Project protocol

ENdometrial cancer SURvivors' follow-up carE (ENSURE): Less is more? Randomized controlled trial to evaluate patient satisfaction and cost-effectiveness of a reduced follow-up schedule

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Protocol signature sheet:

ENdometrial cancer SURvivors' follow-up carE (ENSURE): Less is more?

Randomized controlled trial to evaluate patient satisfaction and cost-effectiveness of a reduced follow-up schedule

I confirm agreement to conduct the study in compliance with the protocol.

I have read the protocol and appendices. I understand the contents and intend to fully comply with all requirements and the applicable current local and international regulations and guidelines. No changes will be made without formal protocol amendments.

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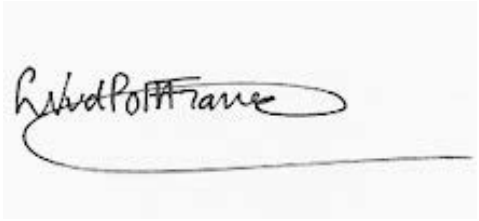
Principal Investigators Prof. dr. L.V. van de Poll-Franse	Netherlands Comprehensive Cancer Organisation (IKNL), Tilburg University		17-10-2016
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The trial is conducted with support of the Dutch Gynaecological Oncology Group

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Protocol synopsis

Title	ENdometrial cancer SURvivors' follow-up carE (ENSURE): Less is more? Randomized controlled trial to evaluate patient satisfaction and cost-effectiveness of a reduced follow-up schedule
Study design	Multicentre randomized controlled trial
Study population	Women with stage 1A or 1B endometrial cancer, for whom adjuvant radiotherapy is not indicated
Intervention	4 follow-up visits, after 3, 12, 24 and 36 months (intervention) vs. regular follow-up according to the guideline, 10-13 visits during 5 years (control)
Study objective	The aim of this study is to compare a reduced follow-up schedule of 4 visits among low-risk, early-stage endometrial cancer survivors, with the schedule according to the current Dutch guideline that includes 10 to 13 visits, on: Primary outcomes: 1. Patient satisfaction with follow-up care (at 6, 12, 36 and 60 months after completion of primary treatment) 2. Costs-effectiveness from the health care perspective (after 3 and 5 years.) Secondary outcomes: • Health care use -gynaecologist, (specialist) nurse, primary care physician and other health or care services-; adherence to the indicated follow-up protocols; reasons for non-adherence • HRQoL, worry including fear of recurrence, anxiety and depression, and satisfaction with information provision • Health care providers' satisfaction with follow-up schedule (gynaecologist, (specialised) nurse) • Time till recurrence and survival.
Inclusion criteria	1. Patients with Endometrioïd type endometrial carcinoma with stage 1 (FIGO, 2009) disease, with the following combination of stage, age and grade: - Stage 1A, any age, grade 1 or 2; - Stage 1B, < 60 years, grade 1 or 2 without LVSI; 2. Written informed consent; 3. Sufficient oral and written command of the Dutch language.

Exclusion criteria	1. Any other stage and type of endometrial carcinoma 2. Histological types papillary serous carcinoma or clear cell carcinoma 3. Uterine sarcoma (including carcinosarcoma) 4. Radiotherapy for current endometrial carcinoma 5. Previous malignancy (except for non-melanomatous skin cancer) < 5 yrs 6. Having metastases of other tumours; 7. Confirmed Lynch syndrome 8. Previous pelvic radiotherapy
Number of centers	Minimally 30, and maximally 50 centres can join the ongoing study after authorization
Number of patients	282
Planned	With an expected participation of 60% we need two year inclusion (alternative scenario: with 40% participation we need 2 year and 8 months inclusion) 5 year follow-up with an evaluation after 3 and 5 years

List of abbreviations

CCMO:	Centrale Commissie Mensgebonden Onderzoek
CRF:	Case Report Form
CT:	Computed Tomography
DGOG:	Dutch Gynaecological Oncology Group
EORTC:	European Organisation for Research and Treatment of Cancer
HRQoL:	Health-Related Quality of Life
QoL:	Quality of Life
IKNL :	Netherlands - Comprehensive Cancer Organisation (IKNL)
CCCS:	Comprehensive Cancer Center South (IKZ)
LVSI:	Lymph-Vascular Space Invasion
MEC:	Medical Ethics Committee
SCP	Survivorship Care Plan
WMO:	Wet Medisch-wetenschappelijk Onderzoek

Study summary

Background: It has often been hypothesized that the frequency of follow-up for patients with early-stage endometrial cancer could be decreased. However, studies evaluating effects of a reduced follow-up schedule among this patient group are lacking.

Objective: Assess patient satisfaction and cost-effectiveness of a less frequent follow-up schedule compared to the schedule according to the Dutch guideline.

Study design: Dutch multicentre randomized controlled trial with a 5 year follow-up. Patients (n=282) are randomized in an intervention group with 4 follow-up visits during 3 years, and a control group with 10-13 follow-up visits during 5 years, according to the Dutch guideline. Patients are asked to fill out a questionnaire at baseline, 6, 12, 36 and 60 months. Patient inclusion will take two years (if 60% of the patients participate).

Outcomes:
Primary: Patient satisfaction with follow-up care and cost-effectiveness.
Secondary: health care use, adherence to schedule, health-related quality of life, fear of recurrence, anxiety and depression, information provision, recurrence, survival

Patients: Stage 1A and 1B low-risk endometrial cancer patients, for whom adjuvant radiotherapy is not indicated

Statistics: linear regression analyses to assess differences in patient satisfaction with follow-up care between intervention and control group adjusted for potential pre-defined confounders.

Expected results: Patients in the intervention arm have a similar satisfaction with follow-up care and overall outcomes, but lower health care use and costs than patients in the control arm. No effects are expected on QALY differences (losses) and satisfaction, but the reduced schedule is expected to save € 144.000 per year in the Netherlands.

Relevance for Dutch Cancer Society: This project fits perfectly in the aims of Dutch Cancer Society to improve the quality of life and care for patients with cancer. This can be achieved by reducing unnecessary care and diminishing wrong patient expectation about follow-up care.

Introduction

Background

The optimal follow-up schedule for patients with endometrial cancer is unknown [1-4]. As a result, guidelines in the Netherlands are consensus-based and do not take risk profile into account. Due to current emphasis on providing good care for lower costs, a critical evaluation of current follow-up practices for cancer patients is needed [5,6]. Endometrial cancer is the most common gynaecological cancer, with 2000 newly diagnosed patients per year in the Netherlands. Today, about 20,000 women living in the Netherlands have survived endometrial cancer. Of them, 7,000 were diagnosed in the past 5 years and are currently receiving follow-up care [7]. Most patients receive 5 year follow-up, with visits each 3 or 4 months in the first 2 years after treatment, each 4 to 6 months in the 3rd year and annually in the 4th and 5th year. Reasons for follow-up include early diagnosis of recurrences -for which curative treatment is available-, signalling consequences of cancer and treatment, psychosocial support, and information provision [8].

There are multiple reasons to decrease follow-up frequency. First, there is no survival benefit in the detection of asymptomatic recurrences at routine follow-up, compared with symptomatic recurrence or interval detection [1,4,9,10], probably because the recurrence rate of early-stage endometrial cancer survivors is low (3%) and because most recurrences (70%) present with symptoms [1]. The majority (70-100%) of the recurrences occur within 3 years [1]. Second, consequences of cancer and treatment are found in only 6% of the stage 1 patients who received surgery (hysterectomy and salpingo-oophorectomy) alone [11,12]. Third, follow-up visits evoke distress around the time of the visits [10,13-16]. Finally, alternative follow-up schedules in other cancer populations do not show decreased patient satisfaction or Health-Related Quality of Life (HRQoL) [17,18]. Reasons to retain follow-up are that follow-up is beneficial for patients for reassurance [14,15,19], to provide support for psychosocial, physical and sexual problems [8,11,18], and to provide information [20].

These findings strongly suggest that most early-stage endometrial cancer patients do not need intensive follow-up to detect recurrences, improve survival or discuss consequences of treatment, but patients may need *some* follow up to detect information needs and provide psychosocial counselling. Therefore, the current follow-up schedule for low-risk early-stage endometrial cancer

patients -about 55% of all patients with endometrial cancer- should be reduced to eliminate unnecessary care, decrease patient worry around visits, prevent wrong patient expectations and save health care costs [4-6].

Additionally, it is increasingly recognized that cancer survivors should be provided with tailored information about their disease, treatment, care providers, physical and psychosocial consequences of their cancer and its treatment, care services and health promotion information[21]. The Institute of Medicine advices the use of Survivorship Care Plans (SCPs) to provide cancer survivors this information [21]. However, large scale implementation of SCPs is currently lacking.

To obtain evidence on the effects of a reduced follow-up schedule we propose to conduct a nationwide randomized controlled trial (RCT) to study the effects of a reduced follow-up schedule for patients with endometrial cancer. The research question was encountered in the clinical practice of gynaecologic oncology as an urgent need to critically evaluate the possibilities to implement a reduced follow-up practice for endometrial-cancer survivors. If the reduced follow-up schedule results in a similar patient satisfaction at lower costs, the current guideline will be adapted and the reduced schedule can be implemented throughout the Netherlands.

Pilot studies for this trial

Two pilot studies have been performed to support this study. First, specialists' opinions were assessed during a meeting of the Dutch Gynaecologic Oncology Group (DGOG) in June 2012 and a nationwide questionnaire among all gynaecologists and radiotherapists participating in the Dutch Gynaecologic Oncology Group (Werkgroep Oncologische Gynaecologie, WOG) of the Dutch Society of Obstetrics and Gynaecology in January 2013. Results showed that the intervention is compatible with current opinions and needs of gynaecologists and specialised nurses in the Netherlands. This support will increase the likelihood of guideline implementation, if indeed the findings of the trial show equal patient satisfaction with care and cost savings. Adaptation of the guidelines and Implementation of the outcomes will further be enhanced by the participation of two members of the Guideline Development Group in our project group.

Second, to take the patients' needs and opinions into account, we started a patient participation group which was launched with a focus group in January 2013. In this focus group some patients supported our trial and ideas about follow-up, but others preferred the current follow-up as they were satisfied with the current practice and they wanted to be able to discuss questions and fears. As a result we emphasised in our intervention the explicit facility for patients to have prompt access to hospital care in case of questions and symptoms, as this appeared an important barrier for trial participation.

In addition, all study participants will be provided with a SCP. Our experience with and results of the ROGY Care study shows our ability to develop and implement such SCP [22]. In the trial among 12 hospitals in the Southern Part of the Netherlands, 100 endometrial cancer patients have received a SCP and were compared to 100 endometrial cancer patients who did not receive a SCP. Preliminary results show promising results regarding the information provision and satisfaction favouring the patients in the SCP group.

Study aims and outcomes

The aim of this study is to compare a reduced follow-up schedule of 4 visits in 3 years among low-risk, early-stage endometrial cancer survivors, with the schedule according to the current Dutch guideline that includes 10 to 13 visits in 5 years, on:

Primary outcomes:

1. Patient satisfaction with follow-up care
2. Costs-effectiveness from the health care perspective

Secondary outcomes:

- Health care use -gynaecologist, (specialist) nurse, primary care physician and other health or care services-; adherence to the indicated follow-up protocols; reasons for non-adherence
- HRQoL, worry including fear of recurrence, anxiety and depression, and satisfaction with information provision
- Health care providers' satisfaction with follow-up schedule (gynaecologist, (specialised) nurse)
- Time till recurrence and survival.

Due to the very limited number of expected recurrences and excellent survival, we cannot power this study on time till recurrence or survival outcomes. However, we will assess recurrence and survival for over five years post treatment.

Self-reported patient outcomes will be evaluated at 6, 12, 36 and 60 months after completion of primary treatment; health care use and costs after 3 and 5 years; and health care providers' satisfaction at the end of the study. We chose a follow-up period of this study of 5 years (with analyses after 3 and 5 years) because follow-up duration according to the guideline is 5-years. To make a valid comparison between the intervention and control group, it is important to evaluate health care use and patient-reported outcomes over these five years. However, to have results more rapidly and since the major risk for a recurrence lies within 3 years, we will additionally perform an analysis after 3 years.

We hypothesize that endometrial-cancer patients in the intervention arm of the study are not less satisfied with the follow-up care, and do not report worse HRQoL, fear of recurrence, anxiety, depression and information provision satisfaction. We furthermore hypothesize that health care use

and associated costs will be lower in the intervention arm, resulting in a cost-effective intervention. More precisely, we expect that by reducing the follow-up schedule from 10-13 to 4 visits the costs of these visits will be saved, although some substitution might appear to care by the specialist, specialized nurse or general practitioner. From a healthcare perspective we expect this alternative follow-up schedule will save € 144.000 in the Netherlands, annually (see appendix 1).

Study outline

Study design

A national multicentre (non-inferiority) RCT among 282 endometrial cancer survivors will be conducted. Patients will be randomized 1:1 in the intervention or control group. Since differences in outcomes between groups are expected to be most pronounced within the first 3 years of follow-up and the largest cost-saving is achieved within 3 years, we will evaluate this study in a two-step approach, with an evaluation after 3 and after 5 years. After 5 years the follow-up according to the guideline ends.

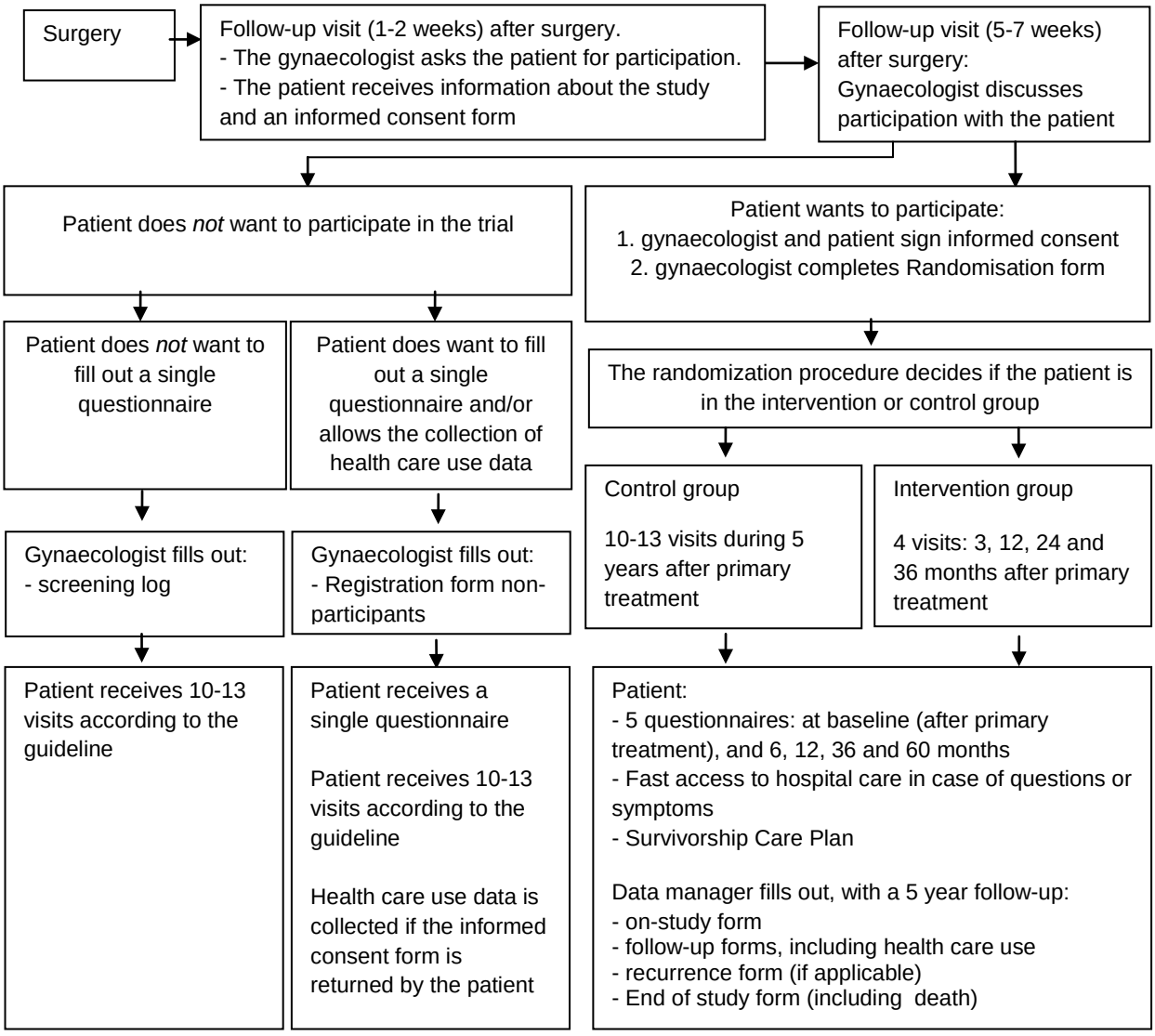

Figure 1 Schedule of study design and activities of patient, gynaecologist and data manager.

Doctors and patients cannot be blinded for intervention or control group assignment. A questionnaire will be send to all patients at baseline (after primary treatment), and 6, 12, 36 and 60 months later. The baseline questionnaire will be assessed before the intervention under study, that is

the different follow-up schedules, starts. Health care use, recurrences, survival and costs will be assessed after 3 and 5 years. A schedule of the study is presented in Figure 1. All health care professionals will receive a questionnaire at the end of the study in order to assess their experiences and satisfaction with the follow-up schedules. In addition, a non-participation study will be performed registering hospital health care use and assessing patient reported outcomes using a questionnaire. Medical Ethics approval will be obtained before the start of this project.

Study population

Early-stage low-risk endometrial cancer survivors who receive no adjuvant (radio)therapy after initial surgery will be included in the study.

Inclusion criteria

1. Patients with endometrioid type endometrial carcinoma with stage 1 (FIGO, 2009) low-risk disease, with the following combination of stage, age and grade will be eligible:
   - Stage 1A, any age, grade 1 or 2;
   - Stage 1B, < 60 years, grade 1 or 2 without LVSI;

2. Written informed consent;

3. Sufficient oral and written command of the Dutch language.

Tumour stage, grade and type should be histological confirmed by the pathologist prior to inclusion. These inclusion criteria indicate that the patient is in complete remission is after surgery.

Exclusion criteria

1. Any other stage and type of endometrial carcinoma;
2. Histological types papillary serous carcinoma or clear cell carcinoma;
3. Uterine sarcoma (including carcinosarcoma);
4. Receive radiotherapy for current endometrial carcinoma;
5. Previous malignancy (except for non-melanomatous skin cancer) < 5 yrs;
6. Having metastases of other tumours;
7. Confirmed Lynch syndrome;
8. Previous pelvic radiotherapy**.**

Our inclusion criteria are complementary with another ongoing (inter-)national study among endometrial cancer patients, the PORTEC-4 trial [23].

Requirements for participating centres

All general and specialized hospitals can participate in this trial on the condition that there is a research declaration according to the 'Centrale Commissie Mensgebonden Onderzoek' (CCMO).

Intervention and control groups

The control group receives follow-up according to Dutch guideline (Richtlijn Endometriumcarcinoom, versie 3.0) . This guideline proposes follow-up visits each 3-4 months during the 1st and 2nd year, each 4-6 months during the 3rd year and every 12 months during the 4th and 5th year after the end of treatment irrespective of stage and grade [11], resulting in a total of 10 to 13 visits in five years. In the intervention group, this schedule will be limited to four follow-up visits at 3, 12, 24 and 36 months, under the specific condition that patients have easy and prompt access to care (specialised nurse or gynaecologist) if symptoms or questions occur. The content of the follow-up visits will be similar for both groups.

In both arms a Survivorship Care Plan, including signs of recurrence, will be provided [26]. This Survivorship Care Plan is generated from the inclusion information that is completed in the CRF using a format for the intervention and control group. Our research group has developed and implemented such a Survivorship Care Plan within the ROGY Care trial, of which first results are promising [26].

Procedures, patient and data collection

Trial bureau and the collection of patient-reported outcomes

The national Trial Bureau of the Netherlands Comprehensive Cancer Organisation (IKNL) will organize data collection. Patient reported outcomes will be obtained by questionnaires[27]. Within the ROGY Care trial among endometrial cancer survivors, we reached a response of about 75%. Our extensive experience in collecting questionnaire data within our institution ensures a smooth data collection of the patient reported outcomes.

Randomisation

Patients will be randomized via a randomization programme, using a computer-generated list of random numbers. Block randomisation will be used (no stratification) to assure approximately equal numbers in both groups. Concealment of randomisation allocation is guaranteed by the fact that only after written informed consent, the trial manager obtains the randomisation allocation from the randomization programme and sends it to the gynaecologist.

Blinding

Patients and gynaecologists cannot be blinded for intervention allocation.

Patient inclusion

Informed consent will be asked by the treating gynaecologist during the post-operative visit. The patient is provided information about the study and an informed consent form. Patients have 2-4 weeks to consider the proposal and can ask questions for instance during an extra visit or a telephone call. In the visit 5-7 weeks after diagnosis, the patients signs written informed consent and provides address information, in case she is willing to participate. The gynaecologist fills out the Randomisation Form and sends it to the IKNL Trialbureau, who will perform the randomisation. The patient receives the paper questionnaire and a pre-stamped envelope, to be completed at home. The patients send the completed questionnaire to the IKNL Trialbureau. At 6, 12, 36 and 36 months the participant will receive a questionnaire plus pre-stamped envelope at their home address. Non-respondents will be sent a reminder letter and questionnaire within six weeks. Only for the baseline questionnaire this procedure will be faster to assure a proper baseline measure (reminder through the local principal investigator or research nurse after 2 weeks). If the patient moves to another hospital a form will be used to obtain patient data from the new hospital (appendix 3).

If the patient does not want to participate in the trial, she is still asked to fill out a single questionnaire and consent to assess health care use information, allowing the researchers to compare participants and non-participants. If the patient agrees, the gynaecologist completes the Registration form non-participants and sends it to the IKNL trialbureau. The gynaecologist provides the patients with a set including a short one-time questionnaire, an informed consent form to assess health care use data and a pre-stamped envelope. No other CRFs will be completed for this patient.

Withdrawal of patients

Patients can leave the study at any time for any reason without consequences. However, changing their follow-up schedule will not lead to withdrawing from the study; rather, patients will be analysed according to study arm (intention-to-treat) and actual health care use will be recorded. If patients withdraw their consent before providing follow-up information, the data manager fills out the End of Study Form.

Quality control

The IKNL Trialbureau will perform extensive consistency checks on the informed consent forms and the CRFs, and obtain any missing information to complete data collection. To enable inspections from Health Authorities, the local investigator (e.g. physician) keeps records, including the identity of all participating and non-participating patients (sufficient information to link records) and all original signed Informed Consent Forms. The local IKNL data manager assures the presence of the patient list, the Informed consent forms, and the in- and exclusion criteria for quality control. The central IKNL data managers keeps record of all CRFs. To comply with international regulations, the local investigator and the central IKNL data managers retain the records for 15 years.

Regional kick-off meetings will be organized to provide participating centres with relevant information. If a centre cannot attend, the local investigator will be informed personally or by telephone and provided written information to outline the study procedures.

The independent local data managers will check written informed consent and eligibility, before obtaining additional information from the patients' medical files, being a first quality check on the data. Only in sites where local datamanagement is not done by IKNL datamanagers, a qualified and independent monitor will visit the site. This monitoring will be performed by independent IKNL monitors, monitoring written informed consent, eligibility, CRFs, procedures, inclusion and loss-to-follow up. All records will be maintained in accordance with local regulations and in a manner that ensures security and confidentiality.

The local trial manager must assure that the subject's privacy will be maintained on all documents submitted to the IKNL Trialbureau. Each subject will be identified in the CRF by a subject identification number.

Administration

The IKNL trialbureau is responsible for hospital randomisation, supply of CRFs, and receipt of the CRFs.

The investigator will submit a summary of the progress of the trial to the accredited MEC once a year. Information will be provided on the date of inclusion of the first patient, number of patients included, and number of patients that have completed the trial, and any problems.

If any substantial changes are made to the trial, an amendment will be submitted to the MEC.

The principal investigator will notify the accredited MEC and all participating hospital at the end of the study. In case the study is ended prematurely, the investigator will notify the accredited MEC within 15 days, including the reasons for the premature termination.

Non-participation study

To understand the women who do not want to participate in the trial and assess the generalizability of the trial outcomes, we will perform a non-participation study along with the trial. This part of the trial is often disregarded in other studies but of essential importance to interpret the data. Non-participants will be compared with the control group regarding health care use and with the trial participants regarding patient-reported outcomes.

Patient-reported outcomes

Patients who do not want to participate in the trial are asked to complete a single questionnaire. Questions will include demographics, worry (including fear of recurrence), illness perceptions and satisfaction with care.

Hospital health care use

For patients who provide informed consent to assess health care use, hospital health care use (number of visits to the gynaecologist and the specialised nurse) will be registered.

Outcome assessment

Required examinations

At the start of the study, the pathology report is needed to decide if the patient meets the inclusion criteria. This includes histology, stage, grade, and LVSI. No other examinations are needed.

Patient and medical outcomes assessed at the start and during the study

During the study the following outcomes will be assessed using CRFs.

- Patient related: month and year of birth, other malignancies during the past 5-years, WHO-performance status, weight, height, comorbidity, menopausal status
- Pre-operative investigations: CT or X-ray of the chest, CT or MRI of the abdomen and pelvis, Ca-125 (as being standard of care)
- Surgery related: date of surgery, date of hospital discharge, type of surgery, blood loss, transfusion, complications of surgery, if the patients was in intensive or medium care, if there was a re-intervention for complications
- Pathology: histology, FIGO stage, FIGO grade, size of the tumour, myometrial invasion, minimal distance between the tumour and the serosa, LVSI
- Follow-up: date of follow-up visit, being a regular or extra visit, performance status, disease status, health care use (gynaecologist, oncology nurse), investigations (CT or X-ray of the chest, CT or MRI of the abdomen and pelvis, PET scan, echo, Ca-125)
- Recurrence: symptomatic/asymptomatic recurrence, localisation, date, new treatment
- End of study: date lost to follow-up, reasons loss to follow-up, date and cause of death

Health care use comprises consults with the specialist, the (specialist) nurse, and the primary care physician, hospital admissions, length of hospital stay, and diagnostics (X-ray, CT, MRI, PET scans, echo, Ca-125).

Cost-prices will be obtained from guideline on cost research from the CVZ [28].

Patient-reported outcomes and quality of life

We will use existing evidence based instruments to measure the patient reported outcomes that we hypothesised to be affected by the follow-up visits: Patient satisfaction with follow-up care, (Health related) Quality of Life, worry (including fear of recurrence), anxiety and depression, information provision and satisfaction, and health care utilisation. As we have conducted several survivorship

studies, also among endometrial cancer survivors, we have tested and used this set of questionnaires in previous studies in this population. We therefore know that this number of questions and content is well accepted by cancer survivors and we do not need to test the questionnaires extensively again for the proposed study.

- Patient satisfaction with follow-up care will be assessed using the Dutch version of the Patient Satisfaction Questionnaire III of which the psychometrics have been assessed in a Dutch oncologic sample[24]. This includes three aspects of health care: technical competence (10 items), interpersonal aspects (14 items), and access to care (12 items). The questionnaire can be used as a one-dimensional model, which will be used as the main outcome (PSQ total score).

- Overall QoL will be assessed using the EQ-5D[29], a standardised instrument which provides a descriptive profile and a single index value for health status. The measure will be used for the economic evaluation, as it can be used to compute QALYs.

- Cancer-specific HRQoL will be measured using the EORTC-QLQ-C30[30]. Much of the content of the questionnaire is appropriate for extended monitoring of health status, including scales assessing physical, role, cognitive and emotional functioning, fatigue and sleep problems, and overall health and QoL.

- A condition specific supplement, the EORTC-QLQ-EN24, will be used to assess tumour-specific complaints[19]. The module assesses lymphedema, urological symptoms, gastrointestinal symptoms, body image, sexual/vaginal symptoms, back/pelvic pain, and chemotherapy side effects.

- Worry, including fear of recurrence, will be assessed using a module from the validated IOCv2[31] questionnaire. The module consists of six questions including items about worry about the future, worry about health because of the cancer, and worry about a recurrence. This module is a concise measure to assess fear of recurrence and worry.

- Anxiety and depression will be assessed using the Hospital Anxiety and Depression Scale (HADS), an often used and validated scale in this population[32,33].

- Patient satisfaction with information disclosure will be measured using the EORTC-INFO25 module[34]. This questionnaire aims to evaluate the (satisfaction with) information received by cancer patients on different areas of the disease, diagnosis, treatment and care. The questionnaire contains the following scales: (a) information about the disease, (b) information about medical tests, (c) information about treatment, (d) information about other services, and

single items (a) written information, (b) information on CD or tape/video, (c) satisfaction with the amount of information, (d) desire for more information, (e) desire for less information, and (f) helpfulness of information.

- Illness perceptions will be assessed using the Brief Illness Perceptions Questionnaire (BIPQ), an 8-item instrument to assess cognitive and emotional representation of the illness {Broadbent, 2006}.

- Besides objectively measured, health care use will also be assessed by asking the frequency of contact with the primary care physician and medical specialist. These questions are similar as the questions asked by Statistics Netherlands. We will also ask the patient how often these visits were related to cancer. In addition, we will assess how often the patients used additional care services (e.g. psychologist, rehabilitation course, physiologist).

- The Self-administered Comorbidity Questionnaire [35] will be used to measure the comorbidities at the time of questionnaire completion.

- Socio-demographic characteristics such as educational level and employment status.

Health care provider perspective

Since the satisfaction of the health care provider is also of interest in this project we will assess the satisfaction of the specialists with the follow-up schemes using a short questionnaire.

Power calculation and data analyses

Sample size calculation

The power calculation is performed on the first primary outcome 'satisfaction with follow-up care'. The maximal difference between the groups that we find acceptable (non-inferiority margin) is 6 points (< 0,5 SD) on a scale from 0 to 100, with a standard deviation (SD) of 14.3[24], based on the rule of thumb as supposed for the EORTC-QLQ-C30 questionnaire [25]. Therefore, with alpha .05 and beta .80 we need a sample size of 180 (90 per study arm). In this sample size we assume that between 30 and 50 centres will participate and as a consequence we adjusted the number needed in the analysis to account for the clustering of patients within hospitals (Appendix 4). With an expected loss-to-follow-up of 20% and patient who die (16%) we need to include 282 patients. Assuming that 60% of the patients will participate, we need 470 eligible patients. In the Netherlands there are 450 patients per year who meet the inclusion criteria. However, since not al hospitals will start inclusion at the same time we expect an inclusion period of 2 years.

We expect that 60% of the patients will participate. Since we cannot be sure that we will accomplish this we also calculated alterative scenarios. When 50% of the patients participate we need an inclusion period of 2 years and 4 months. When 40% of the patients participate we need an inclusion period of 2 years and 8 months.

Time points

Data will be analysed after three year and five year follow-up.

Intention-to-treat

All patients will be included in the analyses and all patients will be analysed according to the arm to which they were assigned (intention-to-treat).

Analyses

Data will be analysed using descriptive statistics, linear and logistic regression analyses. Primary outcome is satisfaction with follow-up care. Multilevel multivariate linear and logistic regression analyses will be conducted for continuous and dichotomous outcomes, respectively. Analyses will be adjusted for known confounders to improve the power. Differential effects by stage and fear of recurrence will be evaluated by adding the interaction term (group*moderator) to the model.

We will carry out repeated measures analyses using generalized estimating equations (GEE), which accounts for the intra-patient dependency of the repeated measures. Missing outcomes will be

assumed missing at random (MAR). An advantage of GEE is that all patients can be included in the analyses, regardless if they have been missing some follow-up measurements.

All tests will be two-sided and considered significant if $p < .05$. Clinically meaningful differences will be determined with Norman's 'rule of thumb', whereby a difference of > 0,5 SD indicates a threshold of discriminant change in health status scores of a chronic illness [25].

Missing values

If we have the baseline data of a patient, we will include this patient in the analysis. Scales with multiple items will be mean imputed if at least half the questions of the patient are completed. Missing data on single time points will be handled using mixed models.

Cost-effectiveness and budget impact analyses

The cost-effectiveness analysis will be performed from a health care perspective with a time horizon of 36 months and will be expressed as the incremental cost per QALYs (based on the EQ-5D) and the incremental costs per satisfied patient. Based on results up to 36 months, 5-year cost-effectiveness results will be estimated. Patient adherence to the reduced follow-up schedule will explicitly be addressed in the cost-effectiveness analysis.

A budget impact analysis will be performed according to the ISPOR guidelines [36]. The budget impact analysis addresses the financial stream of consequences related to the implementation of and compliance with the reduced follow up scheme to assess affordability. The budget impact will depend on both the cost-savings due to reduced follow-up visits, the uptake by specialists, adherence of patients as well as potential cost increases e.g. at the level of the primary care physician.

Ethical considerations

Ethical approval

Medical Ethics approval will be obtained by a Medical Ethics Committee (MEC) before the start of this project. The guidelines “CCMO-richtlijn Externe Toetsing 2012” will be applicable. A local research declaration will be obtained for each participating hospital and the Board of Directors need to approve participation. The study will be conducted in full conformation with the ethical principles of the Declaration of Helsinki Seoul, 2008 and the WMO.

Informed consent

Informed consent will be asked by the treating gynaecologist during the diagnosis visit. The patient is provided information about the study and an informed consent form. Patients have 2 weeks at minimum to consider the proposal and are asked by the gynaecologist for informed consent after treatment. Both the gynaecologist and the patient sign the informed consent form.

Stopping rules

We do not implement specific stopping rules. If a patient expresses the need for more frequent visits, this will be allowed and monitored, since this is also one of the outcomes of our study.

Trial insurance

According to the law (WMO), every participating institute should have an insurance against the legal liability resulting from medical procedures. As the ENSURE trial involves follow up care, additional trial insurance is not required, as determined by the Medical Ethical Committee

Publication and implementation

All project group participants will be co-author on a protocol and main outcome paper. This will be implemented by publishing as the “ENSURE study group”. All participating centres with the local investigators will be mentioned in an appendix. These papers will be offered for publication in international scientific journals.

Moreover, results will be published in a Dutch journal for professionals and in a patient journal, such as the magazine of the patient organization ‘Olijf’. Further, with the participation of two members of the Guideline Development Group in our project group we have ensured that positive trial results will lead to adaptation of the guidelines.

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Appendices

Appendix 1: Potential cost savings

Appendix 2: WHO performance status

Appendix 3: Toestemmingsformulier voor overdracht patiëntgegevens

Appendix 4: Sample size needed in the analysis

Appendix 5: Questionnaires

APPENDIX 1: Potential cost savings

The incidence of early stage endometrial cancer patients is 2,6 per 100.000 per year and the prevalence is 12 per 100.000 per 5 years. In the Eindhoven Cancer Registry there were 65 early stage endometrial cancer survivors who meet the inclusion criteria in 2010. This region comprises of 15% of the Dutch inhabitant leading to 450 patients in the Netherlands (17.000.000 inhabitants).

The follow-up is generally 5 years, so the prevalence of early stage endometrial cancer survivors who are in follow-up is 2087 (5-year survival is 85%, assuming every year 3% of the patients dies; 443+430+417+405+392).

Data was derived from the Eindhoven Cancer Registry were used to compute the number of patients and the 5-year survival. These numbers are comparable with the numbers from the Netherlands Cancer Registry (www.cijfersoverkanker.nl).

The average Health-Related Quality of Life is 0.65 based on the SF-36 [Oldenburg, 2013]. As no differences in quality of life and survival are expected the difference in QALYs with a time horizon will be (close to) zero.

The saving due to reduction in follow up visits, using a conservative estimate for the regular number of visits (10 instead of 4) will amount to €156.735 per year. Assuming in the intervention group that 4% of patients will immediately fall back in the regular follow up scheme, that 25% of patients will have one extra visit and that 3% of patients will have an extra visit to the GP, the savings decrease to €143.765. Cost-prices have been obtained from the Dutch guidelines for cost calculations in health care [Hakkaart et al. 2010].

Expected costs to be saved: 144.000 euro per year.

APPENDIX 2. Performance status (WHO-ECOG)

Grade 0 Fully active, able to carry out all normal (pre-disease) activity without restriction

Grade 1 Restricted in physically strenuous activity but ambulatory and able to carry out light work, e.g., light house work, office work

Grade 2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

Grade 3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours

Grade 4 Completely disabled; cannot carry out any self-care; totally confined to bed or chair

APPENDIX 3: Toestemmingsformulier voor overdracht patiëntgegevens

Toestemmingsformulier voor overdracht patiëntgegevens

Instructie: deze gegevens zijn vereist voor administratieve doeleinden. Dit formulier dient te worden ingevuld ten behoeve van de betrokkenen, d.w.z. ZOWEL lokale onderzoekers ALS lokaal datamanagers.

Gelieve dit formulier te sturen of faxen naar:

IKNL Trialbureau

Postbus……..

Postcode + plaatsnaam

E-mail: ……..

Fax: ……. <mogelijk versies maken voor elke regio>

Vul dit formulier in wanneer u de verantwoordelijkheid voor dataverzameling voor een specifieke patiënt wilt overdragen van het ene naar het andere ziekenhuis.

1. **De onderzoeker en de lokaal datamanager (LDM) van het ziekenhuis waar de patiënt eerst onder viel dienen dit formulier te ondertekenen en de naam van het nieuwe ziekenhuis + de betreffende onderzoeker in te vullen.**
2. **De oorspronkelijke onderzoeker stuurt het formulier naar het nieuwe ziekenhuis en de nieuwe onderzoeker EN stuurt een kopie naar IKNL Trialbureau**
3. **De onderzoeker van het nieuwe ziekenhuis en eventueel een gemachtigde voor het nieuwe ziekenhuis ondertekenen dit formulier (ter bevestiging van de overdracht) en sturen dit terug naar de oorspronkelijke onderzoeker & LDM.**
4. **Het volledig ingevulde 'Toestemmingsformulier voor overdracht patiëntgegevens' wordt vervolgens door de oorspronkelijke onderzoeker & LDM teruggestuurd naar IKNL Trialbureau. Zij behouden een kopie ter plaatse.**
5. **Na ontvangst van het ondertekende formulier draagt IKNL Trialbureau zorg voor overdracht van de patiënt binnen het betreffende onderzoek.**

Wanneer de nieuwe onderzoeker of LDM weigert te bevestigen, dan zal IKNL Trialbureau de overdracht niet voortzetten en alle communicatie aangaande deze patiënt in dit onderzoek blijven richten aan de oorspronkelijke onderzoeker / LDM.

*N.B. Na overdracht van de verantwoordelijkheid van dataverzameling zullen alle query's en dataverzoeken m.b.t. deze patiënt gestuurd worden naar de onderzoeker / LDM van het nieuwe ziekenhuis. Deze overdracht heeft alleen betrekking op dataverzameling door IKNL Trialbureau. Het heeft **geen** invloed op procedures m.b.t. financiële compensatie zoals vergoeding / terugbetaling van de kosten voor datamanagement door het CKTO of KWF.*

Naam onderzoek	…… ……
Studienr patiënt	☐☐☐☐☐☐☐☐☐
Naamcode patiënt	……
Geboortedatum patiënt	☐☐ - ☐☐ - ☐☐☐☐

Oorspronkelijk ziekenhuis

Naam ziekenhuis	
Plaatsnaam	……
Naam lokaal onderzoeker	……
Datum	☐☐ – ☐☐ – ☐☐☐☐
Handtekening	……
Naam lokaal datamanager	……
Datum	☐☐ – ☐☐ – ☐☐☐☐
Handtekening	……

Nieuw ziekenhuis

Naam ziekenhuis	
Plaatsnaam	……
Naam lokaal onderzoeker	……
Datum	☐☐ – ☐☐ – ☐☐☐☐
Handtekening	……
Naam lokaal datamanager	……
Datum	☐☐ – ☐☐ – ☐☐☐☐
Handtekening	……

APPENDIX 4: Sample size needed in the analysis

Output of the PASS program 2008.

Power Analysis of a Non-Inferiority Test of The Difference of Two Means
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Numeric Results for Non-Inferiority Test (H0: D <= -|E|; H1: D > -|E|)
Test Statistic: T-Test

Power	N1/N2	Equivalence Margin (E)	Actual Difference (D)	Significance Level (Alpha)	Beta	Standard Deviation1 (SD1)	Standard Deviation2 (SD2)
0.80010	2783/2783	-1.000	0.000	0.05000	0.19990	15.000	15.000
0.80020	696/696	-2.000	0.000	0.05000	0.19980	15.000	15.000
0.80091	310/310	-3.000	0.000	0.05000	0.19909	15.000	15.000
0.80087	175/175	-4.000	0.000	0.05000	0.19913	15.000	15.000
0.80010	112/112	-5.000	0.000	0.05000	0.19990	15.000	15.000
0.80015	78/78	-6.000	0.000	0.05000	0.19985	15.000	15.000
0.80324	58/58	-7.000	0.000	0.05000	0.19676	15.000	15.000
0.80660	45/45	-8.000	0.000	0.05000	0.19340	15.000	15.000

References
Chow, S.C.; Shao, J.; Wang, H. 2003. Sample Size Calculations in Clinical Research. Marcel Dekker. New York.
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Report Definitions
Group 1 is the treatment group. Group 2 is the reference or standard group.
Power is the probability of rejecting a false null hypothesis. Power should be close to one.
N1 is the number of subjects in the first (treatment) group.
N2 is the number of subjects in the second (reference) group.
|E| is the magnitude of the margin of equivalence. It is the largest difference that is not of practical significance.
D is the mean difference at which the power is computed. D = Mean1 - Mean2.
Alpha is the probability of a false-positive result.
Beta is the probability of a false-negative result.
SD1 and SD2 are the standard deviations of groups 1 and 2, respectively. Based on M Hagedoorn et al., Medical Care 2003, 41 (2): 254

To compensate for the clustering of patients within hospitals we need more patients, depending on the number of patients per centre and the number of centres participating. Per arm we might need up to 85 patients. We rounded this number off at 90 patients, resulting in a total of 180 patients needed in the analysis.

initial sample size	pts per center (n)	ICC	design effect	total no of pts (=n*m)	no of centers (m)
78	1	0.043	1.00	78	78
78	1.5	0.043	1.02	80	53
78	3	0.043	1.09	85	28

ICC=intra class correlation, Based on JV Selby et al., Medical Care 2010, 48 (2): 133
Design effect=1+(n-1)*ICC
Total no of pts=initial sample size*design effect
m=total no of pts/n

APPENDIX 5; Questionnaires