PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	What Happens after Menopause? (WHAM): Protocol for a prospective multicentre, age-matched cohort trial of risk-reducing bilateral salpingo-oophorectomy in high-risk premenopausal women
AUTHORS	Hickey, Martha; Trainer, Alison; Braat, Sabine; Davey, Mary-Ann; Krejany, Efrosinia; Wark, John

VERSION 1 – REVIEW

REVIEWER	Nick Panay Imperial College London UK I have lectured and acted in an advisory capacity for a number of pharma companies
REVIEW RETURNED	23-Aug-2017

GENERAL COMMENTS	This is generally speaking a well designed study which should begin to address important clinical questions in an area where there is an unmet need for data, especially regarding the subsequent sexual health of women undergoing RRBSO. It is vital that to ensure that QOL is being maintained in women having these prophylactic procedures and we first have to understand the scale of the problem we are creating iatrogenically. My key concerns with the protocol are as follows which I would like the authors to address: 1) Women with a personal history of breast cancer are being included - are the authors not concerned that this will create some heterogeneity in the study population? These women will potentially have a higher incidence of pre and post surgical morbidity compared to those who have not suffered breast cancer, and it will also mean that they are less eligible/not eligible for HRT post surgery. 2)Was it wise to recruit friends and relatives as objective controls when they may have also suffered a degree of psychological morbidity as a result of their nearest and dearest carrying a high risk gene and undergoing risk reducing surgery? 3) The FRAX score has not been validated in women below the age of 40y 4) My main concern is the possibility of controlling for HRT usage post RRBSO.

	Women who are eligible for and wish to use HRT (which may include androgen replacement) may have better outcomes than those not eligible for, or not wanting to use HRT, even if HRT may not fully mitigate symptoms. Both HRT and non-HRT users should of course be studied, but will there be sufficient statistical power to perform sub-group analyses of HRT and non-HRT users v controls? Consideration should therefore be given to recruiting sufficient numbers of post-RRBSO HRT users and post-RRBSO non-HRT users to facilitate sub analysis of SQOL/QOL and other outcomes in both these groups v controls. Ideally, it would also be possible to sub-analyse the group of androgen users and those able to use unopposed estrogen following hysterectomy. I note that recruitment commenced in April 2013 and the projected timeline for recruitment was 3-4 years. Is there still a possibility to ensure that adequate numbers are recruited to answer these important questions or is recruitment about to close / has it closed already?

REVIEWER	Lee-may Chen University of California, San Francisco USA We are active in studying the cardiovascular outcome of risk-reducing surgery in BRCA1 & BRCA2 mutation carriers.
REVIEW RETURNED	30-Aug-2017

GENERAL COMMENTS	The authors plan to study menopause in genetic high risk patients undergoing RRSO versus observation. TIming of RRSO and menopause is still a key issue in patient decision making.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 - Dr Nick Panay

Q1) Women with a personal history of breast cancer are being included - are the authors not concerned that this will create some heterogeneity in the study population?

RESPONSE: We agree that women with a personal history of breast cancer may introduce some heterogeneity into the study population and impact on our outcomes of interest. Based on current recruitment rates, we estimate that around 10% of high-risk women undergoing RRBSO (intervention group) will have a personal history of breast cancer at baseline or will develop breast cancer during the two year follow-up period.

In order to determine whether a personal history of breast cancer affects our outcomes of interest we will compare the outcomes between those with and without a history of breast cancer and with

controls. We have updated the statistical methods section to include comparison between women with and without breast cancer undergoing RRBSO.

Q 2)Was it wise to recruit friends and relatives as objective controls when they may have also suffered a degree of psychological morbidity as a result of their nearest and dearest carrying a high risk gene and undergoing risk reducing surgery?

RESPONSE: We agree that close relatives and potentially friends may be emotionally affected by their relative or friend carrying a high-risk gene and undergoing risk reducing surgery. To date, only two control patients (out of 24 recruited) are friends of women undergoing RRBSO and none are relatives. We are recruiting widely for the control population and going forward we are happy to amend our protocol to exclude immediate family members as controls. The manuscript has not been changed since it reflects our current protocol.

Q 3) The FRAX score has not been validated in women below the age of 40y.

RESPONSE: We acknowledge that this is correct and apologise if we have not been clear in the manuscript. We plan to collect FRAX-based risk factors for all participants and these are very well-validated risk factors for fracture (1). However, we do not plan to use the FRAX algorithm to calculate 10-year fracture risk in women under age 40 since these calculations have not been validated in women under 40 and are usually not clinically helpful in younger women because absolute fracture risk is so low. We have amended the manuscript to reflect this.

Q 4) My main concern is the possibility of controlling for HRT usage post RRBSO. Women who are eligible for and wish to use HRT (which may include androgen replacement) may have better outcomes than those not eligible for, or not wanting to use HRT, even if HRT may not fully mitigate symptoms. Both HRT and non-HRT users should of course be studied, but will there be sufficient statistical power to perform sub-group analyses of HRT and non-HRT users v controls? Consideration should therefore be given to recruiting sufficient numbers of post-RRBSO HRT users and post-RRBSO non-HRT users to facilitate sub analysis of SQOL/QOL and other outcomes in both these groups v controls. Ideally, it would also be possible to sub-analyse the group of androgen users and those able to use unopposed estrogen following hysterectomy.

RESPONSE: We agree that use of HRT following RRBSO is likely to impact on the outcomes of interest. Because this is a prospective study, we cannot determine at recruitment (which is prior to RRBSO) whether women will be HRT users or non-users following RRBSO. Based on published data and recruitment to date, we anticipate that around 40% of high-risk women will take systemic HRT following RRBSO (2). Similarly, based on published data (3,4), we anticipate that use of HRT following RRSBO will mitigate but not completely resolve sexual dysfunction following RRBSO, as indicated by the reviewer.

Based on these publications we estimate a rate of sexual dysfunction of 30% in high-risk women who take systemic HRT following RRBSO and a rate of 55% in those who do not take systemic HRT following RRBSO, compared to a rate of 24% sexual dysfunction in controls. Based on these assumptions, our sample size (after loss-to-follow-up) of n=89 high-risk women, of whom around 40% (35/89) take systemic HRT post-RRBSO and around 60% (54/89) do not take HRT after RRBSO, and n=89 controls will have a power of 56% to detect a difference in sexual dysfunction between HRT users and non-users following RRBSO (FSFI score <26.55) at the two-sided 5% level of significance. In addition, we will have 63% power to detect a mean difference of 0.5 standard deviations in the MENQOL score between HRT users and non-users following RRBSO.
Assuming an overall rate of 45% sexual dysfunction in the intervention group (RRBSO) and 24% in controls, our study will have 80% power to detect a significant difference between the intervention

group overall and controls at the two-sided 5% level of significance, as stated in the sample size section of the manuscript.

In the manuscript we have included the power calculations for the primary outcome (sexual function after RRBSO compared with controls) and for the key secondary outcomes. We have also updated the statistical methods section to include the anticipated proportion of women likely to undergo hysterectomy at the time of RRBSO, the proportion likely to commence HRT after RRBSO and the proportion of high-risk women likely to have had breast cancer and the plan for analysing these sub-groups.

Q 5) Would it also be possible to sub-analyse the group of androgen users and those able to use unopposed estrogen following hysterectomy?

RESPONSE: Use of supplemental androgens in high-risk women is uncommon in our setting. To date none of those recruited have taken supplemental androgens following RRBSO. For this reason we do not expect this study to be able to comment on the role of supplemental androgens on sexual dysfunction following RRBSO. This has not been changed in the manuscript.

To date, around 25% have undergone concurrent hysterectomy with RRBSO of whom approximately 40% subsequently commenced systemic HRT. As indicated above, whilst we will have moderate power to determine the impact of systemic HRT on our outcomes of interest following RRBSO the study will not be powered to detect differences between estrogen-only and combined HRT in our outcomes of interest. No changes were made in the manuscript.

Q 6) I note that recruitment commenced in April 2013 and the projected timeline for recruitment was 3-4 years. Is there still a possibility to ensure that adequate numbers are recruited to answer these important questions or is recruitment about to close / has it closed already?

RESPONSE: We are still recruiting for this project and will try to ensure that sufficient numbers of subjects are included to address these important questions. In addition, the US based WISP study (Women Choosing Surgical Prevention, https://clinicaltrials.gov/ct2/show/NCT02760849) is comparing RRBSO with bilateral salpingectomy alone in premenopausal women with the primary outcome of sexual function, measured using the same tools as the WHAM study. First author (Martha Hickey) is an investigator for WISP and this will provide an opportunity to combine data from both trials in order to increase the power to examine outcomes that are currently underpowered in each individual trial. This has not been changed in the manuscript.

References

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VERSION 2 – REVIEW

REVIEWER	Nick Panay Imperial College London
REVIEW RETURNED	04-Oct-2017

GENERAL COMMENTS	I am happy with the authors' responses.