Protocol ENDORISK clinical implementation study (ENDORISK-I)



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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AUC	**Area under the curve**
CV	**Curriculum Vitae**
DSS	**Disease Specific Survival**
EC	**Endometrial cancer**
ER	**Estrogen receptor**
ESMO	**European Society of Medical Oncology**
FIGO	**International Federation of Gynaecologic Oncology**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
GOCN	**Gynaecologisch oncologisch centrum Nijmegen**
GOCZ	**Gynaecologisch oncologisch centrum Zuid**
HRQoL	**Health related quality of life**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IHC	**Immunohistochemical**
LNM	**Lymph node metastases**
LVSI	**Lymphovascular space invasion**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
NEEC	**Non-endometrioid endometrial cancer**
NCCO	**Netherlands Comprehensive Cancer Organization**
NFU	**Dutch Federation of University Medical Centers**
OS	**Overall survival**
PPV	**Positive predictive value**
PR	**Progesteron receptor**
RFS	**Recurrence free survival**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
TCGA	**The Cancer Genome Atlas**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**

WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Preoperative identification of patients at risk for lymph node metastasis (LNM) is challenging in endometrial cancer (EC). Therefore, a Bayesian network model called ENDORISK was developed and validated in three external cohorts to improve preoperative risk stratification. The next step is to implement and evaluate whether use of the model improves daily clinical practice.
Objective: The ENDORISK implementation (ENDORISK-I) study aims to prospectively evaluate whether implementation of ENDORISK in daily clinical practice improves preoperative risk stratification.
Study design: A stepped wedge non inferiority study in which two oncology regions will consecutively start implementation of ENDORISK with one year interval. The ENDORISK model will be filled in and used in preoperative treatment counselling. Results will be compared to current standard clinical care which is prospectively evaluated in both regions since March 2022 in the 'evaluation of care in endometrial cancer' study (2021-7400).
Study population: all consecutive patients recently diagnosed with early stage EC who are eligible for surgical treatment, who understand Dutch and/or English and are able to fill in a digital or paper questionnaire can be included.
Main study parameters/endpoints: The ENDORISK implementation (ENDORISK-I) study aims to prospectively evaluate implementation of ENDORISK in daily clinical practice by investigating:

- The proportion of identified LNM in patients with lymph node staging (positive predictive value (PPV)) compared to *standard care*
- Proportion of patients who decide to have lymph node status assessed in ENDORISK care compared to *standard care*
- Preoperative information provision for patients and shared-decision making with the use of ENDORISK compared to *standard care*
- Patients' disease- specific-, overall survival, and health-related quality of life compared to *standard care*
- Patients' and doctors' use of and experiences with the ENDORISK-model
- Impact of ENDORISK on regional care costs

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: In the ENDORISK-I study, eligible patients will be asked by their treating gynaecologist or nurse specialist for participation in this study. Patients are asked to watch a short information video and given an optional folder with additional information about endometrial cancer and ENDORISK. After inclusion, their treating gynaecologist will fill in the ENDORISK model and then use this information for shared-decision making with their patient to determine whether their lymph node status needs to be surgically assessed:

- *Standard care* decisions for type of surgical treatment are based on patient factors (e.g. age, comorbidity, diagnostic tests), For example, if a patient has a high CA125 level, additional imaging is done in *standard care* to assess tumor extension beyond the uterus.
- Within the ENDORISK-I study, the results from these diagnostic tests are entered in the ENDORISK model, which then calculates a patients' personal risk of lymph node metastases (LNM). *ENDORISK care* decisions for type of surgical treatment are based on *standard care* in addition to the calculated result from ENDORISK. So, treatment decisions should not be made based on the calculations by ENDORISK alone, but in collaboration

with the patient and always based on all available patient information by a specialized treating clinician.

Currently used risk stratification systems recommended in endometrial cancer guidelines are based on tumor grade and have area under the curves (AUC) of 0.69-0.70 for predicting LNM [1]. ENDORISK has AUCs of around 0.82 [2-4]. The ENDORISK model was trained on patient data from 763 patients from different hospitals in Europe, including several hospitals from the Netherlands that will be participating in the ENDORISK-I study [3]. This includes data from a variety of hospital laboratories and clinical care paths. External validation was performed on three cohorts with similar patient characteristics as the prospective study population [2-4]. Patients are informed that although accuracy of ENDORISK is superior, inaccuracies may still occur with use of ENDORISK.

Regardless of study participation, patients with grade 3 EC will all be recommended to be send for referral to tertiary hospitals for counseling, as counseling of these patients is already more complicated due to other factors and tertiary hospitals have more experience with this.

No additional hospital visits are needed while participating in this study: *ENDORISK care* counselling will be incorporated in routine care. Treatment options are the same as in standard care (hysterectomy and bilateral salpingo-oophorectomy with or without determining lymph node status by lymphadenectomy or sentinel node procedure).

In addition to the extra information participants receive from ENDORISK during preoperative counselling, participants are asked to fill out two questionnaires: one within three months after primary treatment and the second one a year after primary treatment. This will take approximately 15-30 minutes per questionnaire.

We hypothesize that the use of ENDORISK will mainly add to counselling information and quality and risk of suboptimal treatment is expected to be low.

1. INTRODUCTION AND RATIONALE

In the Netherlands, endometrial cancer (EC) care is organized within clinical oncology networks. Collaborating hospitals discuss all treatment plans of gynaecologic oncology patients at regional tumour boards. *Standard care* for primary surgical treatment of EC consists of hysterectomy with bilateral salpingo-oophorectomy which can be performed in all hospitals in the Netherlands.

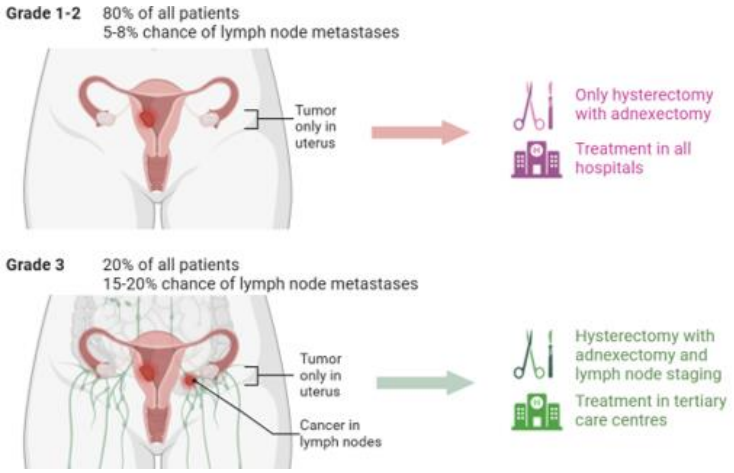


Figure 1: Standard care for primary surgical treatment of endometrial cancer.

Treatment decisions are based on the preoperative tumour grade, as outlined in clinical guidelines [5]. For women with grade 1-2 tumours (low-risk), the standard approach consists of a hysterectomy with bilateral salpingo-oophorectomy, without additional imaging unless specific indications are present (**Figure 1**). Imaging is only performed when clinical suspicion of advanced disease arises or when CA125 levels are elevated, as practiced in the GOCN (Nijmegen) and GOCZ (Brabant) regions. If imaging does not reveal abnormalities, patients continue with the standard surgical treatment.

In contrast, for women with grade 3 tumours (high-risk), which includes high-grade endometrioid and non-endometrioid EC (NEEC), tertiary care referral is recommended to assess the need for lymph node dissection as part of staging and to evaluate potential adjuvant therapies (**Figure 1**). Treatment decisions for these women are tailored based on their fitness and comorbidities, and if a patient is deemed unfit for additional therapy, lymph node removal may be reconsidered.

Currently, only high-risk women (grade 3 EC) are informed about the likelihood of lymph node metastases [6], while women with low-risk tumours (grades 1-2) do not receive such information as part of *standard care*. Women with advanced-stage EC or those requiring surgical lymph node staging are referred to gynaecologic oncology centres for further management.

This approach is in line with the current Dutch guidelines and is supported by large meta-analyses, which found no survival benefit from routine lymph node dissection in women with

clinical early-stage, low-risk endometrial carcinoma [7]. Internationally, it is recommended that sentinel lymph node biopsy may be considered for staging purposes in patients with low-risk or intermediate-risk disease, but it can be omitted in cases without myometrial invasion. Systematic lymphadenectomy is not recommended in this group [8].

Lymph node metastasis (LNM) represents one of the strongest prognostic factors in EC, and an important indicator for adjuvant therapy [9]. Pelvic and para-aortic lymph node dissection (LND) or a sentinel node procedure (SNP) can be performed as part of the primary surgical treatment, as histology is still the golden standard for assessment of nodal status [6, 10]**.** The clinical relevance of adjuvant therapy in LNM is underlined by five-year survival rates that are approximately 81% in adequately treated patients, compared to 50-60% when untreated and even 15% once further metastasized [11-19]. Most EC patients (85%) have no LNM, and LND is associated with risk of lymphedema [20-22]. While this risk is much lower in the SNP, the SNP fails in up to 20% of patients, for whom side-specific LND could still be needed [23]. Therefore, selective lymph node staging requires balancing between surgical-related comorbidity on one hand, and the clinical benefit of nodal status information for adjuvant therapy on the other hand [6].

Several prediction models in EC were developed combining preoperative histology, serum tumour markers and imaging results [24-31]. However, uptake of these models in clinical practice is slow and could be addressed to several challenges. Only few prediction models rely on preoperative data only allowing pretreatment decisions [30, 32]. So far, none of them have been implemented in to clinical practice.

Hormone receptor expression i.e. estrogen receptor (ER) and progesterone receptor (PR) have consistently shown to be correlated with LNM and belong to the most validated molecular markers in EC [9, 33-36]. Abnormal P53 expression is identified by The Cancer Genome Atlas (TCGA) as a biologically distinct molecular subgroup with the poorest prognosis and associated with high risk of LNM [37-40]. Talhouk et al. demonstrated that abnormal P53 expression was present in 89% of the European Society of Medical Oncology (ESMO) high-risk group but consisted of only 25% of advanced stage (FIGO III-IV) cases, underlining the need of additional prognosticators [39]. Molecular profiling may guide future adjuvant therapy but does not help surgeons to decide when and how to stage EC [41, 42]. L1CAM has repeatedly shown to identify patients with poor outcome and LNM in EC and could further stratify EC patients with no specific molecular risk profile [43-45]. Serum cancer antigen 125 (CA125) has repeatedly been shown to be an important prognostic factor for LNM and advanced stage in both low-, and high-grade EC [46-48]. Integrated risk classification systems rather than either clinical or molecular seem to result in the best solution [49].
The introduction of the SNP has reduced surgical-related morbidity compared to LND. However, this requires additional surgical expertise and 20-25% of cases fail bilateral mapping thus still needing (lateral) LND [50].

Within the European Network for Individualized Treatment of Endometrial Carcinoma (ENITEC) network a powerful Bayesian network (ENDORISK) predicting LNM and outcome was constructed by integrating preoperative clinical, histopathological, molecular and serum markers of EC patients [3]. For the prediction of LNM, external validation has shown a good diagnostic performance of this ENDORISK model (AUC 0.818) when compared to current risk classification (AUC 0.646) [2, 4]. These easily accessible biomarkers were shown to be strongly correlated with high-grade, NEEC, LVSI, myometrial- and cervical stromal invasion [51]. Even though prediction models have been identified by the National Cancer Institute as an area of 'extraordinary opportunity', actual prospective implementation studies remain very scarce [52]. This kind of evaluation is fundamental to investigate clinical utility, including the proper presentation of clinical data in an understandable format, whether it influences doctors' and patients' decisions, is cost effective, and it actually improves outcome.
Moreover, as patients with EC are characterized by frailty and comorbidity, surgical lymph node staging remains relevant only if the patient is fit and willing to receive adjuvant therapy.

Based on earlier studies, ENDORISK seems better at preoperative risk stratification of patients at risk of LNM than *standard care*. The ENDORISK model will be applied exclusively to the low-risk group to calculate the individual probability of lymph node metastases. The decision regarding lymph node surgery will then be made through a shared decision-making process, involving both the patient and the treating physician.

We hypothesize that using ENDORISK together with all available patient information in clinical practice (*ENDORISK care)* will be at least similar to *standard care* in stratifying patients at risk of LNM, which would result in a similar positive predictive value (PPV) compared to *standard care* (non-inferiority). However, the type of patients stratified could be more optimal, as we hypothesize that the use of ENDORISK could contribute to increased information provision and therefore better shared-decision making compared to *standard care*. This could in turn improve health related quality of life (HRQoL).

2. OBJECTIVES

Main outcomes:

- Proportion of patients who decide to have lymph node status assessed in ENDORISK care compared to *standard care;*
- Proportion of patients with LNM within patients undergoing lymph node staging (the positive predictive value, PPV) in ENDORISK care, compared with *standard care*;
- Preoperative information provision for patients and shared-decision making with the use of ENDORISK compared to *standard care.*

Secondary outcomes:

- Patients' 5-year disease- specific-, overall survival (DSS, OS), and health-related quality of life (HRQoL) compared to *standard care;*
- Experiences of patients and clinicians with the use of ENDORISK in preoperative counselling and shared-decision making on treatment;
- Impact of ENDORISK on regional care costs.

3. STUDY DESIGN

We will perform a prospective stepped wedge non-inferiority study to evaluate implementation of the ENDORISK model in clinical endometrial care practice. The ENDORISK model will be sequentially implemented in two oncological regional networks (1 & 2). For the evaluation, '*ENDORISK care'* will be compared to '*standard care'* for which data has been collected in a previous study (evaluation of care in endometrial cancer study, 2021-7400), within the same two oncological networks **(Figure 2).**

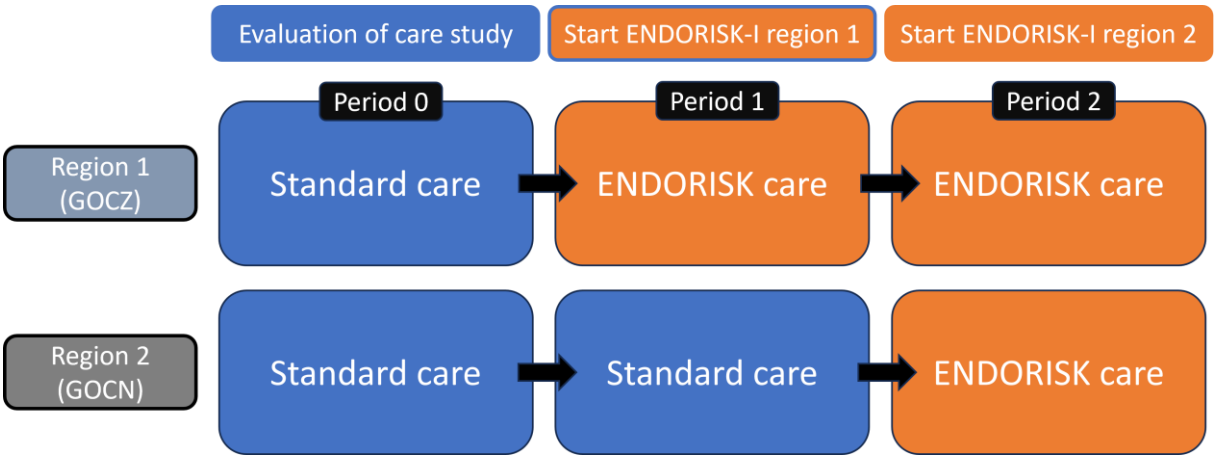


Figure 2: Stepped wedge study design

4. STUDY POPULATION

4.1 Population (base)

All patients recently diagnosed with early stage EC in the participating hospitals of the two oncological networks in the Netherlands will be requested by an independent nurse (specialist) to participate in the prospective study prior to the surgical treatment and informed consent will be obtained. The clinical oncology networks involved in the study can be seen as independent networks: gynecologic oncologic center Nijmegen (GOCN), with hospitals referring to Radboud University Medical Center Nijmegen, and gynecologic oncologic center South (GOCZ), with hospitals referring to Catharina hospital in Eindhoven.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a participant must meet all of the following criteria:

1. Diagnosed with early stage endometrial carcinoma (every grade and stage permitted)
2. Eligible for primary surgical treatment (neo-adjuvant therapy is permitted)

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. Unable to give informed consent
2. No understanding of Dutch or English language
3. Rare types of endometrial cancer, such as endometrial stroma cell sarcoma

4.4 Sample size calculation

Sample size calculation is based on the prevalence of LNM within patients undergoing lymph node staging (PPV), comparing *standard care* with *ENDORISK care.* Switching from *standard care* to *ENDORISK care* not only changes the probability of detection of LNM in patients referred to lymph node staging but might impact the patients referred to oncology centers. Therefore, we will discuss first the number of patients and corresponding LNM prevalence in *standard care* and then for the *ENDORISK care.*

Clinical practice standard care GOCN and GOCZ

Epidemiologic data on the two oncological networks (GOCN and GOCZ) were obtained from the Netherlands Comprehensive Cancer Organization (NCCO) to determine the potential inclusion in the participating oncology regions.

Number of patients

As reported by the NCCO, between 2016-2018 (3 consecutive years), a total of 1,472 patients with EC were treated in the GOCN and GOCZ region. Of these 1,472 patients: 368 patients were diagnosed with grade 3 EC (25% of total population). Of these 368 patients with grade 3

EC, 180 (48.9%) patients underwent lymph node staging, comparable in both regions (47% versus 51%). This was verified and comparable with data of the NCCO of 2021-2022 for these two regions. As these 1472 patients are the total over 2 regions in 3 years, we conclude that there are 245 EC patients per year and per network.
Thus: 30 patients underwent lymph node staging per oncology network, per year in standard care clinical practice.

Probability of detection
42 of these 180 patients that underwent lymph node staging had lymph node metastases (LNM). **Thus: detection probability (PPV) is 23% in standard care.**
Side note: We consider that two networks have similar performance. Based on the data of the NCCO there was no difference in the clinical practice of lymph node directed surgery between 2016-2018 in the two oncological networks. The risk of LNM metastasis in grade 3 EC in the NCCO is in line with previously reported data of 17-21%, irrespective of histological subtype [20, 46, 53, 54]. Lymph node directed surgery seems to be omitted in fewer patients in later reports that were requested from the NCCO from 2021-2022 (not yet public data). We are unsure what caused this, but hypothesize this could be caused by increased use of the SNP which is associated with less morbidity than LND. Therefore, instead of 50%, lymph node staging might occur in 50-75% of patients. This would mean *standard care* detection of LNM would be 245x25%x (50-75%) = 30 to 46 patients per region-year in *standard care*, with 23% of those detected with LNM (7-11 patients in total).

ENDORISK care
The inflow of 245 patients diagnosed with EC, per year, per oncology network will stay the same. When ENDORISK is implemented, patients are counseled for lymph node staging with additional support of the ENDORISK-model. Similar to *standard care*, part of the patients will not undergo lymph node staging: we assume the group of omitted patients will be smaller in the coming years due to further introduction of the SNP in clinical *standard care*.

Number of patients
Based on estimated prevalence in the ENDORISK classes, 33% of the patients have a risk of LNM as calculated by ENDORISK of ≥10% based on external validation of the ENDORISK model [3]. We assume 75% will undergo lymph node staging, as we expect the decrease in omission of staging described in *standard care* to continue, so: 75% x 33% x 245 patients per year per region will be included in the ENDORISK care periods. **Thus: 60 patients per year per oncology network will undergo lymph node directed surgery if a risk cut-off calculated by ENDORISK of 10% is recommended.**

Probability of detection
External validations of the ENDORISK model showed PPVs between 24.7% and 35.7% at a risk cut-off of 10%[2-4]. **The mean detection probability (PPV) of all external validations at a risk cut-off of 10% is approximately 30% and was therefore used to calculate the**

sample size needed. 30% of 60 patients are detected with LNM would result in 18 patients in total.

Non-inferiority

The non-inferiority margin is set at 7% based on the following two arguments:

First, a non-inferiority margin of 7% (together with an assumed 30% detection in ENDORISK) means that the point estimate for PPV of *ENDORISK care* will be similar or better to that of *standard care* (23%).

Second, with this non-inferiority margin at least as many patients with will be detected by ENDORISK as under *standard care*. To see this: in *standard care* per region per period (year):

(i) There are 245 EC patients of which 25% have grade 3 and between 50% to 75% of those have a resection, so 245 x 25% x (50 to 75)% =30 to 46 patients.

(ii) 23% of those are detected with LNM. In conclusion, (23% of 30 to 46, i.e.) 7 to 11 patients in total are detected with LNM.

In ENDORISK care:

(i) Of the 245 EC patients, 33% are expected to be at risk of 10% or more and it is expected that more of those will be willing to have a resection, therefore taking into account 75%. Then 245 x 33% x 75% = 60 patients per region-year in ENDORISK care.

(ii) With a non-inferiority margin of 7 percent points, ENDORISK would detect (30-7)%=23%, so 23% x 60 patients = 14 patients with LNM.

Thus, with a non-inferiority margin of 7%, ENDORISK detects at least as much patients as in *standard care*.

To estimate power, the number of detected LNM per region per year were generated from a binomial probability with the region detection probability and the number of patients having lymph node directed surgery. Data were analyzed using a generalized linear mixed model with identity link, normally distributed random effect, binomial error distribution, and a fixed effect for treatment and fixed effects for region. As no trend in time was observed in the risk of LNM metastasis in grade 3 EC, we will assume that there is no time trend.

Based on power simulations and the design with inclusion of the three retrospective measurements from the 'evaluation of care' study (**Table 1)**, we estimated that power was > 80% (at $\alpha = 0.05$). The years 2020 and 2021 will be excluded due to COVID-19 impacting healthcare during those years. The numbers in yellow marking could differ based on increased lymph node staging in *standard care* to up to 46 patients if 75% are staged instead of 50%. This would actually improve power.

Table 1	**Measurement:**					
Cluster :	**-3**	**-2**	**-1**	**0**	**1 (start ENDORISK-I region 1)**	**2 (start ENDORISK-I region 2)**
Regio 1	**N=30, P=23%**	**N=30, P=23**	**N=30, P=23%**	**N=30, P=23%**	**N=60 P=30%**	**N=60 P=30%**
Regio 2	**N=30, P=23%**	**N=30, P=23%**	**N=30, P=23%**	**N=30, P=23%**	**N=30, P=23%**	**N=60 P=30%**

Conclusion

Assuming an ENDORISK cut-off of 10%, the aforementioned stepped-wedge design will be sufficient to obtain power > 80%, by including: 180 patients retrospectively, **210 patients prospectively who underwent lymph node assessment, with a non-inferiority margin of 7%.** To also research the other study endpoints, **all patients with EC meeting the inclusion criteria will be included**. Therefore, 245x 2 years (region 1) + 245 x 1 years (region 2) = **up to 735 patients could be included in total.** If the sample size is not achieved within the expected two year inclusion period, this period could be extended for both regions.

5. INVESTIGATIONAL PRODUCT

5.1 Name and description of investigational product(s)

The ENDORISK model will be used in a preoperative setting to determine a patients' personal risk of LNM. This model is a Bayesian network that assesses the risk of LNM and predicts survival. Within this study, the model will only be used to assess the risk of LNM. The model will be used as an information tool to provide additional information about a patients' personalized risk of LNM within a larger context of patient characteristics. Treatment decisions should not be made based on the calculations by ENDORISK alone but always based on all available patient information by a specialized treating clinician. As ENDORISK can be used to stratify a patients risk of LNM, and thus to stratify disease stage and determine treatment, it is classified as a class C in vitro device according to the European In Vitro Device Regulation (IVDR, Regulation (EU) 2017/746).

5.2 Summary of findings from non-clinical studies

The ENDORISK model has previously been internally validated and thrice externally validated with consistent area under the curve's (AUC) of >0.80 and recently in a fourth external cohort of patients that only underwent sentinel node procedure which resulted in a comparable AUC (to be published) [2-4]. The benefit of a Bayesian network is that not all variables need to be entered as evidence into the model for a reliable calculation.

Within the European Network for Individualized Treatment of Endometrial Carcinoma (ENITEC) network a powerful Bayesian network (ENDORISK) predicting LNM and outcome was constructed by integrating preoperative clinical, histopathological, molecular and serum markers of EC patients [17]. For the prediction of LNM, external validation has shown a good diagnostic performance of this ENDORISK model (AUC 0.818) when compared to current risk classification (AUC 0.646) [2, 4]. These easily accessible biomarkers were shown to be strongly correlated with high-grade, NEEC, LVSI, myometrial- and cervical stromal invasion [51]. Even though prediction models have been identified by the National Cancer Institute as an area of 'extraordinary opportunity', actual prospective implementation studies remain very scarce [52]. Prospective evaluation is fundamental to investigate clinical utility, including the proper presentation of clinical data in an understandable format, whether it influences doctors' and patients' decisions, is cost effective, and it actually improves outcome.

5.3 Summary of findings from clinical studies

Not applicable.

5.4 Summary of known and potential risks and benefits

ENDORISK should not be used on its own but as an additional information tool besides other known patient characteristics. Oncological safety is part of preoperative counselling including the context of the individual patient, age, comorbidity and willingness to accept side-effects of primary and adjuvant therapy. In the Netherlands, the risk of LNM in grade 1-2 EC (8-10%) is

currently not discussed, while representing 50% of LNM cases, whereas surgical staging is omitted in 50% of NEEC cases. This study does not impose specific treatment plans on patients but seeks to investigate the added value of using the ENDORISK model within the entire process of preoperative risk stratification by a specialized clinician in shared-decision making with their patient.

A 10% threshold will be used as a guiding criterion, based on insights from focus groups with clinicians and patients. Additionally, the patient's comorbidities and overall fitness will be considered, particularly regarding the potential implications of additional chemotherapy or radiotherapy. Use of the model could lead to more low-grade patients feeling confident in omitting this assessment based on the ENDORISK result.

Based on calculations from various validation cohorts, it is estimated that 17% of all low-risk patients will have a probability of >10% for lymph node metastases. Given that the low-risk group represents 75% of all patients with endometrial cancer, this corresponds to 12.8% of the total patient population.

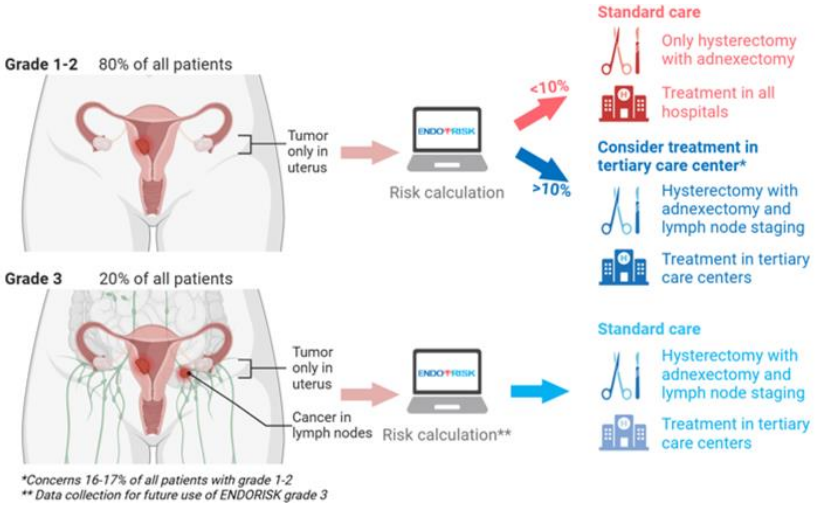


Figure 3: ENDORISK care for primary surgical treatment of endometrial cancer.

In standard care, the negative predictive value (NPV) for patients with grade 1–2 endometrial carcinoma is 8.5%. This figure is based on data from earlier studies in which all patients routinely underwent lymph node dissection (n = 36/423) [9]. The NPV of the ENDORISK model at a threshold value of 10% is currently between 3 and 6.9% and requires further evaluation [to be published].

Women in the high-risk group will continue to follow standard care pathways, including referral to tertiary care and consideration of lymph node surgery. While relevant clinical variables will still be collected for the ENDORISK model in this group, the model's calculations will not be used in clinical decision-making. As in *standard care*, comorbidities, overall fitness and personal preferences will be taken into account when determining whether to proceed with lymph node surgery. In these cases, the ENDORISK result could aid these patients in making an even more informed decision, and clinicians will decide on an individual patient level

whether the patient needs treatment in a tertiary centre or their own local hospital, similar to *standard care.*

5.5 User interface for ENDORISK

A user interface (UI) for ENDORISK was developed as described in the paper by Kleinau et al. (**Figure 4 and 5)** [56].

After initial development and publication, the UI was further updated and tested amongst seven gynecologists with experience in endometrial cancer care: four from the Netherlands, one from Germany and two from Italy using a semi-structured test guide. The UI was iteratively improved for both usability and explainability. Tests were recorded and documented to allow for direct implementation of changes after each test.

Usability improvements included an enhanced tutorial for novel users, presets for common tasks and complete translations in English, Dutch and German. Explanations of model predictions were improved by adding new detail views of individual Bayesian Network nodes, replacing color-coded percentages with more accurate bar charts and adding support for minimizing likelihoods in addition to maximization.

Users enter evidence items locally via the UI. For each model use, a unique study identification number is generated. The evidence items are then sent to the backend for calculations—without transmitting any user-identifiable information. Simultaneously, the input and output, along with the study ID, are automatically exported to a PDF file that must be saved in the patient record. The UI logs the study ID, submitted input, and generated results, allowing traceability of the input data. No personal patient information is stored or retained in the UI. These measures safeguard user privacy and data confidentiality.

Users are able to request assistance with the UI by clicking on a ‘help’ button. Users are then able to send an email to the research-team and are given the option to automatically include all information added up to that point in to the UI. This ensures the research team can provide proper help and feedback. A research phone number is also available to clinicians in the study for more immediate assistance during working hours.

The UI does keep track of what buttons people click on, without cookies and without geographical data besides the country and without tracking individual evidence items. These measures ensure we will be able to track if users click on the correct buttons (e.g. ‘add evidence’, ‘download’, ‘compare’) and we will be able to see which types of explanations they use most without logging sensitive information.

The UI can be accessed through the website https://endorisk.eu and then clicking on the 'open model' button (Figure 5). The UI is hosted on Github and the backend and the database on Heroku.

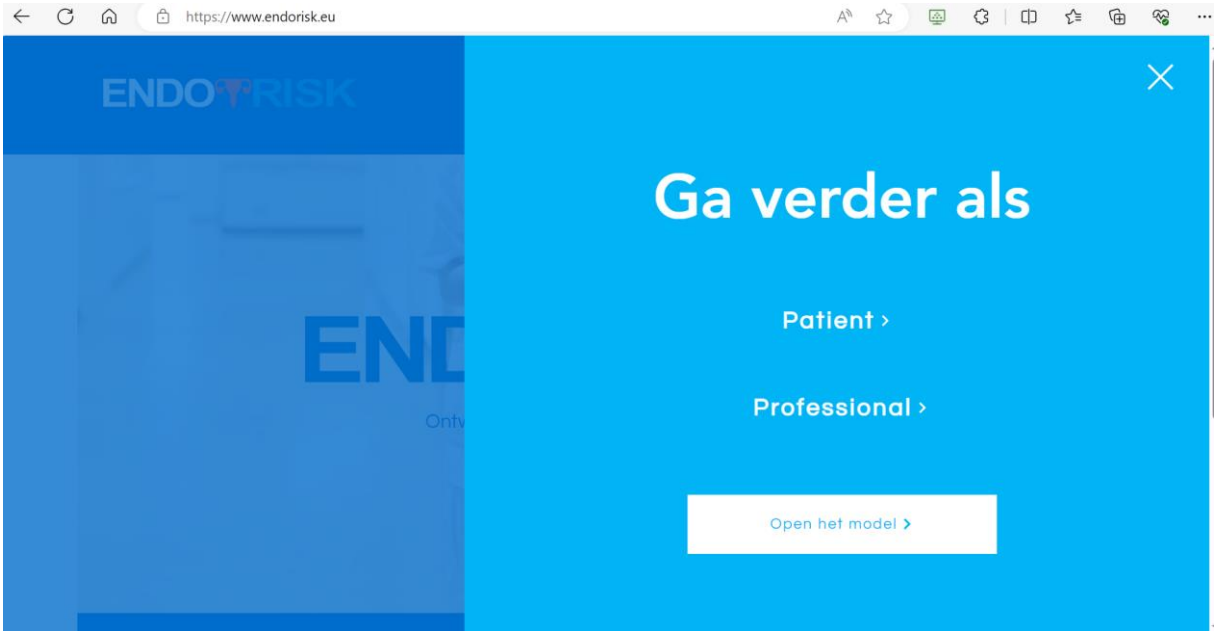


Figure 5: ENDORISK website.

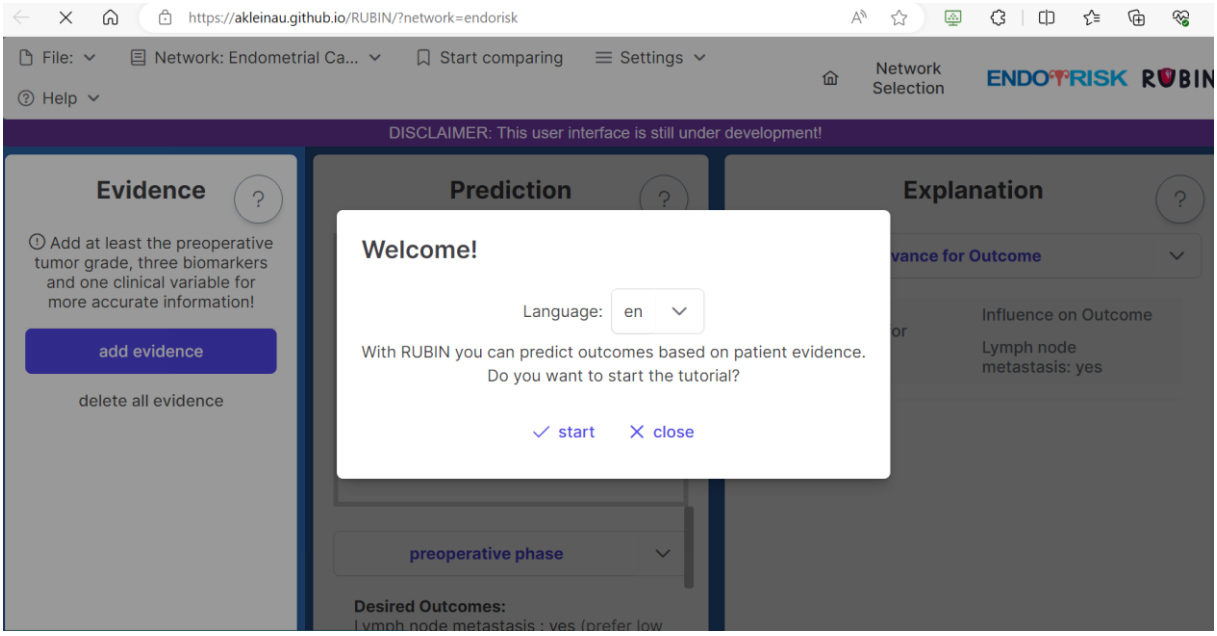


Figure 4: ENDORISK User Interface.

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameters/endpoints

- Proportion of patients who decide to have lymph node status assessed in ENDORISK care compared to *standard care*
- Proportion of patients with lymph node status assessed and LNM (positive predictive value (PPV)) in ENDORISK care compared to *standard care*
- Information provision score
    - Questionnaire: EORTC QLQ-INFO25 [57], with additional questions specific to ENDORISK use, within 12 weeks after primary surgery
- Shared-decision making score
    - Questionnaire: SDM-Q-9 [58], with additional questions specific to ENDORISK use, within 12 weeks after primary surgery

6.1.2 Secondary study parameters/endpoints

- 5-year disease specific survival (DSS): proportion of patients alive 5 years post-surgery (or died due to endometrial cancer)
- 5-year overall survival (OS): proportion of patients alive 5 years post-surgery (or died due to any cause)
- Health-related quality of life (HRQoL)
    - Questionnaire: EORTC QLQ-C30 [59] within 12 weeks and 12 months after primary surgery
- Treatment-related morbidity
    - Questionnaire: EORTC QLQ-EN24 [60] within 12 weeks and 12 months after primary surgery
    - Questionnaire lymphoedema: EORTC IL76 [61] and LYMQOL [62], 12 months after primary surgery
- Clinicians' experiences with ENDORISK care
    - Questionnaire at baseline, and 9 months and 18 months after start of the inclusion period in their hospital
    - Additional in depth interviews with sample of participating clinicians to evaluate user experiences, within 1 year after start of the inclusion period in their hospital
- Impact of ENDORISK on regional care costs

6.1.3 Other study parameters

- Health Literacy questionnaire (included with first questionnaires within 12 weeks after surgery)
- Charlson-index (included with first questionnaires within 12 weeks after surgery as reported by patient and as reported by clinician/researcher from patient records)

Applied clinical care:

Data collection from the NCCO and patient records

- Patients characteristics:
    - Age (at diagnosis)
    - BMI, length and weight
    - Social status
        - Partner yes/no
        - Work
- Diagnostics (if performed):
    - Preoperative histology of tumor: grade (1,2 or 3), histology type and biomarker staining performed on tissue
    - Preoperative performed blood samples: cancer antigen 125, hemoglobin, platelets
    - Imaging: transvaginal ultrasound (TVU), CT, MRI or PET-CT
        - Lymph nodes suspect for LNM visible on imaging yes/no
        - Other suspected metastases on imaging
        - If TVU of MRI performed: suspected invasion of myometrium
    - PAP-smear: yes/no, KOPAC-B
        - Endometrial carcinoma cells in PAP-smear yes/no
- Treatment:
    - Type of surgery
        - Laparotomic surgery or laparoscopic surgery (incl. Robot surgery)
    - Lymphadenectomy yes/no
    - Sentinel lymph node dissection yes/no
    - Additional surgical staging
    - Deviation from guideline recommendations (e.g. :due to comorbidity, patient preferences)
- Pathology

    - Sentinel lymph node positive/negative and/or lymphadenectomy positive/negative
        - Total number of removed lymph nodes
    - Myometrial invasion (MI) yes/no
    - Lymph vascular space invasion (LVSI) yes (focal or substantial)/no
    - International Federation of Gynecology and Obstetrics (FIGO) stage
- Adjuvant treatment
    - External beam radiotherapy (EBRT), vaginal brachytherapy (VBT), chemotherapy (CT), combination chemo- & radiotherapy (CRT)
    - Deviation from guideline recommendations (e.g. :due to comorbidity, patient preferences)
- Follow-up at 1 to 5 years after surgery:
    - Outcome: date of last follow-up visit at gynecologist, date of death, cause of death (EC related of unrelated)
    - Recurrence: date of recurrence, location

- Referral to oncology centre yes/no

6.2 Randomisation, blinding and treatment allocation

Not applicable, the starting region is chosen based on which region first reaches enough inclusions in the prior ‘evaluation of care’ study to switch to ‘ENDORISK-I’.

6.3 Study procedures

Training of clinicians

Prior to start of the inclusion period, clinicians of participating hospitals will be trained in use and counseling with the ENDORISK model according to recommendations from prior qualitative research (focus groups) which also included clinicians from the current study regions (to be published). Researchers will perform site visits to give a demonstration to participating clinicians with an overview of the study, the ENDORISK model and a demonstration of how to accurately use and counsel with the model. Clinicians will then receive an e-learning including a written explanation of the model, a demonstration video of the user interface and several test patients' cases which clinicians can use to become familiar with the user interface of ENDORISK and to train counseling according to additionally provided use and counseling guidelines. These are afterwards discussed with the researcher. Where necessary, follow up visits will be done by researchers for additional individual training.

Screening and inclusion of participants

Patients will be screened and asked for inclusion after initial diagnosis with endometrial cancer (**Figure 6)**. In Radboud UMC this will be done by an independent researcher/research nurse. The procedure will be included in the coordination with the participating centers. All patients that meet the inclusion criteria are given the study information including the informed consent form and are requested to view a counseling video after their diagnosis (consultation). The video discusses endometrial cancer and the use of ENDORISK and will aid in providing uniform counseling information to patients across all participating hospitals. In previous qualitative research in which 18 patients with endometrial cancer were interviewed (to be published), patients recommended giving study participants a choice of extent of information provision. Therefore, prospective participants are also given a patient information folder with information of the counseling video in writing and including more extensive information about endometrial cancer and the ENDORISK model.

Interested patients are given the chance to ask questions regarding the study prior to the next consultation, which is usually one to two weeks after their diagnosis consultation. During the consultation in which treatment is discussed, patients interested in participating return the informed consent form. Patients with grade 3 EC will all be recommended to be send for referral to tertiary hospitals (similar to *standard care)* within the ENDORISK-I study irrespective of their calculated risk of LNM by ENDORISK, as counseling of these patients is more complicated due to other factors and tertiary hospitals have more experience with this. Referring hospitals are responsible for obtaining informed consent for the study prior to consultation in the tertiary hospital.

Counseling of participants with the ENDORISK model

Previous qualitative research (to be published) showed that patients vary in the level of information they prefer for shared-decision making on treatment. Therefore, participants are asked whether they want to know their personalized risk of LNM as calculated by the ENDORISK model which will then be used in standard counseling information to determine their preferred treatment. Participants may also choose to not be told the result from the ENDORISK model and to only let their clinician be informed by it, this option is explicitly noted in the informed consent. Patients in this situation are then told by their clinician which treatment their clinicians deem most optimal for their situation (most similar to *standard care).* Clinicians are requested to document the type of counselling of the patient record.

Use of the ENDORISK model

Important: the ENDORISK score must only be used in the consultation and shared-decision making in low-grade patients (grade 1-2) ≥45 years of age as an aid to diagnose. This is in accordance with the intended purpose of this In Vitro Medical Device (IVD), described in the Investigator's Brochure. Patient's outside this scope, including grade 3 EC patients and patients younger than 45 years of age, *standard of care* must always be the provided, independently of the generated ENDORISK score.

The gynecologist enters the participants information into the ENDORISK user interface based on the diagnostic tests they perform in the context of *standard* care. To ensure a minimum level of accuracy in the calculation (maintaining an AUC >0.80), a minimal set of variables, including the preoperative tumor grade, three out of four biomarkers (ER, PR, p53 and/or L1CAM) and CA-125, are made mandatory to submit by the user before generation of a risk score is enabled. All of the aforementioned variables are part of *standard care*. Participants are told their personalized calculated risk percentage of lymph node metastases based on aforementioned preferences, together with other clinical information deemed relevant by their gynecologist or nurse specialist as is currently performed in *standard care*.

Determining optimal surgical treatment

According to the Dutch clinical guideline, lymph node staging is recommended in patient with clinical early stage, grade 3 endometrial cancer, who have about 20% risk of LNM. As part of the preparatory phase for implementing ENDORISK, eight focus groups including gynecologists, medical oncologists, pathologists and radiation oncologists from the participating hospital regions and several other hospitals in the Netherlands were organized resulting in a final consensus of using a cut-off of 10% risk of LNM (to be published). Above this cut-off, the clinician can consider to recommend assessment of lymph node status (Figure 6**)**. Yet, the choice of removing lymph nodes for assessment is entirely up to the patient together with their clinician according to current practice irrespective of their individual risk percentage. Therefore, the cut-off should only be seen as a background framework for clinicians.

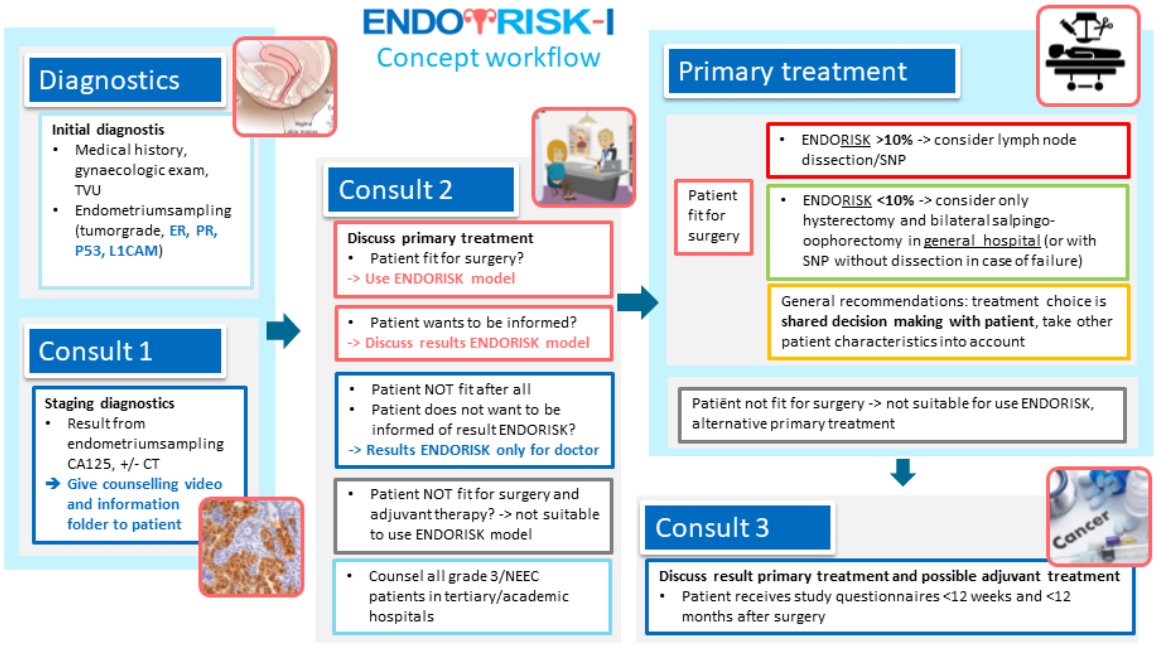


Figure 6: Clinical workflow.

Removal of enlarged lymph nodes during surgery that were not preoperatively recognized, or in patients with clinical suspicion of advanced stage EC and/or enlarged lymph nodes on preoperative imaging is considered as part of standard clinical care in both care models (*standard & ENDORISK care*).

Evaluating ENDORISK implementation in clinical practice

The main outcome parameter is defined as the proportion of LNM in patients who underwent lymph node staging by either SNP and/or LND (PPV) and will be compared to the PPV in *standard care.* As use of the ENDORISK model together with all available patient information could lead to patients making more informed choices to consciously omit lymph node staging, additional outcome parameters will be proportion of patients who decide to undergo lymph node staging compared to guideline recommendations, and preoperative information provision and shared-decision making as compared to *standard care.*

Evaluation of patients' experiences within ENDORISK care

Patients receive a set of questionnaires within 12 weeks after surgery and 12 months after surgery (**Figure 6).** Each set of questionnaires takes approximately 20 to 30 minutes to fill in. Questionnaires are send either digitally by E-mail via CastorEDC or on paper depending on the preferences they indicated during the informed consent procedure.

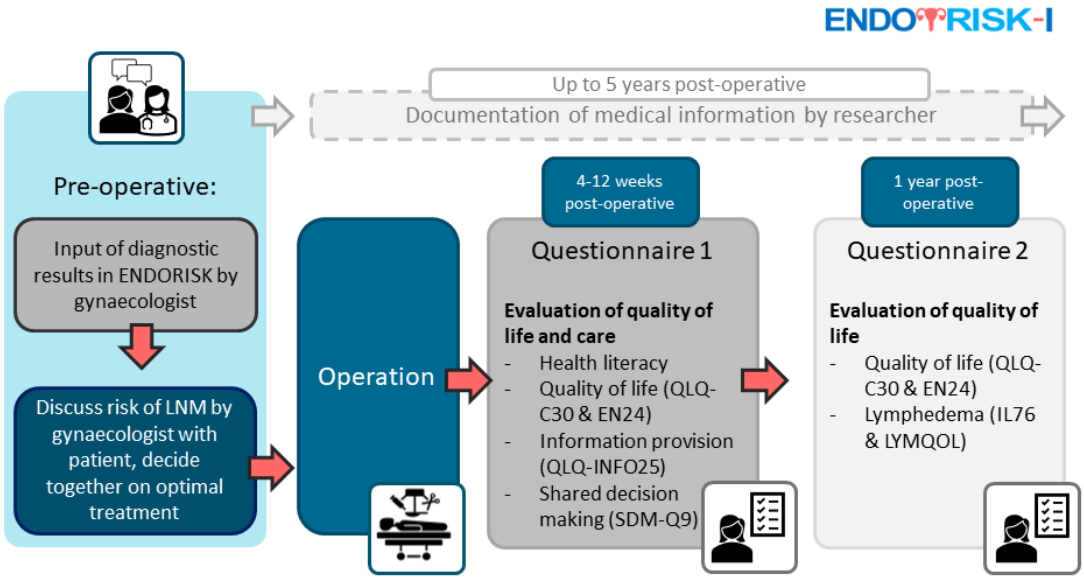
Information provision and shared-decision making will be evaluated by using the validated EORTC QOL-INFO25, and SDM-Q-9 questionnaires [57, 58]. The EORTC QOL-INFO25 serves for evaluation of information provision and satisfaction about EC treatment. The SDM-Q-9 is a 9-item questionnaire, in which patients are asked to score different aspects on shared-

decision making on a six-point scale. These questionnaires will be send within 12 weeks after surgery.

For the evaluation of use and experience of patients with the ENDORISK-model, additional questions about ENDORISK use during counselling were added to the EORTC QOL-INFO25 and SDM-Q-9 questionnaires based on earlier qualitative research within the same study region (to be published), as the questions fit within the domains of these questionnaires. However, they will be analyzed separately from the standardized questionnaires.

Health-related quality of life will be evaluated within 12 weeks after surgery and 12 months after surgery by the EORTC QLQ-C30 and QLQ-EN24 [59, 63]. The EORTC QLQC30 contains five functional scales on physical, role, cognitive, emotional and social functioning, a global health status/QoL scale, three symptom scales on fatigue, nausea and vomiting, and pain, and six single items. The EORTC QLQ-EN24 assesses endometrial cancer specific symptoms: lymphedema, urological symptoms, gastrointestinal symptoms, body image and sexual/vaginal symptoms, back/pelvic pain, tingling/numbness, muscular/joint pain, hair loss, taste change, sexual interest, sexual activity, and sexual enjoyment. Questions about sexual symptoms are not mandatory to answer. In addition, with the questionnaires send 12 months after surgery, the questionnaires EORTC IL76 and LYMQOL will be send to evaluate complaints of lymphedema [62] [61].

Figure 6. study workflow



Evaluation of clinicians' experiences with the ENDORISK model

For the evaluation of use and experience of clinicians with the ENDORISK-model, a questionnaire and interview guide were developed tailored on the requirements for clinicians by earlier qualitative research within the same study region (to be published). The questionnaire will be send at baseline and 12 months to evaluate use and experience of

clinicians over time. A small sample of clinicians will be invited for additional in depth interviews within the first year to evaluate use and experience of ENDORISK in depth.

Data collection
Data collection will be stored into CastorEDC data management software by members of the coordinating research team or by the local researchers.

Patient characteristics (age at diagnosis, BMI, comorbidity (hypertension and DM), preoperative tumor characteristics (tumor type, grade and molecular ER, PR, P53 and L1CAM status done on tumor tissue), serum markers (CA-125, platelet count), results of PAP smear if available, results of imaging if performed, primary surgical procedure (hysterectomy with or without lymph node directed surgery), final FIGO stage, and applied adjuvant therapy (VBT, EBRT, CT, CRT) will be registered, and follow-up (death, recurrence) will be documented till 5 years after primary treatment.

As secondary outcome parameters, 5-year disease specific and overall survival (DSS and OS) and Health Related Quality of Life (HRQoL) in *ENDORISK care* will be compared to *standard care* to evaluate the impact of ENDORISK model use on these parameters. In addition, patients' and doctors' use and experiences with the ENDORISK model will be evaluated and an analysis of the impact of ENDORISK on regional care costs will be performed.

Patients' outcome including recurrence of endometrial cancer and death due to endometrial cancer or other causes will be documented till at least 5 years after primary surgery to calculate DSS and OS.

Evaluating impact of ENDORISK on regional care costs
Potential differences in healthcare expenditures across regions will be assessed, focusing solely on direct costs, considering variations in referral patterns, treatment approaches, and clinical decision-making compared to *standard care*. Specifically, changes in the number and/or type of lymph node assessment. This data will be used to estimate the impact of ENDORISK in an oncology network on regional care costs. By comparing these factors, we aim to determine whether the implementation of the ENDORISK model influences regional healthcare spending regarding lymph node staging in endometrial cancer care. This impact analysis will be generated as a series of scenario analyses. Scenarios will be determined together with relevant stakeholders**.**

6.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. Upon request for withdrawal, participants are asked whether they only wish to withdraw from study actions (e.g. filling out a questionnaire) or wish to withdraw completely (thus also stopping any further data collection from their medical records by the researchers).

Participants are made aware in the study information that study data collected until point of withdrawal can be used by researchers.

6.5 Follow-up of subjects withdrawn from treatment

Not applicable as no study-specific treatment is given.

6.6 Premature termination of the study

No scenario is expected in which premature termination of the study might need to occur.

7. SAFETY REPORTING

7.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

7.2 AEs, SAEs and Device Deficiencies

7.2.1 Adverse events (AEs) (IVDR 2017/746, art 2.60)

Any untoward medical occurrence, inappropriate patient management decision, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of this performance study.

Only study related AEs will be recorded. This means all AEs related to participation in this study protocol, meaning a deviation of *standard care* for primary treatment due to use of the ENDORISK model in preoperative counselling will be recorded. Investigators will record AE's on the Adverse Event form in Castor EDC. All other AEs will not be reported, as no patient benefit is expected from this.

7.2.2 Serious adverse events (SAEs) (IVDR 2017/746, art 2.61)

Any adverse event that led to any of the following:

- a patient management decision resulting in death or an imminent life-threatening situation for the individual being tested, or in the death of the individual's offspring,
- death,
- serious deterioration in the health of the individual for whom the ENDORISK was used in preoperative counseling for treatment decision making that resulted in any of the following:
    i. life-threatening illness or injury,
    ii. permanent impairment of a body structure or a body function,
    iii. hospitalization or prolongation of patient hospitalization,
    iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
    v. chronic disease

An elective hospital admission will not be considered as a serious adverse event.

Our study population has a high risk of complications, including death, which are inherent to their vulnerable condition (endometrial cancer) and these are considered unrelated to the intervention. Only study related SAEs will be recorded and reported immediately by investigators on the Adverse Event form in Castor EDC to the sponsor, in addition to notification of the sponsor by phone for death or life-threatening categories and by e-mail for other categories. This means all SAEs related to participation in this study protocol, meaning a deviation of *standard care* for primary treatment due to use of the ENDORISK model in preoperative counselling, will be recorded and reported, including any new findings in relation to any of these SAEs. All other SAEs will not be reported, as no patient benefit is expected from this.

7.2.3 Device deficiency (IVDR 2017/746, art 2.62)

Any inadequacy in the identity, quality, durability, reliability, safety or performance of the ENDORISK model for this performance study, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate will be recorded by investigators on the Adverse Event form in Castor EDC and reported by the sponsor, including any new findings in relation to any of these device deficiencies.

7.2.4 Reportable events (IVDR, art 76, sub 2)

A reportable event is:

a) any serious adverse event that has a causal relationship with the device, the comparator or the study procedure or where such causal relationship is reasonably possible;
b) any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate;
c) any new findings in relation to any event referred to in points (a) and (b).

All causality assessments will be done according to section 9 of MDCG 2020-10/1. The period for reporting shall take account of the severity of the event. Where necessary to ensure timely reporting, the sponsor may submit an initial report that is incomplete followed up by a complete report.

The sponsor will report the reportable events using the MDCG 2020-10/2 table through the web portal *ToetsingOnline* to the accredited METC that approved the protocol,
without undue delay but not later than 2 calendar days (and 2 calendar days for any new follow-up information) for death and life threatening and 7 calendar days for other categories (and 7

calendar days for any new follow up information) after awareness by sponsor of the event/new finding to it.

7.3 Follow-up of adverse events

All SAEs that fit the aforementioned criteria will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

7.4 [Data Safety Monitoring Board (DSMB) / Safety Committee]

Based on the structured risk analysis as described in chapter 11 and the criteria described by the Dutch Federation of University Medical Centers (NFU), this study can be classified as low risk. Therefore, no DSMB is needed.

8. STATISTICAL ANALYSIS

The data of the historical and prospective time periods will be analyzed using a generalized linear mixed model with identity link, normally distributed random effect, binomial error distribution, and a fixed effect for treatment and fixed effects for region.

Baseline characteristics will be compared between the two study arms using descriptive statistics to assess for imbalance. Analysis follow the intention-to-treat principle. Reasons for missing data will be collected as much as possible but as primary analysis, missing-at-random will be assumed for the outcomes.

8.1 Primary study parameter(s)

For the main outcome, identified LNM (PPV) in patients with lymph node staging in these patients will in compared between the risk difference between *standard care* and *ENDORISK care* using the generalized linear mixed model mentioned for the sample size calculation. The estimated intervention effects will be reported as the difference in percentage for binary outcomes between the intervention and control arms. If the model does not converge, we will fall back on a logit link (i.e. logistic regression with a odds ratio as effect measure). The impact of *ENDORISK care* on information provision (EORTC QLQ-INFO25) and shared-decision making (SDM-Q-9) will be evaluated with a linear mixed model.

8.2 Secondary study parameter(s)

Secondary outcome measurements will be compared between *Standard care* and ENDORISK care. For patients' outcome measurements we will focus on comparing the health-related quality of life between *Standard care* and *ENDORISK care*. For these secondary outcomes,

mean scores and standard deviations (SD) will be calculated for the multi-item and single-item scales according the recommended analysis of the validated questionnaires [57-59, 63]. Changes in HR-QoL in the EORTC-QLQ-C-30 and EN-24 between baseline and 12 months postoperatively will be calculated and compared between arms using a Linear Mixed Model analysis. Follow-up will be documented at 1 year up until 5 years after primary surgery and will include recurrence and mortality (overall (OS) and caused by EC (DSS).These outcomes will be analyzed using Cox regression with region as strata. The patients' and doctors' experiences with the ENDORISK model will be described using mean and 95%-CI (as this concerns no comparison). Impact on regional care cost will be analyzed based on the scenario's that will be developed with relevant stakeholders.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki, version of October 2013.

9.2 Recruitment and consent

Patients will be recruited by their treating gynaecologist or nurse specialist after initial diagnosis with endometrial carcinoma. The patient folder and counselling video will be distributed to them to provide further information on ENDORISK and this study. They will be given until their next consult in which they discuss their treatment to consider if they want to participate in the study. This time can range from one to two weeks. If patients are referred to a tertiary/academic centre, the referring hospital is responsible for obtaining informed consent prior to consultation in the referral centre.

9.3 Benefits and risks assessment, group relatedness

Current risk estimation of lymph node metastases is based mostly on tumor grade. Patients with grade 3 endometrial carcinoma have approximately 20% risk of LNM and are therefore recommended by guidelines for lymph node status assessment [6, 20]. However, research shows that LNM are prevalent in about 8-10% of grade 1 and 2 patients as well [6, 20]. These patients are currently missed with *standard care* and therefore undertreated. With the SNP, risk of lymphedema is low, but for the 20% of patients with bilateral failure, side-specific LND might steel be needed [23]. LND leads to lymphoedema in 5-20% of patients which can have a large impact on their quality of life [21, 22, 64]. This means that 80% of grade 3 patients are at risk of lymphedema without having LNM and are therefore overtreated. The ENDORISK model (AUCs >0.80) seems to be more accurate than standard risk estimation of LNM (AUCs 0.69-0.70) and could therefore reduce undertreatment and overtreatment [1-4].

9.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

9.5 Incentives (if applicable)

Patients or clinicians of patients participating in the study will receive additional information about their personal preoperative risk of lymph node metastasis by allowing their clinician to use the ENDORISK model. Apart from this additional information, there are no incentives for patients participating in the study.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

Data of patient records and patient questionnaires will be pseudo-anonymized for other researchers and stored in CastorEDC data management software.

Data will be stored at the department of Obstetrics and Gynaecology, Radboudumc. The non-anonymized patient records will only be accessible for the treating gynaecologist and researcher or research-supporting staff collecting data for the participating centre. Patient questionnaires and data collection in Castor will be pseudo-anonymized. The key for patient identification will only be accessible for the research team that included the patient. If the coordinating research team assisted in the informed consent procedure for a local hospital, all identifying information will be transferred to the original hospital and anonymized in the database of the coordinating team at the end of the inclusion period. Keyfiles and filled in informed consent forms will be archived at the hospital from which a patient was included.

After all eCRFs are locked, a non-adaptable export including an export of the CastorEDC audit trail and an empty export of the study structure will be archived together with other pseudonymized study files, separate from identifiable study files, on department files with access restricted to the research team. This will also include adaptable anonymized files used for analysis of study data. The non-adaptable anonymized eCRF export and audit trail export will also be send to the participating hospitals for archiving and audit-purposes.

Only anonymized datasets (without patient numbers, date of birth or name) will be shared with other people relevant to the study or relevant to additional studies as reported in the patient information folder.

Interviews with clinicians are audio-recorded and then transcribed leaving out identifying information. Audio recordings will be stored separately from the transcriptions on a restricted department file.

Study documents will be archived for 15 years after conclusion of the study period: physical source documents in a locked department storage and digital documents in restricted department files, all only accessible by the research team of the local hospital.

10.2 Monitoring and Quality Assurance

This study will be monitored by a monitor from the team of Clinical Research Monitoring of the Radboud university medical center. Based on criteria by the NFU, this study falls in the lowest risk class for monitoring. While ENDORISK is a medical device, it is used digitally via an internet browser and only used to obtain additional information from diagnostic tests from *standard care*. Therefore, the guidelines for 'other research' from the NFU are most applicable to this study as opposed to the guidelines for medical guidelines. All centres will remotely be visited for monitoring approximately a month after first exclusion except for the Radboudumc and Catharina hospital. Two interim visits will be held in the Catharina hospital: one after first inclusion and one after the last inclusion. After the first inclusion in the Catharina hospital, an interim visit will be held in the Radboudumc to monitor the Trial Master File. In the Radboudumc, additional interim visits will be held within a month after first inclusion there and the third one after the last inclusion. The separate monitoring plan for this study can be observed for additional information.

10.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

10.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the moment that the 5-year follow up data has been collected for all included and still participating patients.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.6 Public disclosure and publication policy

This study will be registered in a public trial registry before the first patient is recruited. Results of the study will unreservedly be published in a peer reviewed journal, and if possible, will be published with open access.

11. STRUCTURED RISK ANALYSIS

11.1 Potential issues of concern

a. Level of knowledge about mechanism of action

The ENDORISK model has previously been internally validated and thrice externally validated with consistent area under the curve's (AUC) of >0.80 and recently in a fourth external cohort of patients that only underwent sentinel node procedure which resulted in a comparable AUC (to be published)[2-4]. The benefit of a Bayesian network is that not all variables need to be entered as evidence into the model for a reliable calculation. This was validated in the original paper by Reijnen et al. and validated on the other external cohorts by the research team (to be published)[3].

The ENDORISK model was constructed by integrating preoperative clinical, histopathological, molecular and serum markers of EC patients [17]. For the prediction of LNM, external validations have shown a good diagnostic performance of this ENDORISK model (AUCs >0.80) when compared to current risk classification (AUC 0.65-0.70)[1, 2, 4]. Biomarkers included in the model were shown to be strongly correlated with high-grade, NEEC, LVSI, myometrial- and cervical stromal invasion and all variables in the model are already part of *standard care* are recommended in international guidelines [6, 51].

b. Study population

The ENDORISK model was trained on 763 patients from several hospitals in Europe, including hospitals in the current study region [3]. It was also validated with comparable good results on three external cohorts from Norway, Germany and Czech Republic with similar patient characteristics to the prospective study population [2-4].

c. Interaction with other products

While on its own, the ENDORISK model already performs well in preoperative prediction of LNM, it must be used together with other clinically relevant patient characteristics to determine optimal treatment, similar to current practice in *standard care*. Variables in the ENDORISK model have already been in use within *standard care* for years and are recommended for preoperative risk stratification by international guidelines[6].

d. Predictability of effect

All previous external validations resulted in similar AUCs >0.80, with PPV ranging from 24-35% which are all at least comparable compared to *standard care* PPV as described by published NCCO data.

11.2 Synthesis

The ENDORISK model was consistently validated with AUCs >0.80 in study populations comparable to the prospective study population. As there is still a risk of error in risk calculation by the ENDORISK model, clinicians are recommended to also keep other patient characteristics, e.g. comorbidity, age, diagnostic tests not part of the model and patient preferences, in consideration when determining optimal treatment together with their patient. Based on earlier published results, ENDORISK could be comparable to even superior compared to current risk stratification systems. Patients are already exposed to a risk of error in preoperative risk stratification in *standard care* and are therefore currently already at risk of under- or overtreatment.

High grade patients in *standard care* are referred to tertiary centers for preoperative risk assessment, as counselling and treatment of these patients is more complex. To ensure safety, high grade patients within *ENDORISK care* will all be referred to tertiary centers as well, irrespective of their result from ENDORISK. High grade patients might still choose to omit lymph node assessment, however other factors, e.g. comorbidity and therefore less suitability for surgery, will be more important in this choice, comparable to current practice in *standard care.*

As ENDORISK is only one of the many factors involving treatment decision, the risk of under- or overtreatment is not expected to be larger for participants of the study. Using the model could even improve preoperative counselling and therefore patients' experiences within endometrial cancer care. Therefore, we deem the risk of participating in this study acceptable.

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