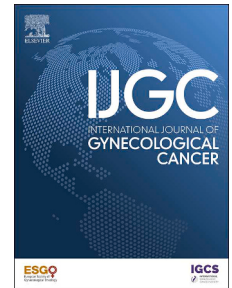


CLINICAL TRIALS

FIMBRIMENOP-2402 trial: evaluating fimbriectomy with delayed oophorectomy in patients with high-risk tubo-ovarian cancer



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ABSTRACT

Background: Bilateral salpingo-oophorectomy is the gold-standard risk-reducing surgery for women at high risk of tubo-ovarian or primary peritoneal cancer. Fimbriectomy with delayed oophorectomy has emerged as a promising alternative, potentially reducing tubo-ovarian cancer risk while minimizing the adverse effects of premature menopause. Larger cohorts and longer follow-up are required to confirm these findings.

Primary Objectives: To evaluate the effectiveness of the chosen care pathway in controlling the risk of advanced-stage tubo-ovarian carcinoma, and more specifically to determine whether prophylactic fimbriectomy with delayed oophorectomy is non-inferior to standard bilateral salpingo-oophorectomy in women at high risk and with germline mutations.

Study Hypothesis: Fimbriectomy with delayed oophorectomy is non-inferior to bilateral salpingo-oophorectomy in preventing oncological risk and reduces menopause-related health disorders.

Trial Design: This multi-center, non-randomized, pragmatic, preference-based controlled trial allows participants to choose their preventive surgical strategy between standard bilateral salpingo-oophorectomy (according to national guidelines) and fimbriectomy (considered from the age of 35, once childbearing is completed), followed by delayed oophorectomy at age 50 or at clinical menopause. Participants will undergo annual long-term follow-up until age 70. The association between the chosen care pathway and outcomes will be estimated using an inverse probability-weighted, cause-specific Cox model, with age as the time scale.

Major Inclusion/Exclusion Criteria: This study will be proposed during oncogenetic counseling to pre-menopausal women aged 30 to 50 years with a documented pathogenic germline mutation (*BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, or *PALB2*). Exclusion criteria include prior bilateral oophorectomy or salpingectomy and a personal history of tubo-ovarian cancer.

Primary Endpoint: Advanced-stage tubo-ovarian or primary peritoneal carcinoma.

Sample Size: A total of 1100 patients is planned.

Estimated Dates for Completing Accrual and Presenting Results: Recruitment will last 5 years (2026-2031). The first interim analysis is planned 6 to 8 years after study initiation (2032-2034). Final analysis is planned when all patients reach age 70 (around 2071).

Trial Registration Number: NCT06726330.

Keywords:

Radical Fimbriectomy; Delayed Bilateral Oophorectomy; Risk-Reducing Surgery; Tubo-Ovarian Cancer Prevention; Hereditary Breast And Tubo-Ovarian Cancers

INTRODUCTION

According to the World Health Organization 2020 classification, tubo-ovarian carcinoma refers to a Müllerian epithelial carcinoma involving the ovary, fallopian tube, or peritoneum, which is

considered a single disease entity due to its shared origin and biological behavior, particularly for high-grade serous carcinoma.¹ Tubo-ovarian cancer is one of the leading causes of cancer-related mortality in women. Approximately 20% of cases are attributed to

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genetic predisposition (for example, *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *PALB2*).² Women with *BRCA1* mutations have a lifetime risk of 18% to 54% of developing ovarian cancer, while women with *BRCA2* mutations have a lifetime risk ranging from 2.4 to 19%.³ Annual screening has been shown to be ineffective in detecting early-stage tubo-ovarian cancer or reducing tubo-ovarian cancer mortality in women at high risk.⁴ To date, no screening method is considered a safe alternative to risk-reduction strategies. Current guidelines recommend bilateral salpingo-oophorectomy as a risk-reduction strategy between ages 35 and 40 for women with a pathogenic germline *BRCA1* mutation, and between ages 40 and 45 for those with a pathogenic germline *BRCA2* mutation.^{5,6} Studies have shown that salpingo-oophorectomy effectively reduces the risk of tubo-ovarian cancer, with a pooled hazard ratio (HR) of 0.19 (95% confidence interval [CI] 0.13 to 0.27), corresponding to an approximate 80% reduction in risk.⁷ However, this strategy induces premature menopause, significantly affecting various aspects of women's quality of life.⁸ Hormone deprivation is responsible for short-term adverse effects, including hot flashes, sleep disturbances, and altered sexual function, as well as long-term effects such as increased risk of cardiovascular disease, osteoporosis-related issues, and cognitive impairment.⁹⁻¹¹ Hormone replacement therapy mitigates, but does not fully eliminate, the adverse effects of premature menopause. Furthermore, it is not an option for women with a history of breast cancer.

For these reasons, there has been growing interest in an alternative risk-reducing strategy for pre-menopausal women at high risk: bilateral fimbriectomy, defined as complete resection of the fallopian tubes along with their mesosalpinx, followed by delayed oophorectomy.¹² This approach is based on the observation that most tubo-ovarian cancers and their precursors originate in the fallopian tubes.¹³ Removing the tubes may therefore reduce oncological risk while preserving ovarian function. To date, prospective studies (TUBA and WISP trials) have shown that fimbriectomy with delayed oophorectomy avoids surgical premature menopause, allowing better quality of life and sexual health.^{8,14} A French prospective phase II multi-center trial, along with a retrospective cohort study, was conducted to evaluate the oncological safety of this approach.^{15,16} The results are promising, with no cases of pelvic invasive cancer reported after a median follow-up of 7.3 years and no abnormalities identified in delayed oophorectomy specimens. However, these findings require validation in larger cohorts with longer follow-up.

In the present study, we hypothesize that bilateral fimbriectomy performed after completion of childbearing, followed by delayed oophorectomy at age 50 or upon confirmation of clinical menopause, is non-inferior to the current standard of bilateral salpingo-oophorectomy at age 40 for *BRCA1* and age 45 for *BRCA2* and other predisposing germline mutations in reducing the risk of tubo-ovarian or primary peritoneal cancer.

METHODS

Trial Design

FIMBRIMENOP-2402 is a prospective, multi-center, non-randomized, preference-based controlled trial. Participation in the trial may be proposed to all eligible women during an oncogenetic

counseling visit at the participating centers, regardless of their decision regarding tubo-ovarian prophylactic surgery. Each woman will report her preferred strategy for prophylactic tubo-ovarian surgery (standard bilateral salpingo-oophorectomy vs fimbriectomy followed by delayed oophorectomy) at the time of study entry, or at the next oncogenetic counseling visit performed 6 to 12 months after study entry, according to standard practice. She will have the possibility to switch her choice at any time until the first surgery. For the analysis, we will define the chosen care pathway based on the first preventive surgery performed, or the last expressed preference in the absence of preventive surgery.

The primary objective is to evaluate the non-inferiority of fimbriectomy with delayed oophorectomy compared with standard salpingo-oophorectomy in preventing advanced-stage tubo-ovarian or primary peritoneal carcinoma. In addition, the trial will assess the benefit-risk balance of the two preventive surgical strategies. A schematic overview of the study design is presented in [Figure 1](#).

The FIMBRIMENOP-2402 trial includes a translational research program to identify and validate molecular, immunological, and microbiome biomarkers derived from fallopian tube tissue, blood, saliva, cervicovaginal swabs, and peritoneal washings that are associated with the different stages of ovarian carcinogenesis.

Control Arm

Standard bilateral salpingo-oophorectomy will be recommended from age 40 in women with *BRCA1* mutations and from age 45 in other cases, while also considering the age at diagnosis of affected relatives when relevant, in accordance with French national guidelines.¹⁷

Experimental Arm

Inclusion in the study may be proposed from the age of 30; however, fimbriectomy will only be performed from the age of 35, to ensure that childbearing is complete.

Delayed bilateral oophorectomy after fimbriectomy will be performed at age 50, or earlier upon confirmation of clinical menopause or at the patient's preference ([Fig. 1](#)).

Funding and Regulatory Requirements

The trial will be conducted across 26 comprehensive cancer centers and university hospitals in France, all with expertise in gynecologic oncology and hereditary cancer management, with the potential for inclusion of additional international sites. The trial is sponsored by the Oscar Lambret Cancer Center. The study will be launched after approval by the French Ethics Committee and the French Drug Agency. It is registered in [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT06726330). The trial is partially funded by a "PHRC-K-2023 grant".

Participants

Participation in the study may be proposed to women aged 30 to 50 years who are identified as having an increased risk of tubo-ovarian or primary peritoneal carcinoma, based on germline mutational status (eg, *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, *PALB2*). Additional susceptibility genes may be incorporated in future protocol amendments if deemed clinically relevant. The main exclusion criteria are prior bilateral oophorectomy or

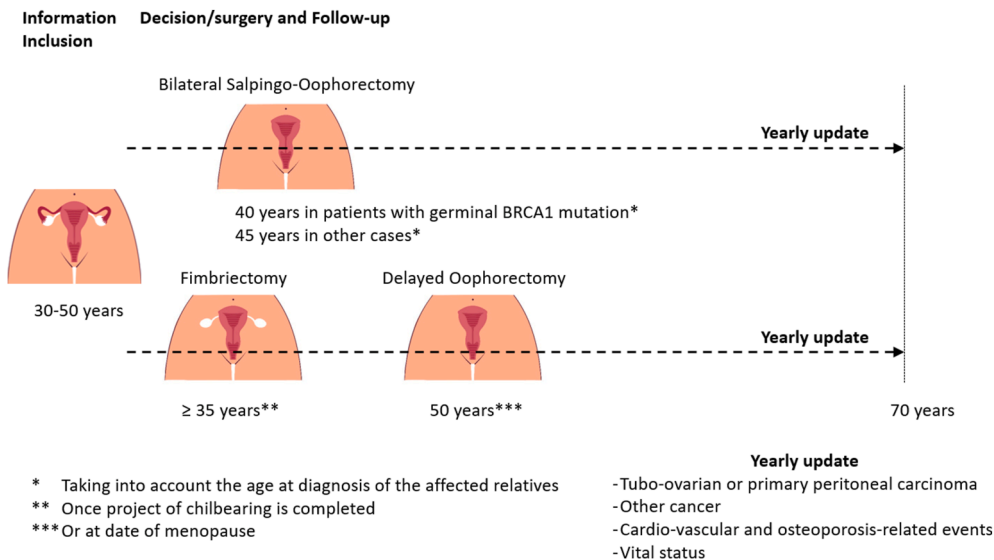


Figure 1 FIMBRIMENOP trial flowchart according to the patients' choice.

salpingectomy, a personal history of ovarian, fallopian tube, or primary peritoneal cancer, or established menopause. We also exclude patients who refuse any prophylactic surgery *a priori*. Detailed inclusion and exclusion criteria are provided in the [Table](#).

Surgical Considerations

The procedure for both salpingo-oophorectomy and radical fimbriectomy should follow the recommendations of the American College of Obstetricians and Gynecologists Committee.¹⁸ This includes a thorough pelvic and supra-mesocolic exploration to identify any abnormalities, as well as peritoneal cytology performed prior to any adnexal manipulation. The ovarian vessels should be ligated and resected at least 2 cm above the ovaries, and the entire length of the fallopian tube should be removed up to the uterine cornua. In both procedures, it is essential to excise the mesosalpinx close to the pelvic brim. Care must be taken to avoid any manipulation of the ampullary portion of the fallopian tube ("no-touch" technique), and cold scissors should be used to ensure high-quality, artifact-free pathological evaluation and, if necessary, accurate margin assessment (Video S).

Supplementary video related to this article can be found at <https://doi.org/10.1016/j.ijgc.2026.104715>

When the fimbria is firmly adherent to the ovary, the outer one-fifth of the ovary should be removed while preserving the gonadal vessels (extended fimbriectomy; [Fig. 2](#)).

In both study arms, an abdominal minimally invasive approach is the reference. The choice between single-port and multi-port techniques, as well as the specific instruments used to safely perform the procedure, is left to the surgeon's discretion. Surgical specimens should be retrieved using an endoscopic bag, and in some cases, double protection (single-port device and endoscopic bag) may be employed. No mandatory pre-operative evaluation is required before surgery in asymptomatic women. Any abnormal finding, such as peritoneal effusion or suspicious lesions, must be sampled for cytological or histological examination.¹⁹

Pathological analysis in accordance with the Sectioning and Extensively Examining the FIMbriated end (SEE-FIM) protocol²⁰ is a

crucial and mandatory component of this alternative strategy of upfront fimbriectomy. It must be performed by an experienced pathologist, regardless of the chosen surgical approach, and systematically documented in the pathology report.

At present, there is a lack of consensus regarding the management of tubal lesions identified on pathological examination (eg, serous tubal intra-epithelial lesions, serous tubal intra-epithelial carcinoma). These cases should be discussed in a tumor board to determine surgical management and follow-up according to current guidelines.¹⁵ Currently, management of serous tubal intra-epithelial carcinoma relies on completion surgery to perform adequate staging and to rule out invasive or extra-tubal disease, including at least bilateral oophorectomy and comprehensive peritoneal staging. Participants with these lesions will still be included in the analysis.

Study Endpoints

The primary endpoint is the long-term incidence of advanced-stage (stage III or IV) tubo-ovarian or primary peritoneal carcinoma. Outcomes will be ascertained through standardized annual clinical follow-up, in accordance with national recommendations, up to age 70, whether performed at the reference center or by external physicians. Information will be collected from medical records, online questionnaires completed by patients, databases of the regional oncogenetic network, or phone calls. To ensure completeness of event reporting, data will also be cross-checked prior to each statistical analysis using national health care databases of participating countries (eg, the 'Système National des Données de Santé' in France), providing access to records from the national health data system (including cardiovascular events, osteoporosis-related events, and overall survival). Incidence will be estimated based on the time from study entry to the occurrence of advanced-stage cancer, with death considered a competing event.

Secondary endpoints include additional long-term oncological outcomes, any-stage tubo-ovarian carcinoma, pre-invasive tubo-ovarian lesions, de novo or recurrent breast cancer, overall survival, age at menopause, and long-term morbidity, specifically

Table Inclusion and Exclusion Criteria of the FIMBRIMENOP Study.

Inclusion criteria	Exclusion criteria
– Women aged between 30 y and 50 y. – Addressed to or followed in an oncogenetic counseling. – Identified risk of tubo-ovarian or primary peritoneal carcinoma based on mutational status (eg, <i>BRCA1</i>, <i>BRCA2</i>, <i>RAD51C</i>, <i>RAD51D</i>, <i>PALB2</i>). The list of included mutations may be expanded during the study. – Written informed consent. – Patient must be covered by the French “Social Security” system.	– Prior bilateral oophorectomy and/or bilateral salpingectomy for any reason (prophylactic surgery or other). – Person refusing a priori any prophylactic surgery. – Personal history of ovarian, fallopian tube, or primary peritoneal cancer. – Menopausal status is defined by: <i>In women without prior chemotherapy:</i> - If no prior hysterectomy: absence of menses for at least 12 mo or FSH* >20 IU/L with low estrogen levels and no identified gynecological or endocrine explanation. - If prior hysterectomy: FSH* >20 IU/L with low estrogen levels (with or without vasomotor or genitourinary symptoms). <i>In women with prior chemotherapy,</i> the absence of menses for at least 24 mo. <i>In all women with a progesterone-loaded IUD:</i> FSH >20 IU/L with low estrogen levels. – Inability to comply with the medical follow-up required for the trial (due to geographical, social, or psychological reasons). – Patients under guardianship or curatorship.

Abbreviations: FSH, follicle stimulating hormone, IUD, intra-uterine device.

major cardiovascular events (myocardial infarction, stroke, or heart failure requiring hospitalization) and osteoporosis-related events (hip or vertebral fractures). These outcomes will be identified through routine follow-up, online questionnaires completed by patients, or phone calls, and will be complemented by data extracted from national health care databases.

Additional endpoints include the incidence of surgical and medical complications related to preventive procedures, adherence to the SEE-FIM pathological protocol, and factors associated with patients' choice of preventive strategy.

Sample Size

The mean annual risk of tubo-ovarian or primary peritoneal carcinoma after bilateral salpingo-oophorectomy is estimated at 0.1% to 0.2% for women with *BRCA1* mutations and 0.05% to 0.1% for women with *BRCA2* mutations,²¹ with an expected *BRCA1:BRCA2* ratio of 2:1. For the purpose of sample size calculation only, a constant risk over time was assumed, resulting in an estimated 15-year cumulative incidence of 2.5% overall. We expect that half of the patients will choose standard salpingo-oophorectomy (1:1 ratio) and anticipate a 10% dropout rate over 20 years.

This non-inferiority trial defines the non-inferiority margin as a cause-specific HR (cs-HR) of 2, corresponding to a difference in 15-year cumulative incidence of 4.9% versus 2.5%. This margin is considered acceptable in comparison with the non-inferiority margin used in the TUBA-WISP II study.²² In that study, an absolute difference of up to 2% (1% vs 3%) in women with *BRCA1*

mutations, and 1.5% (0.5% vs 2%) in women with other mutations was accepted at the target ages of 46 years for women with *BRCA1* mutations and 51 years for women with *BRCA2* mutations. This corresponds to a weighted mean absolute difference of 1.83% (0.83% vs 2.67%, assuming a *BRCA1:BRCA2* ratio of 2:1), or a relative risk of 3.2.

Statistical analyses will be performed using a one-sided alpha of 5%, with 3 interim analyses planned.

Based on these assumptions and parameters, a total of 60 events is required to achieve 80% power to demonstrate non-inferiority under the alternative hypothesis (cs-HR 1), leading to an estimated sample size of 1100 patients, recruited over a 5-year period and followed until age 70. The final analysis is expected to be performed approximately 45 years after the start of accrual, assuming recruitment is completed within 5 years.

Statistical Methods

For the primary endpoint, the association between the chosen risk-reducing strategy and the risk of advanced-stage tubo-ovarian or primary peritoneal carcinoma will be estimated in an inverse probability of treatment-weighted, cause-specific Cox model with age as the time scale. The analysis will include all women carrying a germline pathogenic variant in the genes of interest (*BRCA1*, *BRCA2*, *RAD51C*, *RAD51D*, and *PALB2*), in accordance with the study inclusion criteria.

Stabilized inverse probability of treatment weights will be defined based on a logistic regression model in which the

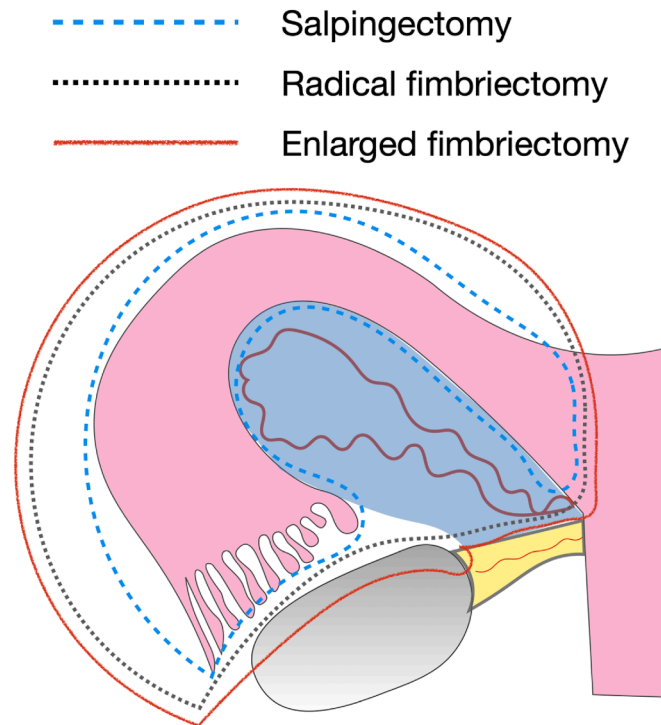


Figure 2 Schematic representation of the fallopian tube and ovary. The blue dashed line indicates the limits of salpingectomy, the black dashed line indicates the limits of radical fimbriectomy, and the red dashed line indicates the limits of enlarged fimbriectomy in cases of adhesion to the ovary.

dependent variable is the actual treatment received (or the last expressed preference if no surgery is performed before the first oncological event). Independent variables will include potential confounders: age at final decision, type of genetic mutation (*BRCA1* vs other), personal history of breast cancer, family history of tubo-ovarian or breast cancer, childbearing project at study entry, socio-economic factors, and recruiting center.

Covariate balance between treatment groups will be assessed after weighting. In the Cox model, each observation will be weighed by its stabilized inverse probability of treatment weight, derived from the observed values of the confounders. Follow-up will be censored in the event of a competing risk (eg, death without prior tubo-ovarian or primary peritoneal invasive cancer) or at the date of the last follow-up if the participant is alive without prior cancer. Age, rather than the time from study entry, will be used as the time scale,²³ because the risk of tubo-ovarian or primary peritoneal carcinoma is age-dependent, and women may be enrolled at different ages (30-50 years). Observations will be left-truncated at the age at study entry.

The effect of fimbriectomy with delayed oophorectomy compared with bilateral salpingo-oophorectomy will be estimated using the cs-HR. This effect will be tested against the null hypothesis of inferiority at a one-sided alpha of 5%. All cs-HRs will be reported with 95% CIs.

We will evaluate whether the effect of the chosen care pathway varies according to the attained age. Regardless of this analysis, we will also estimate the effect of fimbriectomy with delayed oophorectomy compared with bilateral salpingo-oophorectomy specifically over the age band of 30 to 55 years.

Heterogeneity of the effect of the chosen care pathway will also be evaluated according to the type of genetic mutation, using forest plots and interaction tests.

Surgical complications following each type of prophylactic surgery will be reported using descriptive statistics. For each type of adverse event, the maximum observed grade will be tabulated, along with the number and frequency of occurrences. Serious adverse events will also be described separately.

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We plan 3 interim analyses, when approximately 10, 30, and 45 events will be observed, with efficacy and futility stopping rules using Lan-DeMets²⁴ spending function and O'Brien and Fleming boundaries.²⁵

DISCUSSION

The gold-standard risk-reducing strategy for women at high risk of tubo-ovarian cancer is bilateral salpingo-oophorectomy, recommended between ages 35 and 45 depending on the underlying genetic mutation. In France, the National Cancer Institute (INCa) currently authorizes fimbriectomy with delayed oophorectomy only within clinical trial settings. This alternative approach has already demonstrated benefits in delaying menopause and improving quality of life and sexual health.^{8,14} However, its long-term oncological safety remains to be established.

A prospective pilot study conducted between January 2012 and October 2015 included 121 patients who underwent fimbriectomy with delayed oophorectomy.¹⁵ After a median follow-up of 7.3 years, no cases of invasive tubo-ovarian or peritoneal carcinoma were reported. Among the 46 women who subsequently underwent delayed oophorectomy, no abnormalities were found in the oophorectomy specimens. These promising results support the potential of this strategy as an alternative to standard salpingo-oophorectomy, but confirmation in a larger cohort with extended follow-up is required.

Several prospective studies are currently ongoing to assess which risk-reducing surgical modality is most appropriate for premenopausal women. All are non-randomized, preference-based studies, reflecting the challenges of conducting randomized controlled trials in this context. Ultimately, the final decision in determining the timing of oophorectomy belongs to each patient.

The FIMBRIMNOP-2402 trial differs from other ongoing preference-based controlled studies evaluating fimbriectomy with delayed oophorectomy in several key points. The TUBA-WISP-II trial is an international prospective preference-based study, recruiting since 2020, that evaluates fimbriectomy with the postponement of oophorectomy until the ages of 35 to 45 for women with *BRCA1* mutations and 40 to 50 for women with *BRCA2* mutations.²² In contrast, our trial recommends delayed oophorectomy at age 50 or at the onset of the menopause, which is later than the cut-off in TUBA-WISP-II.

Furthermore, our experience suggests that some women may prefer to postpone oophorectomy even longer. These patients should be monitored within the framework of a clinical study to ensure long-term oncological safety.¹⁵ The follow-up of the present trial extends up to age 70, enabling the evaluation not only of long-term oncological outcomes but also of menopause-related morbidity and overall survival.

Two other international trials are also investigating risk-reducing fimbriectomy in high-risk populations. The SOROCK trial (NCT04251052) is a US non-randomized non-inferiority study evaluating fimbriectomy with delayed oophorectomy exclusively in women with *BRCA1* mutations. In contrast, FIMBRIMNOP includes women with *BRCA2*, *RAD51C*, *RAD51D*, or *PALB2* mutations as well, with the possibility of expanding eligible criteria during the study. The British PROTECTOR study (ISRCTN25173360), on the other hand, compares fimbriectomy with delayed oophorectomy, bilateral salpingo-oophorectomy, and no surgery, focusing primarily on sexual and endocrine outcomes while also providing data on oncological safety.^{26,27} In the present study, quality-of-life assessment is not included as an endpoint, as the impact of premature menopause on quality of life has already been extensively investigated. Furthermore, longitudinal assessment of quality of life would significantly increase the complexity and burden of the study.

A meta-analysis of all these studies is planned, aiming to synthesize findings and provide insights that will inform clinical practice and optimize patient care on a global scale.

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Author Contributions SSc, CMG, SR, and MCLD drafted the main manuscript. All authors contributed to the conceptualization of the study, while SR, ED, MV, MCLD, AT, GA, and MB developed the methodology and statistical analysis plan. All authors reviewed and approved the manuscript.

Declaration of Competing Interests Dr Isabelle Ray Coquard (IRC) is an Editorial Board Member of *IJGC*. Given her role as Editorial Board Member, she had no involvement in the peer review of this article and had no access to information regarding its peer review.

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