Clinical study protocol

Early salpingectomy (**TU**bectomy) with delayed oophorectomy to improve quality of life as alternative for risk-reducing salpingo-oophorectomy in ***B****RC****A****1/2* mutation carriers

TUBA study

Verbetert de kwaliteit van leven van BRCA1/2 genmutatiedraagsters door een vroege preventieve eileiderverwijdering (tubae) en het uitstellen van de eierstokverwijdering, als alternatief voor het preventief verwijderen van eileiders en eierstokken tegelijkertijd?

Coordinating investigator/project leader:

Dr. J.A. de Hullu, gynaecologic oncologist, Radboud University Medical Centre Nijmegen

Dr. R.P.M.G. Hermens, IQ health care, Radboud University Medical Centre Nijmegen

Prof. dr. N. Hoogerbrugge, Human Genetics, Radboud University Medical Centre Nijmegen

Trial management group:

Drs. M.G. Harmsen, junior investigator

Drs. A. de Jong, research nurse

Dutch Gynaecological Oncology Group (DGOG)

PROTOCOL TITLE:

Early **TU**bectomy with delayed oophorectomy to improve quality of life as alternative for risk reducing salpingo-oophorectomy in ***BRCA1/2*** mutation carriers

Protocol ID	TUBA study (TUbectomy in BrcA mutation carriers)
Short title	TUBA study
Version	4.0
Date	September 2014
Coordinating investigators	Dr. J.A. de Hullu, gynecologic oncologist Radboud University Medical Centre Nijmegen Department of obstetrics & gynaecology G.Grooteplein 10 6525 GA Nijmegen Phone: 0031 (0)24-3616683 E-mail: joanne.dehullu@radboudumc.nl Drs. R.P.M.G. Hermens, IQ health care, Radboud University Medical Centre Nijmegen Rosella.hermens@radboudumc.nl Prof. dr. N. Hoogerbrugge, Human Genetics, Radboud University Medical Centre Nijmegen Nicoline.hoogerbrugge@radboudumc.nl

Co-investigators/preparation protocol	Centre for Gynaecological Oncology Amsterdam (CGOA) Dutch Cancer Institute - Antoni van Leeuwenhoek Hospital (NKI/AVL) Dept of gynecology Plesmanlaan 121 1066 CX Amsterdam M.van Beurden, gynecologic oncologist University Medical Centre Groningen (UMCG) Dept of gynecology Hanzeplein 1 9713 GZ Groningen M.J.E. Mourits, gynecologic oncologist University Medical Centre Utrecht (UMCU) Dept of gynecology Heidelberglaan 100 3584 CX Utrecht R.P. Zweemer, gynecologic oncologist Radboud University Medical Centre Nijmegen Dept of gynecology G.Grooteplein 10 6525 GA Nijmegen L.F.A.G. Massuger, gynecologic oncologist Erasmus Medical Centre (Erasmus MC) Dept of gynecology 's-Gravendijkwal 230 3015 CE Rotterdam H.C. van Doorn, gynecologic oncologist Leiden University Medical Centre (LUMC) Dept of gynecology Albinusdreef 2 2333 ZA Leiden K.N. Gaarenstroom, gynecologic oncologist Maastricht University Medical Centre (MUMC) P. Debyelaan 25 6229HX Maastricht B.F.M. Slangen, gynecologic oncologist

	GOCZ location Catharina Hospital Eindhoven Dept of gynaecology Michelangelolaan 2 5623 EJ Eindhoven R.H.M. Hermans, gynecologic oncologist GOCZ location Elisabeth-TweeSteden Hospital Tilburg Dept of gynecology Dr. Deelenlaan 5 5042 AD Tilburg J.M.J. Piek, gynecologic oncologist
Study coordinator	M.G. Harmsen Radboud University Nijmegen Medical Centre Dept of gynecology G.Grooteplein 10 6525 GA Nijmegen Phone: 0031 (0)24- 3614755 E-mail: marline.harmsen@radboudumc.nl
DGOG (Dutch Gynaecology Oncology Group) chairman	R.L.M. Bekkers , gynecologic oncologist Radboud University Nijmegen Medical Centre Dept of gynecology G.Grooteplein 10 6525 GA Nijmegen Phone: 0031 (0)24 - 3614725 E-mail: ruud.bekkers@radboudumc.nl
Sponsor	No funding
Independent physician	S. Coppus, gynecologist Radboud University Nijmegen Medical Centre Dept of gynecology G.Grooteplein 10 6525 GA Nijmegen Phone: 0031 (0)24 - 3614792 E-mail: Sjors.coppus@radboudumc.nl
Statistician	S.Teerenstra Radboud University Medical Centre Nijmegen Dept of IQ health care G. Grooteplein 21 6525 EZ Nijmegen Phone: 0031 (0)24- 361??? Email: Steven.Teerenstra@radboudumc.nl

Pathology	Dr. J. Bulten Radboud University Nijmegen Medical Centre Dept of Pathology G.Grooteplein 10 6525 GA Nijmegen Phone: 0031 (0)24- 3614374 E-mail: hans.bulten@radboudumc.nl
Cardiology	Prof.Dr. A. Maas Radboud University Nijmegen Medical Centre Dept of Cardiology G.Grooteplein 10 6525 GA Nijmegen Phone: 0031 (0)24- 3616161 E-mail: angela.maas@radboudumc.nl
Health Economy	Dr. J. Wilschut Radboud University Nijmegen Medical Centre Dept of IQ healthcare G.Grooteplein 10 6525 GA Nijmegen Phone: 0031 (0)24- 3614374 E-mail: janneke.wilschut@radboudumc.nl
BRCA1/2 gene germline mutation carriers	Anonymized
BVN Breast Cancer Support Group (subdivision hereditary cancer)	Anonymized

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Head of Department: Prof. Dr. D.D.M. Braat, gynecologist		26-09-2014
Coordinating Investigator: Dr. J.A. de Hullu, gynecologic oncologist **Junior Investigator:** Drs. M.G. Harmsen, junior investigator	 	26-09-2014 26-09-2014

Table of contents

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ANOVA	**Analysis of Variance**
BRCA	**BReast CAncer**
BMI	**Body Mass Index**
BVN	**Dutch Breast Cancer Support Group (Dutch: Borstkanker Vereninging Nederland)**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CGOA	**Center for Gynecologic Oncology Amsterdam**
CRF	**Case Report Form**
CVD	**Cardiovascular Disease**
CWS	**Cancer Worry Scale**
DGOG	**Dutch Gynecologic Oncology Group**
DSMB	**Data Safety Monitoring Board**
EORTC-QlQ-C30	**European European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30**
FSFI	**Female Sexual Function Index**
GCP	**Good Clinical Practice**
GCS	**Greene Climacteric Scale**
GOCZ	**Gynecologic Oncologic Center South (Dutch: Zuid)**
HRT	**Hormone Replacement Therapy**
HYSTUB	**HYSterectomy with or without TUBectomy study**
IES	**Impact of Event Scale**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**

PTSD	**Post Traumatic Stress Disorder**
QALY	**Quality Adjusted Life Year**
QoL	**Quality of Life**
(S)AE	**(Serious) Adverse Event**
RRS	**Risk-reducing Salpingectomy**
RR(S)O	**Risk-reducing (salpingo-)oophorectomy**
SEE-FIM	**Protocol for Sectioning and Extensively Examining the FIMbriated end of the fallopian tube**
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.**
SF-HLQ	**Short-Form Health and Labour Questionnaire**
(S)TIC	**(Serous) Tubal Intraepithelial Carcinoma**
WBP	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**
NFU	**Nederlandse Federatie van Universitair Medische Centra (Dutch Federation of University Medical Centers)**

PROTOCOL SYNOPSIS

Title	Early **TU**bectomy with delayed oophorectomy to improve quality of life as alternative for risk reducing salpingo-oophorectomy in ***BRCA1/2*** mutation carriers
Study design	Multicenter non-randomized study
Study population	Female *BRCA1/2* gene germline mutation carriers who choose for prophylactic surgery to reduce the risk of ovarian cancer after having completed childbearing
Intervention	Risk reducing salpingo-oophorectomy (RRSO) Or Risk reducing salpingectomy (RRS) with delayed risk reducing oophorectomy (RRO)
Primary Study **Objective:**	Comparing short-term effects on (menopause-related) quality of life
Secondary Study **Objectives:**	Comparing long-term effects on (menopause-related) quality of life, CVD risk factors, incidence of (pre)malignant findings in tubes/ovaries, perioperative morbidity and mortality, incidence of ovarian and breast cancer and cardiovascular diseases, and a cost-effectiveness analysis.
Inclusion **Criteria:**	• Premenopausal women with a documented *BRCA1* and/or *BRCA2* germline mutation • Age 25-40 years for *BRCA1* mutation carriers and 25-45 years for *BRCA2* • Childbearing completed • Presence of at least one fallopian tube • Participants may have a personal history of non-ovarian malignancy • Informed consent must be obtained and documented according to national and local regulatory requirements and the local rules followed in the institution.
Exclusion Criteria:	• Postmenopausal status (natural menopause or due to treatment) • Wish for second stage RRO within two years after RRS • Legally incapable • Prior bilateral salpingectomy • A personal history of ovarian, fallopian tube or peritoneal cancer • Evidence of malignant disease at enrollment • Current treatment for malignant disease

	• Inability to read or speak Dutch
Number of centers:	Multicenter, 11 hospitals
Number patients	See power calculation: 510 patients
Planned	5 years inclusion, 5 years follow-up for primary outcome measure 15 years follow-up to build a database for long-term follow-up

SUMMARY

Rationale: In *BRCA 1/2* gene mutation carriers, a risk-reducing salpingo-oophorectomy (RRSO) is recommended around the age of 40, based on first, a 10-40% life-time risk of ovarian cancer in this population, second, disappointing results of ovarian cancer surveillance for early detection and third, the high mortality rate of ovarian cancer. Effects of RRSO are a decrease in ovarian cancer risk (80-96%) on one hand and immediate onset of menopause and non-cancer related morbidity on the other hand. The fifty percent breast cancer risk reduction after RRSO has recently become disputable. Based on recent studies showing that most high-grade serous ovarian cancers develop at the distal end of the Fallopian tube, an innovative strategy for RRSO has been developed for this study proposal: risk-reducing salpingectomy (RRS) with delayed risk-reducing oophorectomy (RRO). However, the safety of this strategy has not been proven yet. Before offering this innovative strategy to *BRCA 1/2* gene germline mutation carriers, consequences of implementation need to be studied.

Objective: To evaluate RRS after childbearing with delayed RRO as an alternative for RRSO in *BRCA1/2* gene germline mutation carriers. We hypothesize that delay of menopause leads to an improvement of quality of life and sexual functioning, and a decrease in cardiovascular risk factors without a significant increase in ovarian cancer mortality.

Study design: A prospective non-randomized study.
Study population: 510 *BRCA1/2* gene germline mutation carriers recruited from ten hospitals that already participated in a recently conducted feasibility study. A historical cohort study will be performed in 250 *BRCA1/2* gene germline mutation carriers who received standard RRSO in 2011-2013 to obtain baseline data on quality of life.
Treatment options: Standard treatment: RRSO (*BRCA1* at age 35-40; *BRCA2* at age 40-45); innovative treatment: RRS when childbearing is completed with a delayed RRO (*BRCA1* at age 40-45; *BRCA2* at age 45-50). *BRCA 1/2* gene germline mutation carriers who opt for early RRS but still want RRO at the age of the current standard treatment (*BRCA1* 35- 40, *BRCA2* 40-45), can choose for the innovative treatment as well, provided that at least a 2-year interval between RRS and RRO is expected at baseline.

Main study parameters/endpoints: Primary study outcome is the difference in menopause related quality of life, measured by the Greene Climacteric Scale (GCS). Secondary study outcomes include changes in cardiovascular risk factors, incidence of breast and/or ovarian cancer and cardiovascular disease, the effect on ovarian reserve, the cost-effectiveness, surgery-related outcome and pathologic findings of the removed fallopian tubes. Total duration of follow-up will be 15 years.

Nature and extent of the burden and risks associated with participation: Participants will be asked to fill in questionnaires on quality of life and medical conditions at several time points (1 week before and 3 and 12 months after surgery; subsequently biennial until 15 years after RR(S)O). Blood samples to measure cardiovascular risk factors are taken around the time of surgery and after 5 years (CVD risk factors). Therefore, two extra site visits are required. The most important risk for participants is the risk of developing ovarian cancer within the interval between RRS and RRO. We estimate that risk about 1-2% when RRO is postponed for five years in the scenario that the earlier tubectomy does not reduce ovarian cancer risk at all. Furthermore, in the innovative treatment, the participant will

undergo a laparoscopy twice. Known complication rates for RRSO in a comparable population vary from 1.5-5% for major and 3.9-10% for minor complications. Risks might be lower for RRS alone.

1. INTRODUCTION AND RATIONALE

Papillary serous carcinoma of the female genital tract is the most lethal epithelial malignancy. Primary carcinomas in ovary, fallopian tube and peritoneum are Müllerian in nature, could be regarded as a single disease entity and are often considered as "ovarian carcinomas" with respect to treatment and prognosis. It is estimated that 5% to 10% of all ovarian carcinoma patients have a hereditary basis (1-4). *BRCA1/2* gene germline mutations account for the majority of autosomal dominant hereditary breast and ovarian carcinoma families and molecular testing has become widespread (5). *BRCA1/2* gene germline mutation carriers have a life-time risk of 40-80% of developing breast carcinoma. Estimates for ovarian carcinoma vary between 10 and 65%, while the risk of sporadic ovarian carcinoma in the general population is 1.7% (6, 7). In *BRCA1* and *BRCA2* gene germline mutation carriers the risk of ovarian carcinoma before the age of 40 is still low, respectively 3% and 0.7% (6). The risk of ovarian carcinoma increases in the next decade (40- 50 yr) to 6.7% and 1.9%. The highest risk for ovarian carcinoma is between age 50-70 years: 34% in *BRCA1* and 14% in *BRCA2* carriers, so approximately 80% of all ovarian carcinomas are diagnosed > 50 years.

Screening for ovarian carcinoma is highly ineffective (8, 9). Therefore a risk-reducing salpingo-oophorectomy (RRSO) is recommended to all *BRCA1/2* gene germline mutation carriers: around the age of 40 in *BRCA1* and at 40-45 year in *BRCA2* (10). RRSO reduces the risk of gynecological carcinoma by 80-96% and when performed in not affected *BRCA1/2* gene germline mutation carriers before menopause also reduces the risk of breast carcinoma by 50% (10, 11). However, the latter has recently been questioned by several authors (12, 13) (manuscript Heemskerk-Gerritsen submitted JNCI 2014). Due to the high risk of ovarian carcinoma at higher age, RRSO is also justified after the age of 60 (14). After RRSO there is only a limited risk on primary peritoneal carcinoma in *BRCA1/2* gene germline mutation carriers (15, 16). Adverse effects associated with prophylactic surgery in premenopausal women are loss of fertility and immediate onset of menopause. RRSO is associated with significantly lower levels of cancer worries (17) but will lead to an increase of climacteric and sexual symptoms, which may not be fully alleviated by the postsurgical use of hormone replacement therapy (HRT) (18). Short-term HRT use does not negate the possible protective effect of RRSO on subsequent breast carcinoma risk in *BRCA1/2* gene germline mutation carriers, while there is limited literature on the effects of long-term HRT (19). It has been suggested that premenopausal RRSO (especially < 45 year without HRT) may result in an increased risk for coronary heart diseases, cognitive dysfunctions and osteoporosis (20-22). While health care providers are discussing side effects of RRSO, women undergoing this surgery appeared to have other concerns that should be addressed. Factors such as prophylactic mastectomy and previous breast carcinoma may be factors of influence in making a decision on RRSO. About sixty percent of the women would have preferred more information on the impact of RRSO on their sex life and the risk of coronary heart disease (23). In conclusion, the favorable effects of RRSO in terms of reduced incidence of ovarian and (arguably) breast carcinoma and low perceived cancer risk as well as the timing of RRSO (+/- HRT) need to be weighed against the increase in non-carcinoma-related morbidity such as endocrine, cardiovascular and sexual symptoms. Originally, after the identification of BRCA1/2 gene mutations, risk reducing surgery consisted of prophylactic oophorectomy. After the Dutch report on the possible role of the

fallopian tube in the origin of serous ovarian carcinoma, prophylactic surgery was extended to RRSO (24).

Based on recent scientific insights, the fallopian tube is considered as THE site of origin for ovarian carcinoma nowadays (25-28). It is suggested that benign tubal epithelium can transform into tubal intraepithelial carcinoma (TIC) or invasive tubal carcinoma. The (pre)malignant cells can exfoliate from the tubal epithelial lining and migrate to the ovary and abdominal cavity. Earlier studies showed the presence of TIC with an incidence of 36-100% (29, 30). Several investigators performed p53-IHC staining and p53-mutation analysis in ovarian/peritoneal carcinomas and in their corresponding TICs; they found that TIC is indeed a precursor lesion of ovarian serous carcinoma (31, 32). Crum and others focused on the removed fallopian tubes of *BRCA1/2* gene germline mutation carriers, showing the presence of TIC in 1-17% (33-35); nearly all TICs were localized in the distal fimbrial ends of the tubes.

Currently, the key question is: To what extent is post-reproductive risk-reducing salpingectomy (RRS) followed by risk reducing oophorectomy (RRO) at a higher age (e.g. 40-50) an alternative for RRSO at younger (current guideline) age, both from professional and patient's perspective.

An appreciation of the concept that the serous ovarian carcinomas likely originate from the fimbriated end of the fallopian tube should have immediate consequences for prevention and therapy. Above mentioned data urge specialists of the family cancer clinics in the Netherlands to develop a nation-wide strategy to give the optimal care to female *BRCA1/2* gene germline mutation carriers now and in the future. Currently, a randomized trial between RRSO and RRS is not ethical as the carcinogenesis is not completely clear yet; moreover, it is not ethical to omit oophorectomy considering the favourable effects in reduction of the risk of ovarian and possibly breast carcinoma. But, three assumptions will lead to potential advantages of RRS, namely:

1. A large proportion of *BRCA1/2* related serous carcinomas arises in the fallopian tube
2. These fallopian tube carcinomas can be prevented by RRS
3. Risks that are associated with delaying menopause are offset by benefits that are related to removal of the tubes at a younger age.

Prophylactic surgery in two tempi, post-reproductive RRS before age 40 followed by RRO around the age of 40-50 may be an attractive alternative. The individual situation of the *BRCA1/2* gene germline mutation carrier (own medical history and family history of carcinoma and cardiovascular disease/osteoporosis) will determine the optimal planning for prophylactic surgery of tubes and ovaries with optimal quality of life for each individual. Green et al summarized important potential advantages of post-reproductive RRS followed by second stage oophorectomy (36):

1) Proportion of ovarian carcinoma risk that would otherwise be experienced by *BRCA1/2* gene germline mutation carriers who decline RRSO might be eliminated by removing the fallopian tubes (majority of occult carcinomas are found in tubes, i.e. 68% (43-100%));

2) Reduction of HRT use and/or non-carcinoma-related morbidity by reduction of premature menopause;

3) Early laparoscopic evaluation: histological evaluation of tubes, inspection of pelvis, collection of cytology and biopsies if necessary. This could result in early detection and treatment of (occult) carcinoma;

4) Postponement of premature infertility (given the option of in-vitro fertilization), at least giving possible emotional benefit;

5) Patient empowerment (after childbearing immediate RRS instead of waiting until RRSO around the age of 40).

Potential disadvantages are:

1) Evidence on the role of the fallopian tube as origin of serous carcinoma is growing, however more detailed information lack, e.g. what percentage of ovarian carcinoma has been developed in the tubes and can be prevented by removing the tubes?;

3) Data are lacking about the optimum of the second stage oophorectomy with respect to the reduction of ovarian carcinoma. What is the optimum time between RRS and RRO and/or what is the optimal age of RRO? Is oophorectomy really necessary?;

4) What is the influence on the incidence of breast carcinoma? Risk reduction of breast carcinoma by oophorectomy is thought to be greatest when the procedure is performed before menopause; however, recent reports question the risk-reducing effect of RRSO on breast cancer at all (12, 13) (manuscript Heemskerk-Gerritsen submitted JNCI 2014).

5) The surgical morbidity of two laparoscopies.

How to move on? After weighing the complex set of pros and cons that relate to RRS, it seems that there may be sufficient merit in this proposal to consider evaluating it in a formal fashion. In *BRCA1/2* gene germline mutation carriers, both from clinical and patient's perspective, we believe that RRS might be a logical and reasonable risk-reducing solution for young women who are reluctant to RRSO due to the adverse hormonal effects. However, what is the opinion about the role of the tube in *BRCA1/2* gene germline mutation carriers themselves and their doctors?

A recent study in our hands investigated the preferences, barriers and facilitators for the concept of RRS followed by RRO among either professionals in 12 hospitals and 44 *BRCA* mutation carriers in focus groups (unpublished data). Both professionals and patients are very keen on participating in a study on this topic and generally choose for a non-randomized study design. The risks of ovarian and breast cancer and the lack of knowledge about short and long term effects of early menopause were important issues. Especially *BRCA1/2* gene germline mutation carriers who daily experienced early menopause after RRSO reported impressive negative side-effects of menopause on quality of life. About 50% of the *BRCA* mutation carriers might choose for the innovative treatment which is comparable with a recent questionnaire-study by Holman et al (37).

2. OBJECTIVES

The aim of the project is to evaluate RRS after childbearing with delayed RRO as an alternative for RRSO in *BRCA1/2* gene germline mutation carriers with respect to quality of life, symptoms related to estrogen deficiency, cardiovascular disease, and safety. We hypothesize that a 5-years delay of menopause compared to current standard treatment leads to a significant improvement of quality of life and sexual functioning, and a decrease in cardiovascular risk factors without a significant increase in ovarian cancer risk.

2.1 Primary objective

The most important goal in clinical research is reducing mortality and morbidity. Issues such as side effects, symptom relief, patients' health-related quality of life and patients' satisfaction with care are also important parameters in the evaluation of medical treatments. New cancer treatments or risk reducing surgeries may produce adverse health-related quality of life effects even when survival is extended. Progress in the acceptance of new therapies is therefore critically dependent on their health-related quality of life consequences. Health-related quality of life is a multidimensional concept that covers the patients' perception of the impact of the disease and its treatment on their physical, psychological and social functioning and well-being.

- **What is the menopause specific quality of life, including psychological, somatic , vasomotor, and sexual aspects, in *BRCA1/2* gene germline mutation carriers with the standard treatment (RRSO) compared to the innovative treatment (RRS with delayed RRO)?**

Hypothesis H0: there is no difference in quality of life in *BRCA1/2* gene germline mutation carriers who underwent RRSO compared to RRS followed by delayed RRO.

Alternative hypothesis H1: quality of life is better after RRS followed by delayed RRO compared with RRSO.

2.2 Secondary objectives

- What are the surgery-related outcomes (perioperative and postoperative complications; pathology results of Fallopian tubes and ovaries)?
- What is the prevalence of risk factors for cardiovascular disease, early signs of atherosclerosis, and cardiovascular diseases?
- What is the prevalence of ovarian and breast cancer in the standard and experimental arm (=safety)?
- What is the cost-effectiveness of both strategies? (direct and indirect costs)
- Building a database for long-term follow-up (15 years after last surgery)

3. STUDY DESIGN

1) Historical cohort study

2) Open nationwide prospective non-randomized multicenter trial

Duration of study:
- Inclusion and analysis of short-term outcomes: 8 years.
- Data collection for database: 15 years.

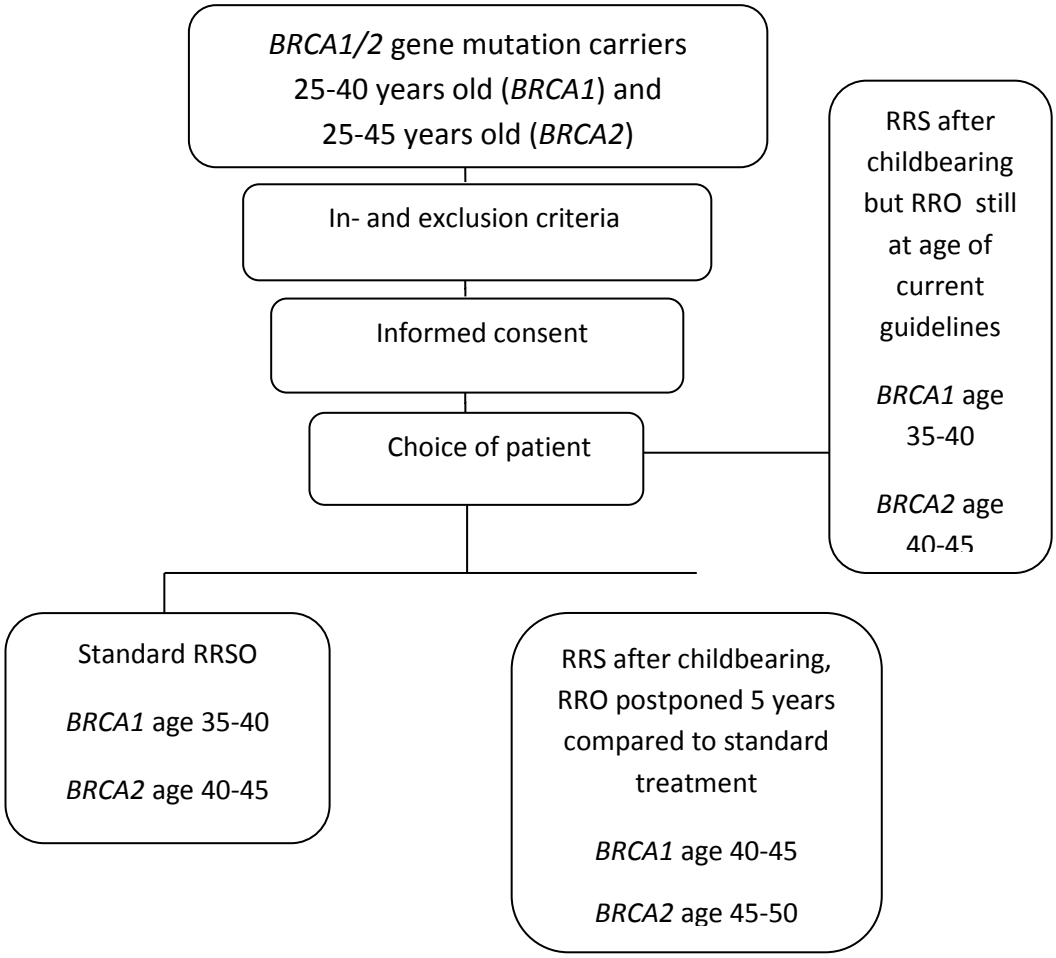
3.1 Justification of the study design

Given current trends regarding the Fallopian tube as the origin of ovarian cancer (as described earlier) and the fact that RRS is currently already offered to *BRCA1/2* mutation carriers in some Dutch hospitals, there is a great danger that the RRS is going to be performed outside a clinical trial without gaining knowledge about the expected improvement in quality of life for RRS with delayed RRO compared to RRSO, about the incidence, morbidity and mortality of ovarian and breast cancer and about cardiovascular risks. This supports the need for this study.
Scientifically, a randomized trial might be the optimal next step, but for a number of reasons a non-randomized study is preferable:
1) We conducted individual in-depth interviews with specialists of all Dutch family cancer clinics in the feasibility study (submitted) with professionals who provide care to *BRCA1/2* mutation carriers; they mentioned that the individual situations of the *BRCA1/2* mutation carriers are very different (e.g. previous breast cancer or risk-reducing mastectomy, family history), and that this group of young self-conscious women probably will not agree on randomization to remain autonomous. In addition, it would mean that young women after completed childbearing do not have the choice to undergo RRS, while clinicians experience that particularly these women are very keen to do something to possibly decrease their risk of ovarian cancer. The majority of health care professionals are fully convinced a randomized trial is not feasible.
2) To gain insight into the opinion of *BRCA1/2* mutation carriers themselves, we performed four focus group interviews with *BRCA1/2* mutation carriers (39 women) at different stages in their lives (submitted). We explained them the new scientific insights and asked them how to move on? ("What should be the role of the fallopian tube for future *BRCA1/2* carriers to prevent ovarian cancer"?). Almost all *BRCA1/2* mutation carriers found the RRS a very attractive alternative but needed information about risks of ovarian and breast cancer; they also mentioned not to participate in a randomized study, because they do not consider themselves to be patients, have no physical symptoms and want to decide themselves about their treatment. The idea that randomization determined their fate was considered very unattractive and would discourage them to participate in any study. In itself, they were very excited to participate in this study, especially for the next generation.

Our research group is aware of the disadvantages of a non-randomized study and will take all possible precautions to reduce these disadvantages. *BRCA1/2* mutation carriers with certain characteristics may rather choose the standard treatment, others may rather choose the innovative

one. For that reason, pre surveys will be conducted on psychological factors. Besides, with regard to psychological and menopause-related quality of life factors, cardiovascular risk factors, surgery-related outcomes and safety, a comparison will be made with a retrospective cohort (women who underwent RRSO without the possibility to choose for one of the treatments like patients in the prospective part of the study have).

Flowchart



4. STUDY POPULATION

4.1 Historical cohort study

4.1.1 Population

BRCA1/2 gene germline mutation carriers who had standard treatment (RRSO) between 2011-2013 in one of the participating hospitals to obtain baseline data on quality of life.

4.1.2 Sample size calculation

Needed: 250; Expected response rate: 50%; Planned to invite: 500.

4.2 Open nationwide prospective non-randomized multicenter trial

4.2.1 Population

Female *BRCA1* gene germline mutation carriers 25-40 years old and female *BRCA2* gene germline mutation carriers 25-45 years old, recruited from a Dutch general or specialized hospital by a health care provider involved in familial cancer care.

4.2.2 Inclusion criteria

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

- Premenopausal women with a documented *BRCA1* and/or *BRCA2* gene germline mutation (when on oral contraceptives: stop at 1 month before first surgery).
- Age 25-40 years for *BRCA1* mutation carriers and 25-45 years for *BRCA2*
- Childbearing completed
- Presence of at least one fallopian tube
- Participants may have a personal history of non-ovarian malignancy
- Informed consent must be obtained and documented according to national and local regulatory requirements and the local rules followed in the institution.

4.2.3 Exclusion criteria

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

- Postmenopausal status (natural menopause or due to (cancer) treatment)
- Wish for second stage RRO within two years after RRS (if clear at enrollment)
- Legally incapable
- Prior bilateral salpingectomy
- A personal history of ovarian, fallopian tube or peritoneal cancer
- Evidence of malignant disease at enrollment
- Current treatment for malignant disease
- Inability to read or speak Dutch

4.2.4 Sample size calculation

Our main outcome measure for the short-term evaluation is the menopause specific quality of life. Menopausal symptoms will be assessed by the Greene Climacteric Scale (GCS) (see questionnaires in detail).

Assumptions for sample size calculation:

- Our main comparison is the difference in GCS between women with RRS treatment and delayed RRO (innovative treatment) and women with RRSO treatment without hormone replacement therapy (HRT), that is about one third of the women with RRSO.
- Difference between RRS and RRSO without HRT in the menopause specific quality of life (GCS) is estimated on 5 points, with sd=7.36, based on the figures of Barentsen et al. (Maturitas, 2001). They found a mean total score of the Greene Climacteric Scale in premenopausal women of 10.53±7.36(=SD), compared to a significantly different score in perimenopausal women and postmenopausal women, respectively 15.78±9.09 and 15.33±9.01.
- Each hospital will provide the innovative (RRS with delayed RRO) and the standard treatment (RRSO), based on patient choice (no randomization)
- Intracluster correlation coefficient ≤ 0.10.
- 10 hospitals are available (have intended to participate).
- 51 patients will participate in each of the hospitals

When we have at least 10 hospitals, with 51 patients per hospital, we expect that the majority of the hospitals (7 hospitals or more) will provide at least 3 patients with the innovative treatment. The remaining hospitals (3 or less) provide 51 patients with standard treatment of whom 16 will be on RRSO without HRT (see appendix 3). This scenario gives an 80% power (alpha=0.05). When each hospital will provide at least 6 patients (or 10 patients) only 5 hospitals (or 4 hospitals) are needed (see appendix 3).

4.2.5 Requirement for participating centres

All general and specialized hospitals can participate in this study. The RRS and RRSO should be performed in a hospital with a trained gyneco-pathologist with facilities to examine the tubes conform the SEE-FIM protocol. Surgery will be perfomed by a gynecologist. For each center, there must be approval by the local Institutional Ethics Committee (METC).

5. TREATMENT OF SUBJECTS

5.1 Standard treatment

RRSO at age 35-40 in *BRCA1* gene germline mutation carriers and at 40-45 in *BRCA2* gene germline mutation carriers (exact ages varying across different hospitals) and when childbearing is completed.

5.2 Innovative treatment

RRS when childbearing is completed with second stage RRO delayed for 5 years compared to the standard timing of RRSO in the specific hospital, i.e. at the age of 40-45 in *BRCA1* and 45-50 in *BRCA2* mutation carriers. Regarding the definitive contraception which is a result of RRS and the age at which RRS is performed, women will be counseled in a similar manner as women consulting the gynecologist for sterilization. *BRCA 1/2* gene germline mutation carriers who opt for early RRS but still want RRO at the age of the current standard treatment (*BRCA1* 35- 40, *BRCA2* 40-45), can choose for the innovative treatment as well, provided that at least a 2-year interval between RRS and RRO is expected at baseline. However, they do not contribute to the calculated 510 inclusions.

Surgery

Risk-reducing surgery (either RRS, RRO and RRSO): patients will undergo laparoscopy with cytology of peritoneal washings. RRSO and RRO will be done according to common practice.

RRS (with radical fimbriectomy) will be done according to Leblanc et al. (38):
The procedure will be performed using a classical 3 or 4 trocar laparoscopy; two 10-mm trocars will be inserted, the former at the umbilicus for the zero degree laparoscope and the latter in the mid-suprapubic area for instruments and specimen retrieval through bags. Two 5-mm trocars will be inserted inside each anterior iliac spine for instruments.
Peritoneal cytology will be performed prior to the thorough abdominopelvic cavity exploration. If normal, bilateral radical fimbriectomy will be performed.
Radical fimbriectomy consists of resecting the fallopian tube from the uterine level to the ovary, resecting the totality of the terminal part of tube or fimbria along with its attachment to the underlying ovary. Bipolar coagulation and scissors will be used to separate the tube from the uterine cornua, avoiding burning the utero-ovarian pedicle that will become the main blood supply of the ovary. It does not seem necessary to resect the cornual portion of the tube since no cancer has ever been described to arise from this area. Tube is then dissected free from mesosalpinx until the fimbria, by simple sharp dissection. At this level the ovary is grasped using atraumatic fenestrated forceps and divided in order to remove along the portion of ovary tethered to the fimbria, while preserving, as much as possible the infundibulo-pelvic blood supply for the remaining gland. At the most, 1/4 of the ovarian volume is removed along with the fimbria.

6. METHODS

6.1 Treatment allocation

Recruited female *BRCA1/2* gene germline mutation carriers will be asked to choose either for the standard or innovative treatment. To facilitate their choice, they will be provided with an extensive amount of information about all advantages and disadvantages and level of evidence. A decision aid will be developed by our study group.

6.2 Study parameters and procedures

6.2.1 Primary study parameter: (menopause-specific) quality of life (QoL)

6.2.1.1 Questionnaires

Greene Climacteric Scale (GCS). The GCS is a self-report measure for menopausal symptoms (39). The GCS contains 21 items divided into various clusters with individual values. The clusters are psychological (11 symptoms) subdivided into anxiety and depression, somatic (7 symptoms), vasomotor (2 symptoms) and sexual (1 symptom). Each symptom is rated according to its severity using a four-point Likert scale (0, not at all; 1, a little; 2, quite a bit; 3, extremely). The Greene Climacteric score is the sum of all 21 scores ranging from 0 to 63. A higher total score corresponds with more menopausal symptoms.

SF-36v2™. The SF-36 is a multi-purpose, short-form health survey with 36 questions (40). It contains items on eight domains: physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. Accordingly, the SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments. Some improvements were added in Version 2.0 of the SF-36. It yields physical and mental component subscores and a total SF-36 score (0-100).

EQ-5D™-3L. Standardized descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of three responses. The responses record three levels of severity (no problems/some or moderate problems/extreme problems) within a particular EQ-5D dimension. Besides the descriptive system, a standard vertical 20 cm visual analogue scale (similar to a thermometer) for recording an individual's rating for their current health-related quality of life state is part of the EQ-5D. It was developed by the EuroQol Group (41). This questionnaire will be used to calculate Quality Adjusted Life Years (QALY) together with the SF-HLQ (see later).

Cancer worry scale (CWS) .The CWS was originally designed as a four item (and later six item) scale to measure worry about the risk of developing cancer and the impact of worry on daily functioning (42, 43). Douma et al. added two items to address worries about family members and future surgery (44). Scores range from 8 to 32; no clinical case cut offs are derived. In this study, women will be asked to rank their worries on the risk of ovarian cancer (including Fallopian tube and peritoneal cancer) and breast cancer in the previous month.

Female Sexual Function Index (FSFI). The FSFI, a 19-item questionnaire, has been developed as a brief, multidimensional self-report instrument for assessing the 6 key dimensions of sexual functioning in women consisting of desire, arousal, lubrication, orgasm, satisfaction,

and pain (45, 46). Higher scores indicate better sexual functioning. A total score of 26.55 or less is defined as female sexual dysfunction.

Female Sexual Distress Score (FSDS). The FSDS is a tool to measure sexually related personal distress in women with a high degree of internal consistency and test-retest reliability. Furthermore, the scale showed a high degree of discriminative ability to distinguish between sexually dysfunctional and functional women (46, 47). It consists of 12 items and each item is rated according to its frequency in the past 30 days on a five-point Likert scale.

Satisfaction with decision (SWD). The Satisfaction with Decision (SWD) scale measures satisfaction with healthcare decisions. It was developed in the context of postmenopausal hormone-replacement therapy decisions. The six-item scale has excellent reliability (Cronbach's alpha = 0.88) (48).

6.2.1.2 Time points and burden

Questionnaires will be sent by the datacenter in Nijmegen, using e-mail with a link to web-based questionnaires or home addresses (separate informed consent needs to be signed). Sending and receiving questionnaires will be coordinated by a research nurse of the Radboud University Medical Center Nijmegen. The participant should complete the questionnaires by herself and return these either by completing the web-based questionnaire or by e-mail or mail (return envelope free of charge will be provided). The average time to complete the entire quality of life questionnaires is approximately 15 minutes.
- Baseline (after informed consent, within a maximum of 6 months before each surgery).
- 3 and 12 months after each surgery, then biennial until 15 years after last surgery.
Participants are asked to complete questionnaires as much as possible at the indicated time points, but no more than one month sooner or later**.**

6.2.1.3 Compliance

Missing data hamper assessment of quality of life in clinical trials. This problem will be minimized by the close follow-up of compliance by one coordinating person, a research nurse, of Radboud University Medical Centre Nijmegen. The coordinating person will be responsible for questionnaire data collection in order to optimise compliance and to ensure the completeness of the data. Patients are eligible for the quality of life assessment in this study if they fulfill the eligibility criteria and complete the baseline quality of life questionnaires. The compliance with the quality of life assessments will be reviewed once a year and will be part of the annual descriptive report.

6.2.2 Secondary study parameters

6.2.2.1 (Risk factors for) cardiovascular disease

Tests:
- Physical cardiovascular examination (blood pressure measurement (mmHg), calculation of body-mass index (BMI in kg/m^2) and waist-hip ratio), performed by the physician involved or by a research nurse at baseline. At follow-up, blood pressure might also be measured by the general practitioner and BMI and waist-hip ratio by the patient herself.
- Venous blood sampling (punction) for cardiovascular risk factor analysis, performed by the local laboratory in the participating hospitals (Hemoglobin, Hematocrit, Sodium, Potassium, Urea, Creatinine, Uric acid, high-sensitivity C-reactive Protein (hs-CRP), Fibrinogen, Glucose, Total cholesterol, High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), Triglyceride, Thyroid Stimulating Hormone (TSH) and a sample to store (in Dutch: spijtserum). Blood samples need to be fasting samples.
- Cardiovascular Questionnaire. This questionnaire collects data about risk factors for

cardiovascular diseases especially for women, because the general questionnaires are mainly focused on men. Gender-specific items such as pregnancy-related diseases and life style items are added.

Time points and burden:
- Baseline (after informed consent, within a maximum of 6 months before surgery); may be combined with regular preoperative blood sampling.
- Five years after surgery (RRS, RRO or RRSO); study-specific visit including fasting venous blood sampling. Blood pressure could be measured by the general practitioner and BMI and waist-hip ratio by the general practitioner or the patient herself after instruction.
- Questionnaire will be sent at baseline (within a maximum of 6 months before each surgery) and after 1 and 5 years after each surgery.

6.2.2.2 Perioperative and postoperative morbidity and mortality

Questionnaires at 6 weeks after every surgery (and investigation of medical file if necessary in order to complete missing/incomplete information). Type of surgery (laparoscopy or laparotomy), conversion, length of hospital stay, re-surgery, readmission.

6.2.2.3 Incidence of (pre)malignant findings in removed fallopian tubes/ovaries

All fallopian tubes will be examined according to the SEE-FIM protocol: *Sectioning and Extensively Examining the FIMbriated End (SEE-FIM) of the Fallopian Tube'* (Appendix 1). When (pre)malignancies are found in an RRS specimen, an additional RRO will be performed in short term.

6.2.2.4 Incidence of ovarian and breast cancer in both arms

Questionnaires will be sent at 3 and 12 months after surgery and then biennial until 15 years after surgery. Investigation of medical file will be conducted if necessary in order to complete missing/incomplete information.

6.2.2.5 Cost-effectiveness of both strategies

Costs of health care. For each patient, an estimation of costs will be made by summing all surgeries, admissions, used medication, specialist/general practitioner consultations etcetera. Average national prices will be used in this calculation. QALY (Quality Adjusted Life Years) will be calculated.

Short-Form Health and Labour Questionnaire (SF-HLQ). The SF-HLQ is a generic and validated measurement instrument to collect data of productivity losses related to health problems in individuals with paid or unpaid work (49, 50). The SF-HLQ consists of three modules (absenteeism from paid work, production losses without absenteeism for paid work and hindrance in the performance of paid and unpaid work).

Time point: Baseline (within 6 months before each surgery) and 6 weeks, 3 and 12 months after every surgery, then biennial until 15 years after surgery.

6.2.2.1 Building a database for long-term follow-up (15 years after last surgery)

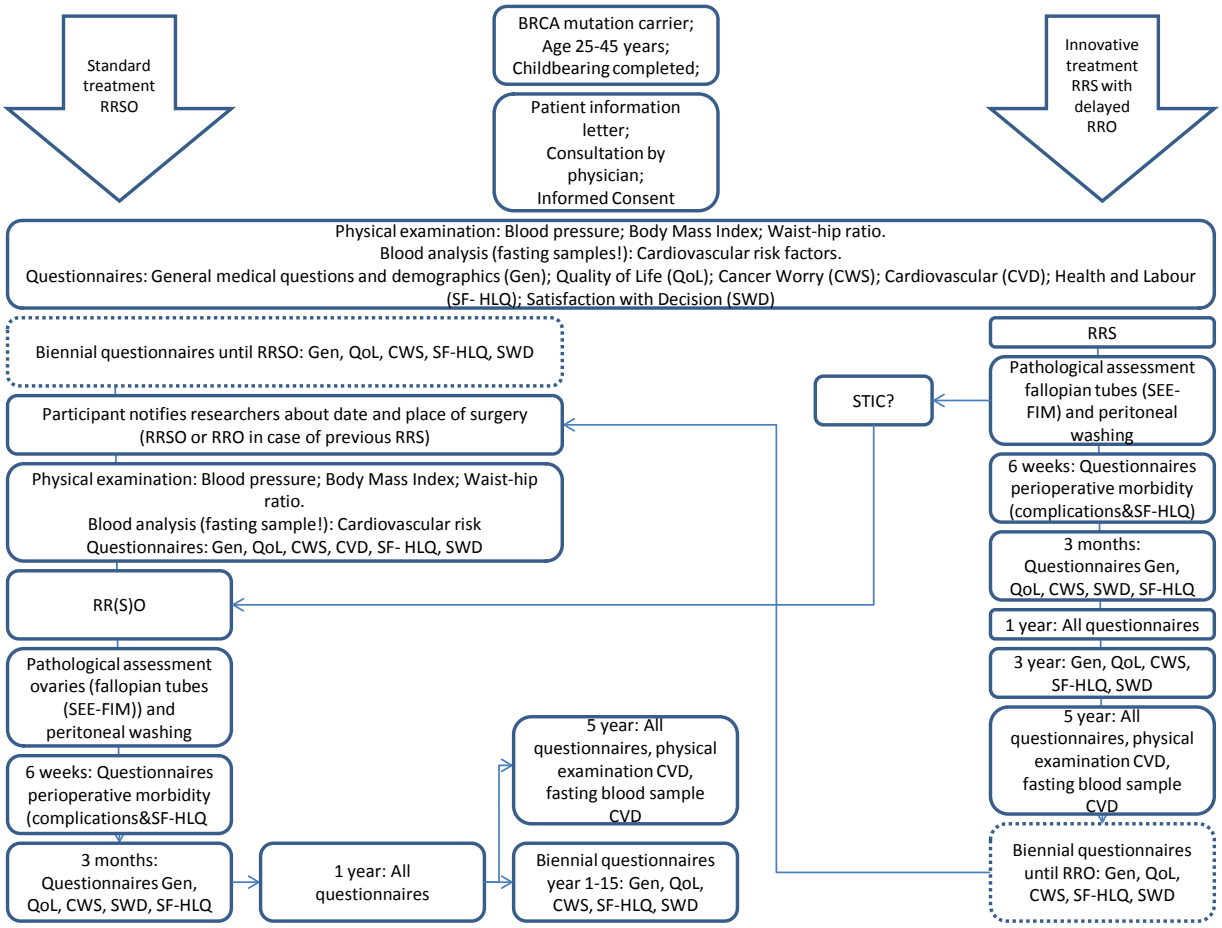
With respect to safety, short biennial questionnaires will be sent to participants until 15 years after the last surgery to be informed about incidence of breast and ovarian cancer and cardiovascular events.

6.2.3 Other study parameters: personal and family medical history

Personal: Cancer, risk-reducing surgery, cardiovascular, menopausal status, use of medication (i.e. HRT), cancer risk perception, main reason to choose for a particular treatment.

Family: cancer, cardiovascular.
Study-specific questionnaire to be filled in at baseline.

6.3 Schedule of data collection



6.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason without consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

6.4.1 Specific criteria for withdrawal

If patient is going off protocol, the reason should be documented on the case report form 'End of study' according to the following listing:

- Adverse event
- Concomitant disease
- Death (due to ovarian carcinoma/ breast cancer/ complications of therapy/ concomitant disease/ other cause)
- Loss to follow up
- Other reasons

6.5 Follow-up of subjects with abnormalities in cardiovascular investigations

Patients with abnormal findings in blood analyses will be referred to their general practitioner to be treated according to the appropriate guideline (e.g. 'Cardiovascular Risk Management').

6.6 **Premature termination of the study**

Safety reviews are planned primarily to guard against unfavorable results patients undergoing the investigational treatment. Death, cancer and failure rates and SAE reports for both treatment arms will be closely monitored in order to pick up any (unexpected) trends. Safety reviews will be presented confidentially to the DSMB every year and/or at request of the DSMB. These annual reviews will include data on number and causality of deaths, incidence of breast and ovarian cancer, and serious adverse events. The DSMB can recommend to modify or stop the study prematurely, if number and causality of deaths, incidence of breast and ovarian cancer and serious adverse events are significantly greater than was foreseen in the literature.

7. SAFETY REPORTING

7.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

7.2 Adverse events (AEs) and Serious adverse events (SAEs)

7.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational treatment (RRS with delayed RRO). All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

7.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

Information about AEs, retrieved by the evaluation of questionnaires or observed by the investigator, will be recorded on the next case report form. Once a year the investigator will report information about adverse events to the accredited METC through the web portal ToetsingOnline.

Information about SAEs is collected and recorded on the Serious Adverse Event Report Form (appendix 4). The SAEs must be reported within 24 hours by fax (fax number 024-3668597) or email to the Coordinating Investigator Dr. J.A. de Hullu. The Coordinating Investigator will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the investigator has first knowledge of the serious adverse events. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report. All SAEs will be reported in the annual report.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report.

7.3 Follow-up of adverse events

All AEs 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)**

An Independent Data Safety Monitoring Board (DSMB) is established comprising of independent experts who have no conflict of interest and agree with the outline of the protocol. Members of the DSMB are Prof.Dr. L.A.L.M. Kiemeney, cancer epidemiologist at Radboudumc Nijmegen, Dr. J.C. Oosterwijk, clinical geneticist at University Medical Center Groningen, and Prof.Dr. J.H.W. de Wilt, surgeon at Radboudumc Nijmegen. The committee will meet once a year to perform an interim analysis with respect to safety. Following this meeting, the DSMB will report to the Study Coordinators about (serious) adverse events, whether or not recruitment is on target and the compliance with the quality of life assessments is adequate. The committee may recommend changes in the conduct of the trial and exclusion of a single center if excessive rates of morbidity are present. All data presented at this meeting will be considered confidential. During the study, the committee may decide to change the frequency of discussion.
The advice(s) of the DSMB will only be sent to the coordinating investigator of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

8. STATISTICAL ANALYSIS

8.1 Primary study parameter: Menopause related quality of Life (Greene Climacteric Scale)

To test differences between the two subgroups on the course of quality of life since baseline, we will carry out a mixed model analysis to accommodate for hospital effects and repeated measurements. Differences in quality of life at each time point will be tested using t-test and adjusted for covariables.

8.2 Secondary and other study parameters

a) Other quality of life questionnaires
b) Comparison with historical cohort
c) Peri- and postoperative complications
d) Incidence of STIC or occult invasive carcinoma in removed fallopian tubes/ovaries
e) Cardiovascular risk factors and incidence of cardiovascular disease
f) Incidence of ovarian and breast cancer
g) Cost-effectiveness

The above mentioned parameters will be analyzed in a similar manner as the primary study parameter (mixed models).

Ad g) Costs per quality adjusted life years (QALY) will be calculated using EQ-5D and SF-HLQ scores.

8.3 Other study parameters: Baseline data

Baseline data will be presented in a descriptive manner. Frequencies, relative frequencies, means and standard deviations will be calculated. To test for differences in baseline data between both treatment arms, the Chi square and analysis for variance (ANOVA) are used for categorical and continuous variables respectively.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study protocol and any amendment that is not solely of an administrative nature will be submitted for approval by the Institutional Ethics Committee (METC). The guidelines “richtlijn toetsingsprocedure multicenter-onderzoek” (active as of January 1, 2001) and “good clinical practice” will be applicable. The protocol will be submitted for review to the Radboud Medical-Ethical Committee (METC). The Board of Directors of the participating centers in the Netherlands will be contacted by the principal investigators for statements of local consent if the Radboud Medical-Ethical Committee (METC) comes to a positive decision. The study will be conducted in full conformance with the ethical principles of the Declaration of Helsinki Seoul, 2008 and the WMO.

9.2 Recruitment and consent

Known *BRCA1/2* mutation carriers from the department of Clinical Genetics of each hospital, who are between 25 and 40 (*BRCA1*) or 45 (*BRCA2*) years old and not known to have already undergone RRSO, will be sent a letter to inform them about this study. This letter will be sent and signed by the treating physician and the study team from the Radboudumc will be listed as well. Contact information will be adjusted to each participating center, e.g. the phone number of a local research nurse can be added. The *BRCA* mutation carriers will be asked to indicate (by e-mail or telephone) if they are interested to participate whether or not. If yes, the patient information form will be sent by either the local physician or the study team and an appointment to explain the rationale, design and aims of the study in person will be made. The patient will have sufficient time (minimal one week) to consider the study before deciding to participate. Written informed consent of the patient is required before participation. This must be done in accordance with the national and local regulatory requirements. A copy of the written informed consent must be sent to the study coordinator, M. Harmsen.
If patients do not respond to the first letter, we will call them by phone to make sure they received the letter and to answer possible questions.
Furthermore, every newly diagnosed *BRCA1/2* germline mutation carrier at the department of Clinical Genetics that fulfills the inclusion criteria will be informed about the study and will be asked for consent as well.

9.3 Compensation for injury

Every participating institute should have an insurance against the legal liability resulting from medical procedures. Patients will receive written information on the trial insurance for this study. This insurance provides cover for damage to research subjects through injury or death caused by the study.

The investigator (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

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

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 **Handling and storage of data and documents**

The Central Datacenter is organized at the Radboud University Medical Center Nijmegen and consist mainly of a study coordinator and research nurse. When a participant signed for informed consent, a case report form (CRF) number will be generated and all further documents will be coded with this CRF number, making it impossible to directly relate data to individuals.

The investigator must assure that the subject's anonymity will be maintained on all documents submitted to the Central Datacenter.

To enable peer review and/or inspections from Health Authorities, the investigator must agree to keep records, including the identity of all participating subjects (sufficient information to link records, e.g. CRFs and hospital records), all original signed Informed Consent Forms, copies of all CRFs. To comply with international regulations, the investigator should retain the records for 15 years.

The handling of personal data will comply with the Dutch Personal Data Protection Act (Wet Bescherming Persoonsgegevens; or WBP).

10.2 **Quality Assurance**

The Central Datacenter will perform extensive consistency checks on the CRFs and returned questionnaires in case of inconsistent data that will be sent to the investigator.

A study initiation meeting to fully inform the investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation is strongly recommended and will be organized by the Study Coordinators.

The decision to perform monitoring visits on-site lies with the Study Coordinators, who may also decide who will perform the monitoring visits. Initial monitoring on informed consent, eligibility and safety will be performed by the study coordinator. All records will be maintained in accordance with local regulations and in a manner that ensures security and confidentiality.

Each subject will be identified in the CRF by a subject identification number. The subject identification number will be a sequential number.

10.3 **Amendments**

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

10.4 **Annual progress report**

The 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 **End of study report**

The investigator will notify the accredited METC and all participating hospitals of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last questionnaire 15 years after the last surgery has been received by the data center. In case the study is ended prematurely, the investigator 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**

Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study to the accredited METC. Publications and abstracts will be published according to CCMO-statement publication policy.
The final publication of the trial results will be written by the study coordinators and is based on the statistical analyses performed by the trial statistician. The study will be published irrespective of the nature of the results. A draft manuscript will be submitted to all co-authors for review. After revision by the co-authors, the manuscript will be sent to a peer-reviewed scientific journal. Authors will include the study coordinators, investigators from the participating centers who have included more than 5% of the evaluable patients in the trial (by order of inclusion), the statistician(s), the review pathologist(s) and others who have made significant scientific contributions depending on the journal's restriction of the number of co-authors. A listing of all participating investigators will be included in an appendix to the publications. Publications regarding specific sub-analyses or side studies (e.g. pathology, economy) will be written by the respective lead investigators in cooperation with the study coordinators.
The study coordinators must approve any publication, abstract or presentation involving patients included in this trial. Such a publication cannot include any comparisons between treatment arms or an analysis of any of the study endpoints unless the final results of the trial have already been published.

11. STRUCTURED RISK ANALYSIS

11.1 **Synthesis**

Risk for participants are not easy to concretize. Since there is still a lack of proof for the tubal origin of ovarian carcinoma, the innovative treatment can turn out to be either safer (because tubes can be removed before the age of 35-40) or more dangerous (because then the ovaries have more time to become malignant). However, with 3-6.7% and 0.7-1.9% for *BRCA1* and *BRCA2* respectively, the risks of getting ovarian cancer before the age of 40-50 stay small, even without risk-reducing surgery at all. For the scenario that the earlier tubectomy does not reduce ovarian cancer risk at all, we estimate the risk of developing ovarian cancer in the meantime about 1-2% for *BRCA1* mutation carriers and about 0.5-1% for *BRCA2* mutation carriers when RRO is postponed for five years.
Once chosen for the innovative treatment, the participant will undergo a laparoscopy twice. Known complication rates for RRSO in a comparable population vary from 0.6-5% for major (conversion, bladder or bowel injury, additional surgery required) and 3.7-10% for minor complications (infection, bleeding, hematoma) (14, 51-53). Risks might be lower for RRS alone.
To investigate the incidence of ovarian and breast cancer in both groups, careful registration is warranted. To minimize missing data on cancer incidence and mortality, patients will be asked to permit the investigators to contact their general practitioner and/or the Statistics Netherlands (Dutch: Centraal Bureau voor de Statistiek (CBS)) to obtain information about their health status and/or cause of death.
A DSMB will be installed to register these incidences and to guarantee the safety of the patients. A database will be built to monitor all participants up to 15 years with respect to cancer and cardiovascular diseases.

According to NFU guidelines, we classify the risk of this study as ‘intermediate’, based on the small chance on severe damage (ovarian cancer).

12. REFERENCES

1. Schorge JO, Modesitt SC, Coleman RL, Cohn DE, Kauff ND, Duska LR, et al. SGO White Paper on ovarian cancer: etiology, screening and surveillance. Gynecol Oncol. 2010;119(1):7-17. Epub 2010/08/10.
2. Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J Clin Oncol. 2012;30(21):2654-63. Epub 2012/06/20.
3. Zhang S, Royer R, Li S, McLaughlin JR, Rosen B, Risch HA, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. Gynecol Oncol. 2011;121(2):353-7. Epub 2011/02/18.
4. Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Kwan E, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet. 2001;68(3):700-10. Epub 2001/02/17.
5. Russo A, Calo V, Bruno L, Rizzo S, Bazan V, Di Fede G. Hereditary ovarian cancer. Crit Rev Oncol Hematol. 2009;69(1):28-44. Epub 2008/07/29.
6. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007;25(11):1329-33. Epub 2007/04/10.
7. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003;72(5):1117-30. Epub 2003/04/05.
8. Oei AL, Massuger LF, Bulten J, Ligtenberg MJ, Hoogerbrugge N, de Hullu JA. Surveillance of women at high risk for hereditary ovarian cancer is inefficient. Br J Cancer. 2006;94(6):814-9. Epub 2006/02/24.
9. Hermsen BB, Olivier RI, Verheijen RH, van Beurden M, de Hullu JA, Massuger LF, et al. No efficacy of annual gynaecological screening in BRCA1/2 mutation carriers; an observational follow-up study. Br J Cancer. 2007;96(9):1335-42. Epub 2007/04/12.
10. Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. J Natl Cancer Inst. 2009;101(2):80-7. Epub 2009/01/15.
11. Kauff ND, Domchek SM, Friebel TM, Robson ME, Lee J, Garber JE, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. J Clin Oncol. 2008;26(8):1331-7. Epub 2008/02/13.
12. Fakkert IE, Mourits MJ, Jansen L, van der Kolk DM, Meijer K, Oosterwijk JC, et al. Breast Cancer Incidence After Risk-Reducing Salpingo-Oophorectomy in BRCA1 and BRCA2 Mutation Carriers. Cancer Prev Res (Phila). 2012;5(11):1291-7. Epub 2012/09/27.
13. Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. J Natl Cancer Inst. 2013;105(11):812-22. Epub 2013/05/01.
14. Kenkhuis MJ, de Bock GH, Elferink PO, Arts HJ, Oosterwijk JC, Jansen L, et al. Short-term surgical outcome and safety of risk reducing salpingo-oophorectomy in BRCA1/2 mutation carriers. Maturitas. 2010;66(3):310-4. Epub 2010/04/23.
15. Finch A, Beiner M, Lubinski J, Lynch HT, Moller P, Rosen B, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. JAMA : the journal of the American Medical Association. 2006;296(2):185-92. Epub 2006/07/13.

16. Dowdy SC, Stefanek M, Hartmann LC. Surgical risk reduction: prophylactic salpingo-oophorectomy and prophylactic mastectomy. Am J Obstet Gynecol. 2004;191(4):1113-23. Epub 2004/10/28.
17. Finch A, Metcalfe KA, Chiang J, Elit L, McLaughlin J, Springate C, et al. The impact of prophylactic salpingo-oophorectomy on quality of life and psychological distress in women with a BRCA mutation. Psychooncology. 2013;22(1):212-9. Epub 2011/09/14.
18. Madalinska JB, van Beurden M, Bleiker EM, Valdimarsdottir HB, Hollenstein J, Massuger LF, et al. The impact of hormone replacement therapy on menopausal symptoms in younger high-risk women after prophylactic salpingo-oophorectomy. J Clin Oncol. 2006;24(22):3576-82. Epub 2006/08/01.
19. Rebbeck TR, Friebel T, Wagner T, Lynch HT, Garber JE, Daly MB, et al. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. J Clin Oncol. 2005;23(31):7804-10. Epub 2005/10/13.
20. Atsma F, Bartelink ML, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. Menopause. 2006;13(2):265-79. Epub 2006/04/29.
21. Svejme O, Ahlborg HG, Nilsson JA, Karlsson MK. Early menopause and risk of osteoporosis, fracture and mortality: a 34-year prospective observational study in 390 women. BJOG. 2012;119(7):810-6. Epub 2012/04/26.
22. Ossewaarde ME, Bots ML, Verbeek AL, Peeters PH, van der Graaf Y, Grobbee DE, et al. Age at menopause, cause-specific mortality and total life expectancy. Epidemiology. 2005;16(4):556-62. Epub 2005/06/14.
23. Campfield Bonadies D, Moyer A, Matloff ET. What I wish I'd known before surgery: BRCA carriers' perspectives after bilateral salipingo-oophorectomy. Fam Cancer. 2011;10(1):79-85. Epub 2010/09/21.
24. Piek JM, van Diest PJ, Zweemer RP, Jansen JW, Poort-Keesom RJ, Menko FH, et al. Dysplastic changes in prophylactically removed Fallopian tubes of women predisposed to developing ovarian cancer. J Pathol. 2001;195(4):451-6. Epub 2001/12/18.
25. Dubeau L, Drapkin R. Coming into focus: the nonovarian origins of ovarian cancer. Ann Oncol. 2013;24 Suppl 8:viii28-viii35. Epub 2013/10/30.
26. Collins IM, Domchek SM, Huntsman DG, Mitchell G. The tubal hypothesis of ovarian cancer: caution needed. Lancet Oncol. 2011;12(12):1089-91. Epub 2011/08/27.
27. Erickson BK, Conner MG, Landen CN, Jr. The role of the fallopian tube in the origin of ovarian cancer. Am J Obstet Gynecol. 2013;209(5):409-14. Epub 2013/04/16.
28. Dietl J. Revisiting the pathogenesis of ovarian cancer: the central role of the fallopian tube. Arch Gynecol Obstet. 2014;289(2):241-6. Epub 2013/10/09.
29. Roh MH, Kindelberger D, Crum CP. Serous tubal intraepithelial carcinoma and the dominant ovarian mass: clues to serous tumor origin? Am J Surg Pathol. 2009;33(3):376-83. Epub 2008/11/18.
30. Kindelberger DW, Lee Y, Miron A, Hirsch MS, Feltmate C, Medeiros F, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. Am J Surg Pathol. 2007;31(2):161-9. Epub 2007/01/27.
31. Roh MH, Yassin Y, Miron A, Mehra KK, Mehrad M, Monte NM, et al. High-grade fimbrial-ovarian carcinomas are unified by altered p53, PTEN and PAX2 expression. Mod Pathol. 2010;23(10):1316-24. Epub 2010/06/22.
32. Folkins AK, Jarboe EA, Saleemuddin A, Lee Y, Callahan MJ, Drapkin R, et al. A candidate precursor to pelvic serous cancer (p53 signature) and its prevalence in ovaries and fallopian tubes from women with BRCA mutations. Gynecol Oncol. 2008;109(2):168-73. Epub 2008/03/18.
33. Crum CP, Drapkin R, Miron A, Ince TA, Muto M, Kindelberger DW, et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. Curr Opin Obstet Gynecol. 2007;19(1):3-9. Epub 2007/01/16.

34. Kurman RJ, Shih Ie M. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol. 2010;34(3):433-43. Epub 2010/02/16.
35. Mingels MJ, Roelofsen T, van der Laak JA, de Hullu JA, van Ham MA, Massuger LF, et al. Tubal epithelial lesions in salpingo-oophorectomy specimens of BRCA-mutation carriers and controls. Gynecol Oncol. 2012;127(1):88-93. Epub 2012/06/20.
36. Greene MH, Mai PL, Schwartz PE. Does bilateral salpingectomy with ovarian retention warrant consideration as a temporary bridge to risk-reducing bilateral oophorectomy in BRCA1/2 mutation carriers? Am J Obstet Gynecol. 2011;204(1):19 e1-6. Epub 2010/07/14.
37. Holman LL, Friedman S, Daniels MS, Sun CC, Lu KH. Acceptability of prophylactic salpingectomy with delayed oophorectomy as risk-reducing surgery among BRCA mutation carriers. Gynecol Oncol. 2014;133(2):283-6. Epub 2014/03/04.
38. Leblanc E, Narducci F, Farre I, Peyrat JP, Taieb S, Adenis C, et al. Radical fimbriectomy: a reasonable temporary risk-reducing surgery for selected women with a germ line mutation of BRCA 1 or 2 genes? Rationale and preliminary development. Gynecol Oncol. 2011;121(3):472-6. Epub 2011/03/18.
39. Greene JG. Constructing a standard climacteric scale. Maturitas. 1998;29(1):25-31. Epub 1998/06/27.
40. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83. Epub 1992/06/11.
41. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy (New York). 1990;16(3):199-208. Epub 1990/11/05.
42. Lerman C, Daly M, Masny A, Balshem A. Attitudes about genetic testing for breast-ovarian cancer susceptibility. J Clin Oncol. 1994;12(4):843-50. Epub 1994/04/01.
43. Watson M, Duvivier V, Wade Walsh M, Ashley S, Davidson J, Papaikonomou M, et al. Family history of breast cancer: what do women understand and recall about their genetic risk? J Med Genet. 1998;35(9):731-8. Epub 1998/09/11.
44. Douma KF, Aaronson NK, Vasen HF, Gerritsma MA, Gundy CM, Janssen EP, et al. Psychological distress and use of psychosocial support in familial adenomatous polyposis. Psychooncology. 2010;19(3):289-98. Epub 2009/04/22.
45. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000;26(2):191-208. Epub 2000/04/27.
46. ter Kuile MM, Brauer M, Laan E. The Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS): psychometric properties within a Dutch population. J Sex Marital Ther. 2006;32(4):289-304. Epub 2006/05/20.
47. Derogatis LR, Rosen R, Leiblum S, Burnett A, Heiman J. The Female Sexual Distress Scale (FSDS): initial validation of a standardized scale for assessment of sexually related personal distress in women. J Sex Marital Ther. 2002;28(4):317-30. Epub 2002/06/27.
48. Holmes-Rovner M, Kroll J, Schmitt N, Rovner DR, Breer ML, Rothert ML, et al. Patient satisfaction with health care decisions: the satisfaction with decision scale. Med Decis Making. 1996;16(1):58-64. Epub 1996/01/01.
49. Hakkaart-van Roijen L. Short Form- Health and Labour Questionnaire. Institute for Medical Technology Assessment, Erasmus University Rotterdam
50. van Roijen L, Essink-Bot ML, Koopmanschap MA, Bonsel G, Rutten FF. Labor and health status in economic evaluation of health care. The Health and Labor Questionnaire. Int J Technol Assess Health Care. 1996;12(3):405-15. Epub 1996/01/01.
51. Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med. 2002;346(21):1609-15. Epub 2002/05/25.

52. Meeuwissen PA, Seynaeve C, Brekelmans CT, Meijers-Heijboer HJ, Klijn JG, Burger CW. Outcome of surveillance and prophylactic salpingo-oophorectomy in asymptomatic women at high risk for ovarian cancer. Gynecol Oncol. 2005;97(2):476-82. Epub 2005/05/03.
53. Manchanda R, Abdelraheim A, Johnson M, Rosenthal AN, Benjamin E, Brunell C, et al. Outcome of risk-reducing salpingo-oophorectomy in BRCA carriers and women of unknown mutation status. BJOG. 2011;118(7):814-24. Epub 2011/03/12.

APPENDICES

Appendix 1: SEE-FIM protocol

Appendix 2: Nota Organisatie van de Gynaecologische Oncologische Zorg

Appendix 3: Sample Size Calculation

Appendix 4: Serious Adverse Events Sheet (SAEs)

Appendix 1: SEE-FIM protocol

Sectioning and Extensively Examining the FIMbriated End (SEE-FIM) of the Fallopian Tube'

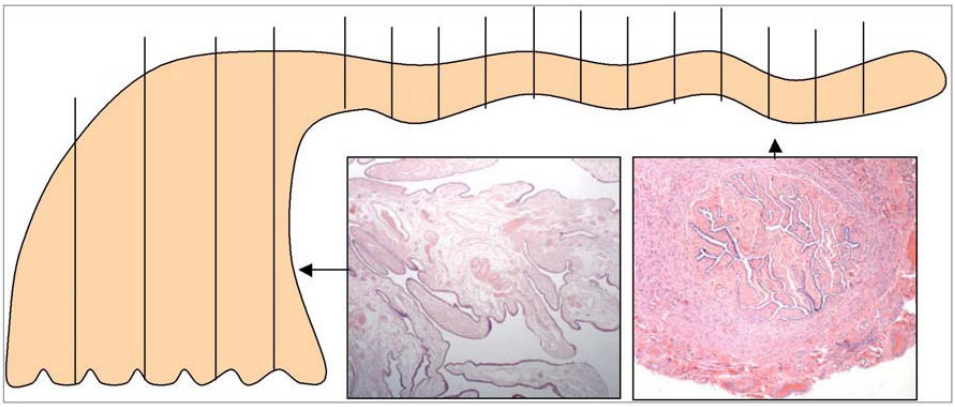


Figure 1. Protocol for Sectioning and Extensively Examining the FIMbriated End (SEE-FIM) of the Fallopian Tube. This protocol entails amputation and longitudinal sectioning of the infundibulum and fimbrial segment (distal 2 cm) to allow maximal exposure of the tubal plicae. The isthmus and ampulla are cut transversely at 2 to 3mm intervals. (From Crum CP, Drapkin R, Miron A, et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. *Curr Opin Obstet Gynecol.* 2007;19:5.)

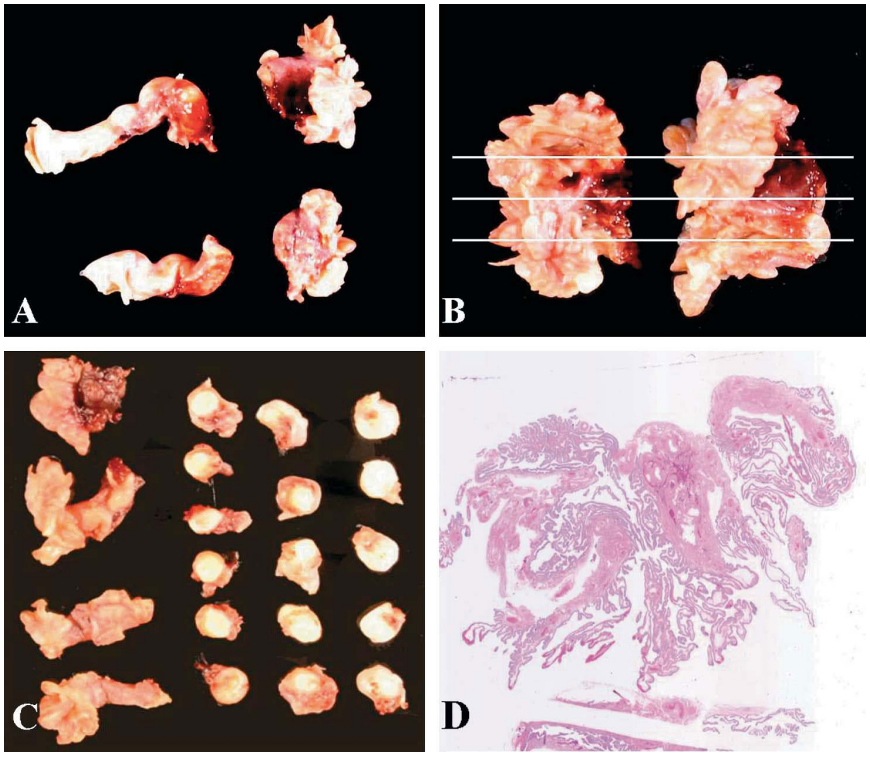


Figure 2. Protocol for Sectioning and Extensively Examining the FIMbriated end (SEE-FIM) of the fallopian tube. The tubes are bisected near the fimbriated end (A). A single tube is shown in B to D. The fimbriated end is sectioned longitudinally in the direction shown (B) and combined with the remainder of the tube sectioned at 2- to 3-mm intervals (C). D, A longitudinally sectioned fimbria displays numerous plicae for examination. (From Chang PS and Crum CP, Chapter 21: The fallopian tube and broad ligament, in Crum CP and Lee KR, Diagnostic Gynecologic and Obstetric Pathology, Elsevier Saunders, 2006, p. 701)

Appendix 2: Nota Organisatie van de Gynaecologisch Oncologische Zorg

NOTA ORGANISATIE VAN DE GYNAECOLOGISCH ONCOLOGISCHE ZORG, DEEL II Versie 1.0

Datum Goedkeuring 21-09-2011
Methodiek Evidence based

Document alleen in PDF, blz 1-3
Link naar PDF

http://nvog-documenten.nl/index.php?pagina=/richtlijn/item/pagina.php&richtlijn_id=902

Appendix 3: Sample size calculation

Our main comparison is the difference in GCS between women with RRS treatment & delayed RRO (innovative treatment) and women with RRSO treatment (= standard treatment) without hormone replacement therapy (HRT) , that is about one third of the women with RRSO.

When each hospital has at least 3 patients on innovative treatment, then 7 hospitals with this scenario are needed for 80% power; when this is at least 6 patients (or 10 patients) only 5 hospitals (or 4 hospitals) are needed, see table below. Treatment applied	Needed number of patients with innovative treatment (RRS)	Needed number of patients with standard treatment (RRSO) without HRT	Total patients needed (RRS plus RRSO without HRT)	Total patients needed (RRS plus RRSO)	Total hospitals needed
Per hospital: 3 patients innovative and 16 patients RRSO without HRT, i.e. in total 48 with RRSO: 48+3=51 patients in total	20	112	132	357	7
Per hospital: 6 patients innovative and 14 patients RRSO without HRT, i.e. in total 42 with RRSO: 42+6= 48 patients in total	25	58	83	240	5
Per hospital: 10 innovative, 10 RRSO without HRT, i.e. in total 30 with RRSO: 30+10= 40 patients in total	35	35	70	160	4

Appendix 4: Serious adverse events sheet (SAEs)

(Serious)Adverse Event Form **(indien SAE: fax formulier binnen 24u naar M. Harmsen, Radboudumc Nijmegen, faxnr: 024-366 85 97)**

Adverse Event (AE) ?	□ Nee	□ Ja
Zo ja, beschrijf Adverse Event	_____ _____ _____ _____ _____	
Startdatum Adverse Event	|__|__| |__|__| |__|__|__|__| (DD-MM-JJJJ)	
Einddatum Adverse Event	□ Nog gaande	□ Einddatum: |__|__| |__|__| |__|__|__|__| (DD-MM-JJJJ)
Ernst Adverse event	□ mild □ matig □ ernstig □ levensbedreigend □ dodelijk	
Relatie tot risico-reducerende salpingectomie of oophorectomie?	□ niet gerelateerd □ twijfelachtig □ mogelijk □ waarschijnlijk □ zeer waarschijnlijk	
Actie ondernomen	□ geen □ behandeling veranderd □ behandeling uitgesteld □ behandeling veranderd en uitgesteld	

	□ uit studie teruggetrokken

Uitkomst	□ Hersteld □ Niet hersteld □ Hersteld met restverschijnselen □ Fataal, geef overlijdensdatum |__|__| |__|__| |__|__|__|__| d d m m j j j j □ Niet bekend	
Serious Adverse Event (SAE) ?	□ Nee	□ Ja
<u>Reden waarom het een SAE is:</u> Verlengde of hernieuwde ziekenhuisopname (graad 3) Blijvende aanzienlijke schade of ernstige invaliditeit/arbeidsongeschiktheid (graad 3) Levensbedreigend: snelle interventie noodzakelijk (graad 4) <u>Resulteert in overlijden (graad 5)</u>	 □ ja □ ja □ ja □ ja	 □ nee □ nee □ nee □ nee
Zo ja, beschrijf Serious Adverse Event	_____ _____ _____ _____	

	_____ _____

Overview of formal amendments to the trial protocol since first approved version (version 4.0)

Prior to 1st inclusion:

Amendment 1 (December 11, 2014): Risk classification is changed from medium risk to negligible.

Amendment 2 (January 16, 2015): sponsor is added, author from the Radboudumc, updated questionnaires (EQ5D-5L instead of EQ5D-3L, iPCQ and iMCQ instead of the SF-HLQ, Decisional conflict and Decisional regret instead of Satisfaction with decision), no storage of spare blood samples.

After 1st inclusion:

Amendment 3 (May 1, 2015): research nurse included, two participating centers added, a local investigator in one of the participating centers changed.

Amendment 4 (December 28, 2015): arrangements about notification of serious adverse advents to medical ethics committee, standardization of abdominal fluid sampling procedure (especially washing with 20 mL of saline in case no abdominal fluids can be aspirated),

Amendment 5 (April 19, 2017): addition of three participating centers, change of coordinating researcher.

Amendment 6 (September 29, 2017): addition of a patient decision aid for all newly recruited participants, questionnaires to evaluate the feasibility of the patient decision aid, alteration in the description of the surgical procedure.

Amendment 7 (May 28, 2018): change of the independent researcher.

Amendment 8 (April 24, 2019): change of local investigator in participating center.

Amendment 9 (March 16, 2020): change of research coordinator, alteration in adverse event registration,