PROTECTOR (Preventing Ovarian Cancer through early Excision of Tubes and late Ovarian Removal) Study FACTSHEET

Design	Observational Cohort Controlled trial with three arms: 'Risk reducing salpingo-oophorectomy' (RRSO), 'Risk reducing early salpingectomy with delayed oophorectomy' (RRESDO) and 'Controls'
Primary Objective	To evaluate the impact on sexual function with 'Early-Salpingectomy' and 'Delayed-Oophorectomy', as a two-step ovarian cancer prevention strategy in premenopausal women at high-risk of OC (ovarian cancer).
Secondary Objectives	1. To evaluate the impact on endocrine function, quality-of-life and satisfaction with ES (early salpingectomy) and DO (delayed oophorectomy). 2. To evaluate the incidence of tubal in-situ / invasive cancers in women undergoing risk-reducing ES. 3. To evaluate the surgical outcomes of ES and DO for OC prevention. 4. To develop utility scores for ES. 5. To determine the cost-effectiveness of an ES and DO strategy for OC prevention. 6. To establish a national register to facilitate long-term follow-up of BRCA1/2 women undergoing ES.
Hypothesis	1. Early-salpingectomy is non-inferior for sexual and endocrine function compared to controls. 2. Early-salpingectomy is superior for sexual / endocrine function, non-inferior in terms of quality-of-life, and equivalent in satisfaction compared to the standard RRSO.
Endpoints/ Outcomes	Primary- Sexual function Secondary- (a) Endocrine function / Menopause (b) Quality-of-Life (c) Satisfaction / Regret (d) Surgical morbidity (e) Psychological health (f) Number of Serous-Tubal-Intraepithelial-Carcinoma (STIC) / invasive (tubal/ ovarian/ peritoneal/non-ovarian) cancers (g) Utility scores for ES (h) Cost-effectiveness (incremental cost effectiveness ratio per quality adjusted life years (ICER/QALY)) of ES and DO (i) A national register of women undergoing ES.
Inclusion criteria	(a) Women at increased risk of ovarian cancer (OC): BRCA1/BRCA2 mutation carriers; RAD51C/RAD51D/BRIP1 mutation carriers; strong family history of breast cancer and OC or OC alone (b) Premenopausal ≥30years (c) Completed family (for surgical arms).
Exclusion Criteria	(a) Previous bilateral-salpingectomy or bilateral-oophorectomy (b) Postmenopausal (amenorrhoea ≥1year (uterus in-situ) / FSH >40) (c) Previous tubal/ ovarian/ peritoneal malignancy (d) <12 months post cancer treatment (e) Pregnancy (f) Clinical suspicion of tubal/OC at baseline (g) Inability to provide informed consent.
Recruitment	Participants will be identified through NHS cancer genetics/ high-risk familial cancer clinics, general gynaecology clinics, gynaecological oncology clinics, GP-surgeries, clinical referrals, supporting charities or by self-referral. A detailed participant information sheet will be provided and eligibility confirmed from information provided by the volunteer and/or clinician. All participants will receive counselling regarding options of management and preventative surgery prior to recruitment. Volunteers will be able to self select which of the three study arms they wish to take part in: RRESDO, RRSO, Control. All volunteers will need to complete baseline questionnaires, and provide a blood sample for FSH measurement. Volunteers in the two surgical arms will have an ultrasound and CA125 prior to surgery.
Sample size	Sample size is based on 90% power and with either alpha=0.05 two-sided (for superiority tests) or alpha=0.025 one-sided (for non-inferiority tests). The primary hypotheses relates to the Sexual Activity Questionnaire (SAQ), where the largest sample size (SAQ-pleasure, Δ= 0.9 non inferiority margin, SD=3.2)=266/arm. As allocation is non-randomised, adjusting tests for potential confounders that might relate to both arm and outcome, the sample size needs to be increased by 25% to maintain power, leading to a sample size= 266*1.25=333/arm (1000 patients overall).

Interventions	(a) Interventional Questionnaires; (b) Blood tests: FSH, Ca125; (c) Surgery: RRSO or RRESDO; (d) Histological and Cytological Assessment
Follow up	Participants will receive histology and peritoneal cytology results from their treating clinicians. They will need to complete follow up questionnaires, and provide a blood sample at regular intervals or until menopause. Questionnaires/samples will be sent, collected and coordinated centrally by the trial team. Should an occult invasive malignancy be identified at early salpingectomy/RRSO they will be referred to their regional cancer centre or gynaecological oncology team for management. With consent, serum, plasma, DNA and tissue together with genetic and epigenetic data will be stored for future research. This is optional.
Duration	10 years
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RRSO- risk reducing salpingo-oophorectomy, SD- standard deviation