patients will be approached for participation and written informed consent will be obtained before surgery. The consent process will include information regarding intraoperative frozen-section assessment and potential intraoperative randomization if all the eligibility criteria are fulfilled.

8.2 Randomization

Eligible patients with apparent early-stage epithelial ovarian cancer, confirmed high grade ovarian cancer intraoperatively by frozen section, will be randomized in a 1:1 allocation ratio to one of the following treatment arms:

1. Arm A (Control arm): Standard surgical staging including systematic pelvic and para-aortic lymphadenectomy

2. Arm B (Experimental arm): Standard surgical staging without systematic pelvic and para-aortic lymphadenectomy

Randomization will be performed intraoperatively, immediately after frozen section confirmation of high-grade epithelial ovarian cancer and confirmation of apparent early-stage disease.

A centralized, web-based randomization system will be used to ensure allocation concealment. Randomization will be conducted using permuted block randomization with variable block sizes, which will not be disclosed to participating investigators.

8.3 Stratification Factors

Randomization will be stratified to ensure balance between treatment arms for key prognostic factors known to influence disease-free survival in early-stage epithelial ovarian cancer.

The following stratification factors will be applied:

1. FIGO Stage: Stage IA–IB, Stage IC1 and IC2-3
Rationale: Stage IC disease is associated with a higher risk of nodal involvement and recurrence compared to IA–IB disease.
2. Histological Subtype: High-grade serous carcinoma and non-serous high-grade epithelial carcinomas (endometrioid, clear cell, mucinous)
Rationale: Histological subtype significantly influences biological behaviour, recurrence patterns, and survival outcomes.
3. Participating Centre by annual case load (>100, 50-100, <50 ovarian cancer surgeries per year)
Rationale: This stratification accounts for potential variability in surgical expertise, staging completeness, and perioperative care across centres.
4. Planned Adjuvant Chemotherapy: Yes/No
Rationale: Adjuvant chemotherapy may impact DFS and recurrence patterns, and stratification ensures balance in systemic treatment decisions.

9. Allocation Concealment and Implementation

Allocation will remain concealed until randomization is completed.

Investigators and surgeons will not have access to future allocations.

Due to the nature of the surgical intervention, blinding of surgeons is not feasible.

Outcome assessors and statisticians will remain blinded to treatment allocation wherever feasible.

9.1 Minimization of Bias

To minimize bias:

- Randomization is centralized and concealed

- Stratification addresses major prognostic variables
- Surgical procedures will follow predefined protocol-mandated standards

All analyses will be performed on an intention-to-treat basis with additional per-protocol analyses planned for the primary non-inferiority endpoint. Given the nature of the surgical intervention, blinding of surgeons and patients is not feasible. The trial will therefore be conducted in an open-label manner. However, standardized definitions for outcomes, central monitoring of data quality, and protocol-driven follow-up schedules will be implemented to minimize potential assessment bias.

10. Surgical Procedure and Quality Assurance

10.1 Standard Surgical Procedure (Both Arms)

Following intraoperative frozen-section confirmation of high-grade epithelial ovarian carcinoma and verification of eligibility, all patients will undergo comprehensive surgical staging for apparent early-stage epithelial ovarian cancer performed by trained gynaecological oncologists.

Mandatory staging components for both treatment arms include:

- Peritoneal washings for cytology (obtained at the start of surgery)
- Systematic inspection and palpation of the entire peritoneal cavity
- Total hysterectomy (or protocol-approved fertility-sparing surgery where applicable)
- Bilateral salpingo-oophorectomy (or protocol-approved fertility-sparing surgery where applicable)
- Infra-colic or total omentectomy
- Random biopsies from standard peritoneal sites (pelvis, paracolic gutters, subdiaphragmatic areas) are recommended

All surgical approaches (open, laparoscopic, or robotic) are permitted, provided oncologic principles are maintained.

10.2 Intervention-Specific Procedures

10.2.1 Arm A (Control Arm): Systematic Lymphadenectomy

Patients randomized to the control arm will undergo systematic pelvic and para-aortic lymphadenectomy as part of surgical staging.

10.2.2 Pelvic Lymphadenectomy

Bilateral removal of lymph nodes from:

- Common iliac
- External iliac
- Internal iliac
- Obturator regions

Boundaries:

- Proximally: Common iliac bifurcation
- Distally: Deep circumflex iliac vein
- Laterally: Genitofemoral nerve
- Medially: Obliterated umbilical ligament

10.2.3 Para-aortic Lymphadenectomy

Removal of lymph nodes: From the common iliac bifurcation up to the level of the left renal vein, Includes:

- Common iliac
- Precaval
- Para-caval
- Inter aorto-caval
- Preaortic
- Para-aortic nodal basins

All lymphatic tissue will be submitted in separate, anatomically labelled containers.

10.2.4 Arm B (Experimental Arm): No Systematic Lymphadenectomy

Patients randomized to the experimental arm will not undergo systematic pelvic or para-aortic lymphadenectomy.

Enlarged or suspicious lymph nodes, if encountered intraoperatively, may be selectively removed at the discretion of the operating surgeon and submitted for histopathological evaluation. Such selective nodal excision will not be considered a protocol violation and will be documented prospectively.

To ensure consistency across participating centres, a detailed surgical manual will be developed describing operative procedures, definitions of suspicious lymph nodes, documentation requirements, and quality assurance measures.

Routine nodal sampling is not permitted.

10.2.5 Sentinel Lymph Node Mapping

Sentinel lymph node mapping is not permitted in either arm, to avoid contamination of the study question and ensure clear interpretability of results.

10.3 Management of Intraoperative Findings

If unexpected macroscopic extra-pelvic disease is identified:

- The patient will continue surgery as clinically appropriate
- Randomization occurs only after confirmation of apparent early-stage disease. If previously unrecognized extra-pelvic disease is subsequently identified after randomization, the patient will remain in the trial and be analysed according to the intention-to-treat principle.
- Conversion from minimally invasive to open surgery is allowed and must be documented with reasons.

10.4 Surgical Quality Assurance

10.4.1 Surgeon Eligibility

Participating surgeons must be certified gynaecological oncologists or equivalent who independently performs each year:

- ≥20 ovarian cancer staging surgeries
- ≥10 systematic pelvic and para-aortic lymphadenectomies

10.4.2 Centre Eligibility

Participating centres must be a tertiary care or high-volume cancer centres or academic institutions with oncological facilities with demonstrated expertise in ovarian cancer surgery and clinical research

And have:

- Dedicated gynaecological oncology services
- Dedicated radiological services with experience in reporting of peritoneal surface malignancy
- On-site frozen section pathology
- ICU and blood bank support
- Facilities for the administration of systemic chemotherapy.
- Institutional Ethics Committee approval and regulatory compliance.
- Availability of trained clinical research personnel for patient recruitment, follow-up, and data management.

10.4.3 Training and Standardization

Prior to study initiation, investigator and research team meetings and training sessions will be conducted to standardize surgical techniques, pathological assessment, data collection procedures, outcome reporting, and follow-up protocols. Regular monitoring, central data review, and quality assurance procedures will be implemented to ensure protocol adherence and consistency across participating sites.

11. Adjuvant Treatment Policy

11.1 General Principles

Adjuvant treatment decisions will be based on final histopathological staging and risk stratification, in accordance with international guidelines and institutional standards. To minimize treatment-related confounding, adjuvant therapy will be standardized across both trial arms and will not be influenced by randomization assignment.

11.2 Indications for Adjuvant Chemotherapy

Adjuvant chemotherapy is recommended for patients meeting any of the following criteria on final histopathology:³

- FIGO stage IA and above with High-grade serous carcinoma and High-grade endometrioid carcinoma
- FIGO stage IC2 and above with Clear cell carcinoma, High-grade mucinous carcinoma (infiltrative pattern of invasion)
- Patients with FIGO stage IA and IB, IC1 with clear cell carcinoma, high grade mucinous carcinoma may be observed at the discretion of the treating team after discussing the pros and cons of adjuvant chemotherapy with the patient

11.3 Chemotherapy Regimen

The recommended adjuvant chemotherapy regimen is:

- Paclitaxel 175 mg/m² IV plus
- Carboplatin AUC 5–6 IV
- Administered every 21 days

Dose modifications and supportive care will follow institutional protocols.

11.4 Timing of Chemotherapy

- Adjuvant chemotherapy should ideally begin within 3–6 weeks after surgery.
- Initiation beyond 8 weeks must be documented with reasons.

11.5 Management of Upstaged Disease

Patients found to have occult nodal metastases or microscopic peritoneal and/or omental disease will:

- Receive adjuvant therapy as per final stage
- Remain in their originally assigned treatment arm
- Be analysed according to the intention-to-treat principle

11.6 Documentation and Compliance

The following will be recorded for all patients:

- Indication for adjuvant chemotherapy
- Chemotherapy regimen and number of cycles
- Dose modifications or delays
- Completion status

Compliance with the adjuvant treatment policy will be monitored centrally.

12. Data Collection Methods

Data for the ROSE trial will be collected prospectively using standardized electronic Case Report Forms (eCRFs) within a secure, web-based REDCap (Research Electronic Data Capture)²⁴ database across all participating centres. Data collection will be performed by trained investigators and research coordinators in accordance with a detailed study manual, standardized operating procedures, and predefined data collection protocols.

All study data will be entered into the REDCap platform, which incorporates built-in range checks, validation rules, audit trails, user-specific access controls, and query management functions to ensure data completeness, accuracy, consistency, and regulatory compliance. Source documents will include medical records, operative notes, pathology reports, laboratory reports, imaging records, chemotherapy records, and patient-completed questionnaires. The REDCap system will facilitate real-time data entry, centralized data management, data monitoring, and secure storage of study information across participating centres.

Data collection will occur at predefined study time points, including baseline assessment, intraoperative assessment, postoperative follow-up, completion of adjuvant chemotherapy, and long-term surveillance visits. The schedule of enrolment, interventions, and assessments is summarized in the study schedule.

The data safety monitoring committee (DSMC) will oversee the compliance of data collection.

Outline of the CRF

Baseline Assessments

At enrolment, the following information will be recorded:

Demographic and Clinical Characteristics

- Age
- Ethnicity
- Height, weight, and body mass index (BMI)
- Menopausal status
- ECOG performance status
- Personal history of cancer
- Relevant medical comorbidities
- Previous abdominal or pelvic surgery
- Family history of cancer

Laboratory Investigations

The following baseline laboratory parameters will be documented:

- Complete blood count
- Renal function tests

- Liver function tests
- Serum CA-125
- Serum CEA
- Serum CA19-9
- Other investigations as clinically indicated

Radiological Assessment

Preoperative cross sectional imaging findings from contrast-enhanced CT and/or MRI or PET CT will be recorded, including:

- Tumour size and laterality
- Presence of ascites
- Evidence of extra-ovarian disease
- Pelvic and para-aortic lymph node status
- Other findings relevant to eligibility determination

Imaging findings will be documented according to protocol-defined criteria.

Intraoperative Data Collection

Operative findings will be documented using standardized surgical forms.

Variables collected will include:

- Surgical approach (open, laparoscopic, robotic)
- Intraoperative frozen-section diagnosis
- Tumour laterality
- Tumour rupture status
- Ascites volume
- Peritoneal findings
- Omental findings
- Presence of suspicious lymph nodes
- Randomization assignment
- Extent of surgical staging performed

Perioperative Measurements

The following perioperative parameters will be prospectively recorded:

- Operative duration (minutes, record incision, record last suture/staple time)
- Estimated blood loss (mL)
- Blood transfusion requirement
- Intraoperative complications
- Additional procedures performed

Pathological Assessment

Histopathological evaluation will be performed according to standardized protocol-defined reporting criteria.

The following variables will be collected:

- Histological subtype

- Tumour grade
- Tumour size
- Tumour laterality
- Ovarian capsule status
- Ovarian surface involvement
- Peritoneal cytology findings
- Omental involvement
- Peritoneal biopsy findings
- Lymph node status
- Number of lymph nodes examined
- Number of metastatic lymph nodes
- Final FIGO stage

Postoperative and Treatment-Related Assessments

Postoperative recovery and treatment-related outcomes will be recorded prospectively. These include:

- Length of hospital stay
- Time to recovery
- Time to initiation of adjuvant chemotherapy
- Readmission within 30 days
- Reoperation
- Completion of planned chemotherapy

Complication Assessment: Postoperative complications occurring within 30 days of surgery will be graded according to the Clavien–Dindo Classification System.

Specific complications of interest include:

- Lymphocele formation
- Lower-limb lymphedema
- Surgical site infection
- Vascular injury
- Nerve injury
- Urinary tract injury
- Bowel injury
- Thromboembolic events
- Reoperation
- Readmission

Quality of Life and Patient-Reported Outcomes

Health-related quality of life will be assessed using the validated Functional Assessment of Cancer Therapy–Ovarian (FACT-O) questionnaire.

Patient-reported outcomes (PROMs) will be collected using validated patient-reported assessment tools to evaluate:

- Physical functioning

- Symptom burden
- Lower-limb symptoms
- Functional limitations

For the predefined secondary endpoint analysis, HRQoL and PROMs will be assessed at baseline, 30 days, and 12 months after surgery. Additional assessments may be performed at other protocol-defined follow-up visits for longitudinal evaluation.

Lower-Limb Lymphedema Assessment

As reduction in lymphatic morbidity represents a major rationale for the study, lower-limb lymphedema will be prospectively assessed throughout follow-up.

Assessment will include:

- Clinical examination
- Presence of limb swelling
- Functional limitation
- Requirement for compression therapy or physiotherapy
- Patient-reported symptoms

Follow-Up Assessments

Patients will be followed according to protocol-defined schedules for a minimum of five years following randomization.

At each follow-up visit, the following information will be collected:

- Clinical examination findings
- ECOG performance status
- Tumour marker results
- Imaging findings (where indicated)
- Disease status
- Recurrence details
- Subsequent treatment received
- Survival status
- Recurrences will be categorized as:
 - Nodal: Pelvic nodal recurrence
 - Para-aortic nodal recurrence
 - Peritoneal recurrence
 - Distant recurrence
 - Multiple-site recurrence

13. Study time line

Evaluation	Pre-op visit	Surgery	Post op visit 1 (within 30 days of surgery)	Post op visit 2 (within 6 weeks after completion of chemotherapy)	Post op visit 3 to 14 every 3 months after visit 2	Post op visit 15 to 20, every 6 months
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Medical history	X					
Clinical examination	X		X	X		
Gynaecological examination	X				X	X
Informed consent	X					
Radiology of chest (CT scan)	X				X*	X*
Radiology of abdomen and pelvis (CT/MRI, MRI peritoneum with CT sections/PET Scan)	X				X*	X*
Tumour marker (CA 125, CA 19-9, CEA)	X			X	X*	X*
Randomization		X				
Systematic LNE or No LNE		X				
Adjuvant treatment details				X		
FACT-O questionnaires	X		X		X (at 12 months)	
PROM questionnaires	X		X		X (at 12 months)	
Complications		X	X			

*If clinically indicated

14. Data quality assurance methods:

Maintaining high-quality, reliable, and reproducible data across participating centres is essential to ensure the scientific validity of the ROSE trial. A comprehensive quality assurance framework will therefore be implemented to standardize study procedures, minimize inter-centre variability, ensure protocol adherence, and maintain data integrity throughout the study period.

Site Selection and Qualification

Only centres with established expertise in gynaecological oncology and adequate research infrastructure will be eligible to participate in the study. Participating institutions must have:

- Dedicated gynaecological oncology services
- Participating surgeons must be a certified gynaecological oncologists or equivalent
- Have independently performed: ≥ 20 ovarian cancer staging surgeries and ≥ 10 systematic pelvic and para-aortic lymphadenectomies
- Access to intraoperative frozen-section pathology
- Experienced gynaecological pathologists
- ICU and blood bank support
- Advanced radiology facilities including PACS
- Availability of systemic chemotherapy services
- Clinical research support personnel
- Capability for long-term patient follow-up

Prior to site activation, participating centres will undergo feasibility assessment to ensure adequate patient volume, infrastructure, and commitment to protocol compliance. Investigator Training and Study Initiation: All investigators, surgeons, pathologists, radiologists, and research coordinators will undergo protocol-specific training in virtual mode before study initiation.

Training will include:

- Eligibility assessment
- Informed consent procedures
- Intraoperative randomization procedures
- Surgical protocol requirements
- Data collection procedures
- Outcome assessment
- Adverse event reporting
- REDCap database training and utilization

Investigator meetings, webinars, training manuals, and periodic refresher sessions will be conducted throughout the study to ensure uniform implementation across centres. This will be overseen by the Trial Management Committee.

Radiological Quality Assurance:

Accurate identification of clinically and radiologically node-negative patients is critical to the study design. All participating centres will perform preoperative imaging using contrast-enhanced CT and/or MRI or PET CT scan according to institutional protocols and study-defined imaging requirements.

To ensure consistency in eligibility assessment, a standardized radiological reporting template will be provided to all participating centres. Pelvic and para-aortic lymph nodes will be systematically assessed and reported using predefined criteria. Lymph nodes will be considered radiologically suspicious if one or more of the following features are present:

- Short-axis diameter ≥ 10 mm
- Rounded morphology with loss of the normal oval shape
- Loss of fatty hilum
- Central necrosis or heterogeneous enhancement
- Irregular nodal borders
- Abnormal FDG uptake on PET-CT, where available and performed

Radiology reports will specifically document:

- Presence or absence of suspicious pelvic lymph nodes
- Presence or absence of suspicious para-aortic lymph nodes
- Largest nodal short-axis diameter
- Radiological features suggestive of metastatic involvement

Patients with radiologically suspicious pelvic or para-aortic lymph nodes will not be eligible for randomization. Participating radiologists will receive protocol-specific imaging guidance, and periodic review of imaging reports and selected scans will be undertaken to ensure adherence to protocol-defined eligibility criteria and reporting standards.

Pathology Quality Assurance:

Given the importance of intraoperative frozen-section diagnosis for trial eligibility, participating centres must have access to experienced gynaecological pathologists and frozen-section facilities. A continuous audit of concordance of the frozen section biopsy with final biopsy result will be undertaken after 10 cases from each centre. An accuracy of 80% (8 out of 10) or above is desirable.

A pathology manual will be developed outlining standardized criteria for:

- Histological subtype classification.
- Tumour grading.
- Staging parameters.
- Nodal assessment.
- Reporting terminology.

Final histopathology reports will follow standardized reporting formats. Periodic central review of selected pathology specimens and reports will be performed to ensure consistency and minimize inter-observer variability.

- Standardized Pathology Manual: A comprehensive study-specific pathology manual will be distributed to all participating sites before activation. This manual outlines standardized criteria for identifying high-grade epithelial ovarian

carcinomas (EOC) and details reporting terminology to minimize inter-observer discrepancies.

- Pre-trial investigator training sessions and periodic pathology review meetings
- Mandatory documentation of concordance between frozen-section and final histopathology.
- Central review of selected pathology slides and reports for quality assurance.
- Statistical Guardrails (Sensitivity Analyses): In accordance with our Statistical Analysis Plan, all randomized patients will be analysed under the Intention-to-Treat (ITT) population. To explicitly account for any discrepancy between intraoperative FS and final paraffin-section histopathology, a pre-specified per-protocol (PP) sensitivity analysis will be executed alongside multivariable Cox regression to adjust for any unexpected diagnostic mismatches.

Surgical Quality Assurance:

As the trial compares two surgical staging strategies, maintaining uniform surgical standards is essential. Participating surgeons must be trained gynaecological oncologists with documented experience in comprehensive ovarian cancer staging procedures.

Operative notes, surgical checklists, and pathology reports will be reviewed periodically to assess protocol adherence.

Key surgical quality indicators will include:

- Completeness of staging procedures
- Lymph node yield in the lymphadenectomy arm
- Protocol compliance rates
- Intraoperative complication rates
- Conversion rates, minimal access to open (where applicable)

15. Data Management Quality Assurance

Data will be captured prospectively using the REDCap electronic data capture platform.

The REDCap system will incorporate:

- Role-based user access
- Automated range and consistency checks
- Mandatory data fields
- Audit trails
- Query generation and resolution systems
- Real-time monitoring of data completeness

Data entry personnel will receive dedicated training before study initiation. Regular data review will be performed by the coordinating centre overseen by the clinical trial management committee (CTMC) and DSMC to identify missing data, inconsistencies, and protocol deviations. Monitoring and Auditing Centralized study monitoring will be performed throughout the trial.

Monitoring activities will include:

- Verification of informed consent documentation
- Eligibility confirmation
- Review of randomization procedures
- Assessment of protocol compliance
- Source document verification for selected cases
- Verification of primary and secondary outcome data

Periodic monitoring reports will be generated and communicated to participating centres. Where required, site audits may be conducted to ensure compliance with Good Clinical Practice (GCP), institutional requirements, and study protocols.

Quality Oversight:

The CTMC and DSMC at the coordinating centre will oversee study conduct, protocol compliance, data quality, and monitoring activities throughout the study period. Regular investigator meetings and interim quality reviews will be conducted to address operational issues, reinforce protocol adherence, and maintain consistency across participating sites.

16. Database Monitoring and Quality Control

The coordinating centre will perform regular centralized monitoring of data completeness, consistency, and protocol compliance.

Monitoring activities will include:

- Review of missing data rates
- Verification of eligibility criteria
- Assessment of randomization records
- Review of primary and secondary outcome data
- Identification of protocol deviations

17. Data Storage and Backup

All study data will be securely stored on institutional servers hosting the REDCap platform, with routine backup procedures implemented to prevent data loss. Automated database backups will be performed at regular intervals according to institutional information technology policies. Backup copies will be maintained in secure locations with restricted access. Study records and databases will be retained for the duration required by institutional policies, regulatory requirements, and applicable clinical research guidelines.

18. Data Lock and Final Analysis

Following completion of recruitment, follow-up, and resolution of all outstanding data queries, the study database will undergo final review and validation. The database will subsequently be locked prior to commencement of the final statistical analysis.

Any modifications after database lock will require formal authorization, documentation, and maintenance of an audit trail.

The final locked database will serve as the source for all primary, secondary, and exploratory analyses specified in the statistical analysis plan.

19. Data Safety Monitoring Committee (DSMC)

An independent Data Safety Monitoring Committee (DSMC) will be constituted, comprising:

- At least two nationally acclaimed senior gynaecological oncologist (not participating in the trial)
- One biostatistician with expertise in randomized trials
- One independent scientist/ethicist

The DSMC will oversee:

- Patient safety
- Trial conduct
- Accrual and data quality
- Interim efficacy and futility analyses

20. Interim Analysis

20.1 Timing

One formal interim analysis will be conducted after approximately 50% of the required events (≈ 150 – 160 events) have occurred.

20.2 Stopping Rules

20.2.1 Safety Stopping Rule

The DSMC may recommend early termination if there is:

- A significantly higher rate of serious adverse events, perioperative morbidity, or procedure-related mortality in either arm
- Unexpected safety concerns related to omission or performance of lymphadenectomy

Safety analyses will be descriptive and continuous throughout the trial.

20.2.2 Inferiority Stopping Rule

The trial may be stopped after interim analysis if the results demonstrate: Clear evidence that omission of systematic lymphadenectomy results in DFS inferior beyond the predefined non-inferiority margin (7%), with high statistical confidence.

20.2.3 Futility Stopping Rule

The DSMC may recommend stopping the trial for futility if: Conditional power calculations suggest a low probability of demonstrating non-inferiority even with full accrual and follow-up

21. Data Protection, Privacy, and Confidentiality

A comprehensive, multi-layered data protection framework will be enforced to protect patient privacy and adhere to data compliance standards.

Pseudonymization:

To ensure absolute confidentiality, all enrolled participants will be assigned a unique, sequential Study Identification Number immediately upon registration. Patient names, hospital registration numbers, or any other personally identifiable information (PII) will not appear on any Electronic Case Report Forms (eCRFs) within the centralized REDCap database or any trial documents transmitted to the central data management unit.

Source Document Security:

The master log linking patient identities to their Study ID numbers will be maintained securely at each individual participating site in a password-protected file accessible exclusively by the site Principal Investigator and authorized clinical trial coordinators.

Data Storage Access Controls:

The web-based REDCap system will utilize end-to-end encryption for data transmission, secure role-based user access controls, and automated session timeouts. Database access privileges will be restricted strictly according to specific study responsibilities. A comprehensive digital audit trail will automatically record the identity of any individual entering, modifying, or viewing participant data. All final dissemination, presentations, and publications resulting from the trial will utilize strictly de-identified, aggregate statistical data to guarantee that no individual participant can be identified.

22. SAFETY REPORTING

Investigators at each participating centre will be responsible for identifying, assessing and documenting AEs and SAEs occurring during the study and for reporting them according to the timelines and procedures specified in this protocol and applicable regulatory requirements. The investigator/researcher must report all SAEs to the respective IRB/EC and the IRB of TMC-K immediately (preferably within 24 hours, and no later than 7 days to the IRB of TMC-K), in accordance with the study protocol and GCP guidelines.

22.1 Definition of an Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject during the study, irrespective of whether it is considered related to the study intervention or procedure. An AE may include an unfavourable or unintended sign, symptom, laboratory abnormality, or medical condition occurring during the study. The definition is consistent with ICH Good Clinical Practice guidance.

Investigators at participating centres will be responsible for identifying, assessing, documenting and reporting AEs and SAEs occurring during the study in accordance with

the procedures and timelines specified in this protocol and applicable regulatory requirements.

Examples of AEs may include new or worsening symptoms or medical conditions, abnormal laboratory findings, postoperative complications, infections, bleeding, thromboembolic events, or other clinically significant medical occurrences occurring during the study.

SAEs will be identified and reported according to the criteria specified in this protocol and applicable regulatory requirements.

Examples of adverse events relevant to the ROSE trial may include postoperative infection, wound complications, bleeding requiring intervention or transfusion, injury to adjacent organs or major blood vessels, urinary or bowel complications, postoperative ileus, lymphocele, lymphoedema, thromboembolic events, readmission, reoperation, prolonged hospitalization, and other clinically significant medical or surgical complications occurring during the study period.

Expected postoperative findings or uncomplicated events associated with routine surgical care will not be considered adverse events unless they result in an untoward medical occurrence or require additional clinical intervention, prolongation of hospitalization, or otherwise meet the criteria for an adverse event as defined in this protocol.

22.2 Definition of Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is any untoward medical occurrence during the study that meets one or more of the following criteria:

- Death
- Life-threatening condition, defined as an event in which the participant was at immediate risk of death at the time of the event
- New inpatient hospitalization or prolongation of an existing hospitalization
- Persistent or significant disability/incapacity
- Other medically significant conditions that, based on clinical judgment, may jeopardize the participant or may require medical or surgical intervention to prevent one of the above outcomes

The term “life-threatening” refers to an event in which the participant was at immediate risk of death at the time of the event and does not refer to an event that hypothetically might have caused death if it had been more severe.

Hospitalization refers to an unplanned inpatient admission or prolongation of an existing hospitalization due to an adverse event. Pre-planned admissions for scheduled treatment, including routine adjuvant chemotherapy, will not be considered SAEs unless the admission is prolonged or an unexpected medical complication occurs.

Other medically significant conditions are those in which medical and scientific judgment should be exercised to determine whether expedited reporting is appropriate. These may include important medical or surgical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require intervention to prevent one of the outcomes listed above.

All SAEs will be assessed and documented by the site investigator and reported according to the timelines and procedures specified in this protocol and applicable institutional, ethical and regulatory requirements. Investigators will complete the Serious Adverse Event Report Form (Appendix D), where applicable, and submit the report through the prescribed reporting pathway.

The severity (grade) of AEs will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0, (Appendix E) where applicable. The seriousness of an event will be determined according to the SAE criteria defined in this protocol.

22.3 Criteria for assessing causality

The site investigator will assess each AE for its relatedness to the trial intervention and/or trial-related surgical procedures. The assessment will consider the temporal relationship, biological plausibility, alternative explanations, and the clinical course of the event. A guide to grading the degree of certainty about such a relationship is available at https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf^{appendix}

Causality will be categorized as follows:

- Unrelated: There is clear evidence that the event is attributable to a cause other than the trial intervention or trial-related procedure.
- Unlikely: A causal relationship is considered unlikely based on the temporal relationship and available clinical information.
- Possible: A causal relationship cannot be excluded, although alternative explanations may also exist.
- Probable: The temporal relationship and clinical characteristics suggest that the event is more likely related to the trial intervention or trial-related procedure than to alternative causes.
- Definite: There is strong clinical evidence supporting a direct causal relationship between the event and the trial intervention or trial-related procedure.

All AEs and SAEs will undergo causality assessment and will be managed and reported according to the procedures specified in this protocol.

22.4 Follow-up of AEs and SAEs

Following the initial report, investigators will follow up all AEs and SAEs until resolution, stabilization, adequate clinical explanation, loss to follow-up, or death.

Relevant follow-up information, including clinical findings, investigations, treatment provided, outcome, and any change in severity or seriousness, will be documented in the study records and reported to the appropriate Ethics Committee/IRB and coordinating centre, as applicable.

Events reported as ongoing will be reassessed at subsequent clinical visits or contacts until one of the following applies:

- Resolution
- Stabilization
- The event has been adequately characterized or explained
- The participant is lost to follow-up
- Death

SAE follow-up reports will include relevant details of the participant's clinical condition, investigations, treatment provided, outcome, and any other information necessary for assessment of the event.

All safety information will be maintained in the trial records and handled in accordance with the study protocol, applicable institutional requirements, and relevant ethical and regulatory requirements.

22.5 Financial Compensation/ Insurance

The Sponsor/Institution will provide clinical trial liability insurance covering all participants enrolled in the ROSE trial across participating centres. In the event of a research-related injury or death attributable to trial participation or trial-related procedures, appropriate medical management and financial compensation will be provided in accordance with applicable ICMR ethical guidelines, regulatory requirements, Ethics Committee recommendations, and the terms and conditions of the clinical trial insurance policy. The Sponsor/Institution will ensure that the necessary insurance coverage remains valid throughout the study period.

23. Ethical considerations

Institutional review board / ethics committee

Study protocol, patient information and informed consent will be submitted to the Institutional Review Board (IRB) of the TMC-K for approval. The study will only be started after being approved by the ethics committee. The principal investigator will inform the ethics committee about any changes in the study protocol which could interfere with the patient's safety. Furthermore, the committee will be informed of the planned or premature end of the study.

The investigators from other centres are obliged to consult their responsible IRB/EC and to wait for approval before including patients into the study, as well as to inform their ethics committee of changes in the protocol and end of study.

Data protection and privacy: The data collection will be performed pseudonymously and the patients' name and other identifiers will not appear on any case report form or in any other trial document submitted to the central data management. All collected data will be kept confidential.

This study is performed in accordance with the revision of the Declaration of Helsinki²⁵

24. Publication

The study's results will be published irrespective of the nature of the results. The principal investigator, co-investigators from the TMC-K, the study coordinators will serve as (co)-authors. Depending on recruitment numbers and absolute number of authors allowed for the respective journal, contributing centres will serve as further (co)-authors.

However, due to the number of investigators expected to participate in this trial, the number of authors may need to be limited because journals often have limitations on the number of coauthors:

1. Calculations regarding the number and position of co-authors will be based on the number of participants recruited by the investigator/institution leading the specific project.
2. This is also dependent on the sites' data completeness and data quality.
3. An investigator/institution/group will be offered a co-authorship position if it has recruited/submitted at least 4% of the total number of randomized trial participants. Every additional 4% will earn another 1 (one) additional co-author, again ensuring data quality and completeness has been adhered to.
4. Investigators/institutions/groups that recruit < 4% of randomized participants should be offered co-authorship on secondary outcome publications, however an institution/group may be considered for first publications should their contributions to trial, adherence to protocol and their data quality be exemplary.
5. The lead author is the author who proposed and developed the specific research question and will typically be the first author.

References

1. Torre LA, et al. Global cancer statistics, 2018. *CA Cancer J Clin.* 2018;68(6):394–424.
2. Di Berardino S, Bizzarri N, Cincia M et al. Value of frozen section to tailor surgical staging in apparent early-stage epithelial ovarian cancer, *International Journal of Gynecological Cancer*, 2025; 35
3. Colombo N, et al. ESMO–ESGO consensus conference recommendations on ovarian cancer. *Int J Gynecol Cancer.* 2019;29(4):728–760.
4. Berek JS, et al. NCCN Guidelines® Insights: Ovarian Cancer. *J Natl Compr Canc Netw.* 2020;18(5):543–557.
5. Prat J; FIGO Committee on Gynaecological Oncology. FIGO staging classification for cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet.* 2014;124(1):1–5.
6. Kleppe M, et al. Lymph node metastasis in stages I and II ovarian cancer: A review. *Gynecol Oncol.* 2011;123(3):610–614.
7. Maggioni A, et al. Randomised study of systematic lymphadenectomy in epithelial ovarian cancer macroscopically confined to the pelvis. *Br J Cancer.* 2006;95(6):699–704.
8. Benedetti Panici P, et al. Systematic pelvic lymphadenectomy vs no lymphadenectomy in early-stage ovarian carcinoma. *J Natl Cancer Inst.* 2005;97(8):560–566.
9. Kim HS, et al. Impact of lymphadenectomy on survival in early-stage ovarian cancer: A meta-analysis. *Ann Surg Oncol.* 2010;17(8):2127–2137.
10. Ditto A, et al. Systematic lymphadenectomy in early ovarian cancer: Is it always necessary? *Gynecol Oncol.* 2012;125(2):371–376.
11. Dowdy SC, et al. Lymphadenectomy-related complications in ovarian cancer surgery. *Gynecol Oncol.* 2009;115(3):431–435.
12. Rossi EC, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging. *Gynecol Oncol.* 2017;145(2):295–300.
13. Cibula D, et al. Sentinel lymph node biopsy in cervical cancer. *Lancet Oncol.* 2011;12(8):785–793.
14. Harter P, et al. A randomized trial of lymphadenectomy in patients with advanced ovarian neoplasms. *N Engl J Med.* 2019;380(9):822–832.
15. Kleppe M, et al. The role of lymphadenectomy in ovarian cancer: A systematic review. *Eur J Cancer.* 2014;50(3):543–551.
16. Rustin GJ, Nelstrop AE, McClean P, Brady MF, McGuire WP, Hoskins WJ, et al. Defining response of ovarian carcinoma to initial chemotherapy according to serum CA 125. *J Clin Oncol.* 1996;14:1545–51.
17. Vergote I. Re: new guidelines to evaluate the response to treatment in solid tumours [Ovarian Cancer]. *J Natl Cancer Inst.* 2000;92:1534–5.

18. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–47.
19. Rustin GJ, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynaecological Cancer Intergroup (GCIg). *Int J Gynecol Cancer*. 2011;21:419–23.
20. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205–213.
21. Katayama H, Kurokawa Y, Nakamura K, et al. Extended Clavien-Dindo classification of surgical complications: Japan Clinical Oncology Group postoperative complications criteria. *Surg Today*. 2016;46:668–685.
22. Basen-Engquist K, Bodurka-Bervers D, Fitzgerald MA, Webster K, Cella D, Hu S, Gershenson DM. Reliability and validity of the functional assessment of cancer therapy-ovarian. *J Clin Oncol*. 2001 Mar 15;19(6):1809-17. doi: 10.1200/JCO.2001.19.6.1809. PMID: 11251013.
23. Piaggio G, Elbourne DR, Pocock SJ, Evans SJW, Altman DG; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA*. 2012;308(24):2594–2604.
24. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377–381.
25. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191–2194.