1. Hysterectomy and opportunistic salpingectomy (HOPPSA): study protocol for a register-based randomized controlled trial. Trials. 2019 Jan 5;20(1):10. doi: 10.1186/s13063-018-3083-8. PMID: 30611296; PMCID: PMC6321720.
2. HOPPSA update: changes in the study protocol of Hysterectomy and OPPortunistic SAlpingectomy, a registry-based randomized controlled trial. Trials. 2023 Mar 24;24(1):222. doi: 10.1186/s13063-023-07244-w. PMID: 36959664; PMCID: PMC10037841.

Statistical Analysis Plan

HOPPSA
Hysterectomy and OPPortunistic SAlpingectomy

2024-09-12

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Revisions

Version	Description of Changes	Date
1.0	Original SAP	2024-09-12

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1 STUDY DETAILS

1.1 Study Objectives

This register-based randomised controlled trial (R-RCT) will study the safety of hysterectomy with bilateral salpingectomy compared with hysterectomy only. The underlying rationale is the potential of opportunistic salpingectomy to reduce the incidence of epithelial ovarian cancer. The specific aim is to analyse if the risk of complications and hormonal side effects do not increase beyond pre-defined non-inferiority margins after hysterectomy with salpingectomy compared with hysterectomy only.

The primary objectives are to test the hypotheses that hysterectomy with salpingectomy, compared with hysterectomy only,

- does not increase the risk for complications perioperatively and up to eight weeks postoperatively beyond a pre-defined non-inferiority margin.
- does not cause an increase in menopausal symptoms, as measured by the Menopause Rating Scale (MRS), from baseline to one year post-operatively, beyond a pre-defined non-inferiority margin.

The secondary objectives are to compare the two randomisation groups regarding the secondary outcomes listed under 3.3.

In a nested trial, ovarian function will be evaluated comparing the mean difference of anti-Müllerian hormone (AMH), assessed preoperatively and one year after surgery.

The present statistical analysis plan (SAP) concerns the analysis of the peri-operative, short and intermediate terms outcomes in HOPPSA. Separate SAPs will be made for long-term outcomes.

1.2 Study Design

HOPPSA is a national register-based randomised controlled non-inferiority trial with parallel groups. Women <55 years scheduled for a hysterectomy due to a benign reason are randomised to either hysterectomy with salpingectomy or hysterectomy only in proportion 1:1, stratified for center, age (<50 or ≥ 50 years), and intended operative route (abdominal, laparoscopic or vaginal). The Swedish National Quality Register of Gynecological Surgery (GynOp) is used for inclusion, randomisation, and follow-up. Blinding is attempted but not guaranteed.

1.3 Treatment Groups

The patients are allocated to undergo hysterectomy with salpingectomy (intervention group) or hysterectomy only (control group).

1.4 Sample Size

Approximately 2800 women should be randomised according to the calculations of sample sizes for the two primary outcomes:

Short-term outcome - *Complications* at eight weeks post-operatively (non-inferiority).
The non-inferiority margin for the absolute difference in risk of complications is defined as up 8 percentage points (pp). Thus, non-inferiority will be declared if the upper limit of the two-sided 95% CI for the absolute difference in risk of complications between the two groups (intervention group – control group) does not exceed 8 pp. The original sample size

calculation was based on an expected baseline complication level (i.e. for hysterectomy only), of 30% as calculated from GynOp data 2015, an expected 3 pp higher complication rate after salpingectomy, and a 7% loss to follow-up.
An interim analysis of HOPPSA was conducted in 2021 based on 1498 randomized women, in which a complication level of 26.5% in the HOPPSA population (pooled groups) was observed.
To ascertain a correct sample size, an aggregated complication rate excluding the HOPPSA population, was retrieved from GynOp by the end of August 2024. Women aged <55 years, having undergone hysterectomy only during the trial period 2017 to 2023 was included comprising 8118 women.The complication rate was 26.7%.
Furthermore, the primary analysis will be conducted on the per-protocol population, and the GynOp statistician have, independently from the steering group, estimated the adherence to protocol (subjects undergoing allocated surgery) for the two study groups. Based on those data, we need to consider that the per-protocol population may constitute 86% of randomized patients.
At that point, approximately 2600 women had been randomized in HOPPSA. Under the current recruitment rate of 50 women per quarter of a year, it was estimated that around 2700 women were to be included and randomized by the end of 2024.
An updated power analysis, based on a baseline complication rate of 26.7%, showed that 86% of 2700 women, i.e. 2320 women, is sufficient to call non-inferiority with 80% power if the true difference in complication rate is 2.8 pp. Although this is smaller than the originally assumed difference of 3 pp, it was still considered a realistic estimate of the complication increase due to salpingectomy. Based on the updated power analysis and the challenges in keeping recruitment running, it was determined to end recruitment when the target sample size of 2700 randomized women was reached.

Intermediate-term outcome – *Absolute change in MRS* at one year (non-inferiority).
The non-inferiority margin for the difference in MRS was defined as up to 4 points. Thus, non-inferiority will be declared if the upper limit of the two-sided 95% CI for the difference in change between the two groups (intervention group – control group) does not exceed 4 points. Assuming a standard deviation (SD) of change in MRS of 6.9 points and a true increase of 3 points in the intervention group, 749 patients per randomization group are needed to reach a power of 80% (β=20%). The calculated sample size of 2700 will allow a sufficient sample for the MRS analysis, also considering losses to follow-up.

2 STUDY POPULATIONS

2.1 Definition of Randomised Study Populations

2.1.1 Intention-To-Treat (ITT) Population

All randomised subjects will be included in the ITT-population.

2.1.2 Full-Analysis-Set (FAS) Population

Subjects must have initiated surgery to be included in the FAS population. There are two separate FAS populations depending on the outcome.
A) All randomised subjects who did not have an eligibility violation are included in the FAS population for the first primary outcome *complications,* according to the ITT principle.
B) Subjects who discontinued participation, and thus did not receive study-specific questionnaires, are excluded from the FAS-population for the second primary outcome *absolute change in MRS.*

2.1.3 Per-Protocol Population

The per-protocol population is defined from the FAS population analysed for complications (A) and where the allocated surgical intervention was initiated. The per-protocol population is defined from the FAS population analysed for change in MRS (B) and where the allocated surgical intervention was completed.

For the first primary outcome *Any complication up to eight weeks post-operatively*, subjects whose intended salpingectomy was abandoned due to a perioperative complication will still be included in the per-protocol population.The reason is to avoid exclusion of a subject with a true complication related to the allocated intervention. The same principle is applied in the reverse scenario.
If a conversion of the allocated procedure NOT related to a perioperative complication occurs, the subject is excluded from the per-protocol population.
The operative route is not part of the intervention, and conversion to laparotomy will thus not conflict with the inclusion of a subject to the per-protocol population.

For the second primary outcome *Change in MRS at one year*, the per-protocol population will be defined by those who underwent the allocated intervention, regardless of conversion to laparotomy for any reason.

2.1.4 As-treated population

The as-treated population is not defined by randomized groups, but instead by actually performed surgery. Thus, the salpingectomy group includes women without any tube left *in situ*, and the no salpingectomy group includes women with at least one tube left *in situ*.

2.2 Definition of Non-randomised Populations

2.2.1 Non-randomised Questionnaire Population

All eligible individuals who have not consented to randomisation but to follow-up questionnaires will be followed and analysed as observational data in separate publications.

2.2.2 Background Population

All individuals, eligible but not randomised in HOPPSA, who underwent a benign hysterectomy, code LCD and were registered in GynOp during the study period of HOPPSA.

3 STUDY VARIABLES

3.1 Baseline Variables

3.1.1 Demographics and Baseline Characteristics

Gynecological symptom, previous pregnancies, gynecological diseases and previous surgery, weight, height, BMI, smoking habits, present or previous diseases, medication, ASA-classification.
Specific study variables added to GynOp (will be presented according to their relevance to outcomes); age at menarche, duration of breast feeding, previous and present use of hormonal contraceptives, previous Chlamydia infection, previous salpingitis and scale for menopausal symptoms.

3.2 Primary Outcome Variables

3.2.1 First Primary Outcome Variable (Short term)

First primary outcome is *Any complication up to eight weeks post-operatively* (as per definition in GynOp, dichotomous). This outcome includes peri- and post-operative outcomes registered by the physician, as well as complications up to eight weeks post-operatively, assessed by the physician after the patient's questionnaire.

3.2.2 Second Primary Outcome Variable (Intermediate term)

Second primary outcome is *Absolute change in menopausal symptom score* (continuous data) measured from baseline to one year follow-up, assessed with MRS, in the study-specific questionnaire.

3.3 Secondary Outcome Variables

3.3.1 Secondary Peri-operative Outcome Variables

Operative time (continuous, min)
Perioperative blood loss (continuous, ml)
Length of hospital stay (continuous, days)

3.3.2 Secondary Outcome Variables in the Short term (up to eight weeks)

Severe complication (as per definition in GynOp, dichotomous)
Complication classified according to Clavien-Dindo (1-5, categorical)
Type/site of complication (descriptive)
Time to daily activities (continuous, days)

3.3.3 Secondary Outcome Variables in the Intermediate term (at one year)

Any complication (dichotomous)
Severe complications (dichotomous)
Complication classified according to Clavien-Dindo (categorical)
Subsequent surgery on salpinges and/or ovaries (dichotomous)
Satisfaction with surgery (1-5, ordinal scale)
Type/site of complication (descriptive)

3.4 Safety Variables

3.4.1 All primary and the majority of secondary outcomes are safety outcomes and described under 3.2 and 3.3.

4 STATISTICAL METHODOLOGY

4.1 General Methodology

The two primary analyses measure different outcomes (*Any complication up to eight weeks post-operatively* and *Absolute change in menopausal symptom score*) at different time points and will be published in separate articles. As they also test two different hypotheses, we will refrain from adjusting the 5% significance level to control the family-wise error rate for multiplicity.

Missing data on the primary outcomes will be replaced with multiple imputation using fully conditional specification in the main analysis. The imputations will be conditioned on the following variables:

Predictor variables	**Scale**
Group	Dichotomous (salpingectomy or tubal occlusion)
Age (years)	Continuous
Any complication	Dichotomous (yes or no)
Surgical route	Three nominal categories (abdominal, laparoscopic or vaginal)
Indication for hysterectomy	Nominal categories
BMI (kg/m^2)	Continuous
Operative time (min)	Continuous
Prior salpingitis	Dichotomous (yes or no)
Adhesion	Dichotomous (yes or no)
Prior abdominopelvic surgery	Dichotomous (yes or no)
ASA classification	Three categories (I, II, III-V)
Smoking	Four categories (Never, former, 1-5cig/day, >5 cig/day)
Imputed variables not used as predictors:	
Complications classified according to Clavien-Dindo	Data available in four ordinal categories (1, 2, 3a, 3b)
Severe complications	Dichotomous (yes or no)
Perioperative blood loss	Continuous

Imputations will performed using the mice function from R package *mice* (1) to generate 30 impuated data sets. The results from the data sets will be pooled using Rubins rule. Predictive mean matching from 10 potential donors will be used for imputating. The function char2seed() from the R package TeachingDemos2 will be used to generate the seed for random number generation, with the string "HOPPSA" as argument.

In addition, a complete case analysis will be conducted as a sensitivity analysis. If both analyses of the two primary outcomes demonstrate non-inferiority, a common conclusion on the safety of the intervention can be inferred
The non-inferiority hypothesis tests will be performed as one-sided test, with a significance level of 2.5%. This is equivalent to the upper limit of a two-sided 95% confidence interval (CI) for the difference between hysterectomy with salpingectomy and hysterectomy only, being lower than the non-inferiority margin. Results will be presented as the difference between groups with a two-sided 95% CI.

The secondary outcomes will be evaluated using two-sided test, with the arms being equal with respect to the outcomes as null hypothesis. All confidence intervals presented will be 95% and two-sided.

All statistical analyses will be made using R as statistical software (2).

4.2 Patient Disposition and Data Sets Analysed

The number of subjects included in each of the ITT, FAS and per-protocol populations will be summarised for each treatment group. The ITT-population will only be used for analysis of baseline characteristics. The number and percentage of subjects randomised and treated will be presented. Number of withdrawals and their reasons will be presented by treatment group.
The main analyses for the primary outcomes will be on the per-protocol population with imputation for missing data and the sensitivity analysis will be on the per-protocol population with a complete case set.
Analyses on the FAS population will also be performed with imputed data.

The HOPPSA population will be compared to the background population regarding baseline characteristics and primary outcomes.

4.3 Protocol Violations/Deviations

Deviations from allocated surgical procedure are expected. The main reasons are
-to refrain from salpingectomy when a severe adhesion state is likely to cause complications
-to perform salpingectomy despite allocated hysterectomy only, when unexpected tubal or ovarian pathology is detected peri-operatively.
These protocol deviations will be summarised.
Any surgical procedure (e.g. peritoneal and ovarian biopsy) added to the allocated intervention will be registered but not considered a protocol deviation. Unilateral oophorectomy performed due to ovarian pathology, is not a protocol violation but may impact on outcomes related to ovarian function.
Oophorectomy performed due to complicated bleeding will be registered as a complication.

4.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarised by treatment group for the ITT, FAS and per-protocol populations and analysed according to the methods described in section "General Methodology" above.

4.5 Prior and Concomitant Medications

Any hormonal treatment for gynaecological indication prior to surgery will be registered as baseline variable and reported per randomisation group. Any post-operative hormonal treatment with a gynaecological indication will be registered and considered as a co-intervention affecting menopausal symptoms.

4.6 Primary Analyses

4.6.1 First Primary Outcome Analysis (Short term)

Primary analysis: The number and percentage of *Any complication up to eight weeks post-operatively* will be presented by treatment groups. The primary effect measure

will be the difference in risk for complication between the groups. To account for the lack of independence introduced by the stratification of the randomisation, the primary analysis will estimate the difference in the complication risk between the two randomised groups with a 95% CI using a generalised estimation equation (GEE) with logistic link function, marginalised over centre, adjusted for the the stratification variables age group and intended operative route. An exchangeable covariance matrix will be used. The two-sided 95% CI of the marginal risk difference will be estimated from the GEE-model using the delta method. Non-inferiority will be declared if the upper limit of the CI does not exceed the non-inferiority margin of 8 pp. For fitting the GEE model, the function *geeglm* from the R package *geepack* will be used, while the CI for the marginal group difference will be estimated from the GEE model using the function *avg_comparisons* from the R package *marginaleffects*.
As a sensitivity analysis, the unadjusted 95% CI for the difference in complications will be calculated according to Farrington-Manning.
Furthermore, unadjusted risk ratio (RR) and adjusted (as above) RR with 95% CI will also be calculated in secondary analyses using a GEE Poisson model with robust standard errors.

4.6.2 Second Primary Outcome Analysis (Intermediate term)

Primary analysis: The mean (SD) of *Absolute change in menopausal symptom score from pre-operatively to one year postoperatively* will be presented by treatment groups. The primary effect measure will be the difference in absolute change between the groups. The primary analysis will estimate the difference in the absolute change between the two randomised groups with a 95% CI using a mixed effects model, adjusted for baseline MRS and stratifcation variables (age groups and intended operative route), with center as a random effect. Non-inferiority will be declared if the upper limit of the 95% CI does not exceed the non-inferiority margin of 4 points on the MRS scale.
The same method, unadjusted for stratifcation variables but still adjusted for baseline MRS, will be carried out as a sensitivity analysis. The ITT approach, using complete cases and the mixed effects model adjusted for baseline MRS and center as a random effect, will be carried out as an additional analysis.

4.7 Secondary Analyses

Secondary outcome variables are given in section 3.3. The secondary peri-operative outcomes, which are all continuous variables with an expected positively skewed distribution, will be presented as median and quartiles, mean and SD, minimum and maximum by treatment group. Operative time will be transformed using the natural logarithm and analyzed using a mixed effects model, adjusting for centre as a random effect and age group and intended operative route as fixed effects. The group difference on the logarithmic scale will be retransformed back to natural scale using the exponential function and interpreted as a ratio of the geometric means of operative time. Furthermore, the group difference in arithmetic mean operative time will be estimated from the marginal means of the model above using R package emmeans. The Clavien-Dindo classifications of complications, perioperative blood loss, and length of hospital stay will be analysed using ordinal cumulative link models with centre as a random effect and age class and intended operative route as fixed effects. Blood loss will be categorised into classes of 5 ml in. Odds ratios (ORs) with 95% CI will be presented. Time to daily activites using a mixed effects model, adjusting for centre as a random effect and age group and intended surgery route as

fixed effects Unadjusted tests of continuous variables will be performed as sensitivity using Fisher's non-parametric permutation tests.

Dichotomous short and intermediate terms secondary outcomes will be presented as numbers and percentages. Their primary effect measure will be relative risks, estimated from GEE Poisson regression model with robust standard errors. Furthermore, risk differences between groups and their 95% CI will be presented.

Patient satisfaction will be analyzed using ordinal cumulative link functions with centre as a random effect and age class and intended operative route as fixed effect, and result presented as an OR with 95% CI

4.8 Safety analyses

Separate safety analyses are not applicable, since the outcomes are safety variables.

4.9 Exploratory analyses

4.9.1 Subgroup analyses

Subgroup analyses for the primary outcomes will be conducted for the following variables: age (</>= median for Complications, </>= 45 for MRS), BMI </>= 25 *and intended operative route (abdominal, laproscopic, vaginal) (for complications).*

4.9.2 Interaction analyses

Interactions of age, BMI, as continuous variables and intended operative route (for complications).

4.9.3 Other exploratory analyses

Analyses based on the as-treated population will be regarded as exploratory.

5 INTERIM ANALYSIS

One interim analysis for safety has been performed. The interim analysis was considered a futility analysis (3) and no adjustment of alpha level will be performed to account for this.

6 SUB-STUDY OF AMH

6.1 Study details

6.1.1 Study objectives

The objective is to test the hypothesis that hysterectomy with bilateral salpingectomy compared with hysterectomy only, does not increase the risk of ovarian impairment one year after surgery.

6.1.2 Study design

This is a single-centre non-inferiority trial, nested within the R-RCT HOPPSA. Women randomised in the HOPPSA trial at the Sahlgrenska University Hospital between 2017

and 2023 were asked to participate in this sub-study. Serum levels of AMH were measured at baseline and one year postoperatively.

6.1.3 Treatment groups

Patients belong to the groups allocated by the HOPPSA randomisation: hysterectomy with bilateral salpingectomy (intervention group) or hysterectomy only (control group).

6.1.4 Sample size

The non-inferiority margin for the difference in change of serum levels of AMH (expected reduction) was defined as 0.125 µg/L. Non inferiority will be declared if the upper limit of the two-sided 95% CI for the difference in change between the two groups (intervention group - control group) does not exceed 0.125 µg/L. Assuming a SD of change in AMH level of 0.1 (µg/L) and estimating the reduction in AMH levels being up to 0.05 larger in the intervention group, 29 patients are needed per randomization group to reach a power of 80% (β=20%). Estimating a 20% loss to follow-up (a second blood sample not taken), 74 patients will be recruited into this nested trial.

6.2 Study populations

Definition of populations

6.2.1 Intention to treat population

All randomised subjects with a first blood sample taken will be included in the ITT-population.

6.2.2 Per-protocol population

The per-protocol population is defined from the ITT population and includes all subjects that underwent the allocated surgical intervention. Women who have undergone any adnexal surgery thereafter will be excluded from the per-protocol population.

6.2.3 As treated population

Subjects in the ITT population not following the allocated treatment will be analysed "as treated". Women who have undergone any adnexal surgery thereafter will be excluded from the "as treated" population.

6.3 Study variables

6.3.1 Baseline variables

Weight, height, BMI, smoking habits, ASA-classification, age at surgery, parity, previous gynaecological diseases including previous abdominal or gynaecological surgery and menopausal and gynaecological symptoms prior to the surgery. Indication for surgery, planned operative route, primary incision.

Specific study variables added to GynOp: Scale for menopausal symptoms (MRS), use of hormonal contraceptives prior to surgery, and duration.

6.3.2 Descriptive covariates

Specific operative study variables: per-operative bleeding, conversion to other operative route, per-operative complications, operative time.

6.3.3 Outcome variables

The primary outcome is absolute change in AMH. Secondary outcomes are relative change in AMH and level of AMH one year after surgery. All outcomes are continous and measured in µg/L.

6.4 Statistical methodology

6.4.1 General methodology

The non-inferiority hypothesis tests will be performed as one-sided test, with a significance level of 2.5%. This is equivalent to the upper limit of a two-sided 95% confidence interval (CI) for the difference between hysterectomy with salpingectomy and hysterectomy only, being lower than the non-inferiority margin. Results will be presented as the difference between groups with a two-sided 95% CI.

The handling of missing data on the primary and secondary outcomes (applies thus to the second sample of AMH) will be made using multiple imputation using fully conditional specification (MICE) with m = 50 datasets, an initial seed of 132557 and based on the following variables; Group (salpingectomy/no salpingectomy), Age at surgery, Surgical route (abdominal, laparoscopic or vaginal), log of operative time, log of baseline AMH, log or classes of perioperative blood loss depending on data distribution, Number of days to 1 year visit (for those without a 1 year visit 365 days will be applied) and log of AMH at 1 year.

In addition, a complete case analysis will be conducted as a sensitivity analysis.

6.4.2 Patient disposal and data sets analysed

The number of subjects included in each of the ITT, FAS and per-protocol populations will be summarised for each treatment group

6.4.3 Protocol violations/deviations

See section 4.3

6.4.4 Baseline variables and descriptive covariates

Baseline variables and descriptive covariates will be analysed and presented as percentages, mean and SD, median and quartiles, minimum and maximum by treatment group.

6.4.5 Prior and concomitant medications

Any hormonal treatment for gynaecological indication prior to surgery will be registered as baseline variable and reported per randomisation group.

6.4.6 Primary analysis

The primary analysis will be per-protocol. The mean (SD), median and quartiles, minimum and maximum of absolute change in AMH levels in serum from pre-operatively to one year postoperatively will be presented by treatment group. The primary effect measure will be the difference in absolute change between the groups. The primary analysis will estimate the difference in the absolute change between the two randomised groups with a 95% CI using an analysis of covariance (ANCOVA) model adjusted for baseline AMH, age groups, intended operative route, and time from surgery to the second sampling of AMH. This time variable may exceed one year, due to the difficulties to come to the hospital during the Covid-19 pandemic. It will be compared between groups to rule out a systematic error using LOESS plot with timepoint of 1 year visit on x axis and group on the y axis. Multiple imputation will be applied. Non-inferiority will be declared if the upper limit of the 95% CI does not exceed the non-inferiority margin of 0.125 µg/L.

The sensitivity analysis on complete cases (no multiple imputation) will apply the same methods and adjustments as described above.

A complementary two-sided 95% CI for the mean difference in absolute change in AMH, also from the per-protocol population, will be constructed using an unadjusted analysis applying the same method as in the primary analysis but without any adjustment variables.

Complementary analyses will also be conducted on the ITT and as-treated populations:

The analysis of the ITT population will be carried out, using ANCOVA models, adjusted for baseline AMH, age groups, intended operative route, and time from surgery to the second sampling of AMH.

The analysis of the as-treated population will be carried out using ANCOVA models, adjusted for baseline AMH, age groups, intended operative route, and time from surgery to the second sampling of AMH.

6.4.7 Secondary analyses

Secondary outcome variables are relative change in AMH and level of AMH one year after surgery and will be presented as mean and SD, median and quartiles, minimum and maximum by treatment group. The outcomes will be tested between the groups using ANCOVA models, with baseline AMH, age groups, intended operative route and time from surgery to the second sampling of AMH as covariates. Multiple imputaion will be applied. The difference in mean relative change and level of AMH one year after surgery will be presented with 95% CI.

7 CHANGES FROM PROTOCOL

-The statistical method for the AMH primary analysis in the protocol from 2019 was decided to be Fisher's non-parametric permutation test. The primary analysis needs to be adjusted for baseline AMH and age and also be able to estimate in a multiple imputation fashion. New statistical method is suggested in this SAP.

-Updated poweranalysis. Based on the reduced complication rate reported from GynOp, a larger than expected proportion of women not undergoing allocated surgery, and reduced recruitment rate, the target sample size was recalculated.

8 REVISIONS

No revision of the statistical analysis plan has been made to this point.

9 REFERENCES

1. Stef van Buuren, Karin Groothuis-Oudshoorn (2011). mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software, 45(3), 1-67. DOI 10.18637/jss.v045.i03

2. R Core Team. R: A language and environment for statistical computing [Internet]. Vienna, Austria; 2021. Available from: https://www.R-project.org/

3. Su Z, Stuntz M. Futility stopping in non-inferiority trials. Contemp Clin Trials Commun. 2018 Dec 4;13:100314.