Detailed Statistical Analysis Plan

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I confirm that I have reviewed this document and agree with the content.

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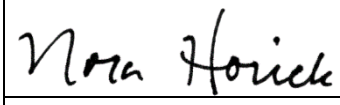	12/20/2023
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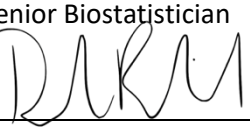	12/20/2023
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1. Overview

Early palliative care (PC) integrated with oncology care in the outpatient setting improves quality of life (QOL), mood, illness understanding, and end-of-life (EOL) care among patients with advanced cancer and their caregivers. Therefore, early integrated PC has become the standard of care for patients with advanced cancer. However, a shortage of PC professionals and lack of capacity within cancer clinics are major barriers to wide-scale implementation of early integrated PC. Novel models of care delivery, such as telehealth videoconferencing, have the potential to increase access to and efficient utilization of limited PC resources in a patient-centered manner. In the REACH study, the evidence-based early integrated in-person PC model was adapted to a telehealth platform using secure videoconferencing, thereby enabling PC clinicians to provide virtual home visits and increase access to specialty services in a patient-centered manner. If the proposed study demonstrates that telehealth is as effective as (or superior to) in-person PC, such findings would address a major evidence gap between the data supporting early integrated in-person PC and lack of data regarding how to disseminate this care model most efficiently, equitably, and effectively.

2. Study Design

REACH is a multicenter randomized comparative effectiveness trial of early integrated telehealth versus in-person PC. 1250 patients with advanced non-small cell lung cancer (NSCLC) and up to 1250 of their caregivers were enrolled through 20 Palliative Care Research Cooperative (PCRC) designated institutions across the United States. The Massachusetts General Hospital (MGH) was the lead site for the study and the additional 19 PCRC institutions. Patients without willing or available caregivers were eligible to participate in the study. Patients were randomized in a 1:1 manner using blocked randomization, and randomization was stratified by enrolling site.

The primary hypothesis is that patients assigned to early integrated telehealth PC will report QOL at 24 weeks from enrollment that is equivalent to patients receiving in-person PC. Secondary hypotheses include (1) demonstrating that early integrated telehealth PC is equivalent to in-person PC with respect to the rate by which patients communicate their EOL care preferences with their clinicians and length of stay in hospice; (2) caregivers of patients who receive early integrated telehealth PC participate in a higher percentage of visits with the PC clinician as well as report better QOL and lower depression symptoms compared with those receiving in-person PC; and (3) patients and caregivers will report greater satisfaction with early integrated telehealth PC compared with in-person PC.

3. Study Populations

The patient and caregiver eligibility criteria mirror those of our prior early PC studies in this patient population.

3.1. Patient Eligibility Criteria

Inclusion Criteria:

1. Diagnosed with advanced NSCLC being treated with non-curative intent, and informed of advanced disease within the prior twelve weeks
2. Eastern Cooperative Oncology Group (ECOG) Performance Status from 0 (asymptomatic) to 3 (symptomatic and in bed >50% of the day)

3. The ability to read and respond to questions in English or Spanish
4. Primary cancer care at one of the three participating sites
5. Age > 18 years

Exclusion Criteria:
Patients are excluded if:
1. They were already receiving outpatient PC or hospice services
2. They have cognitive or psychiatric conditions as determined by the treating oncologist to prohibit study consent or participation

3.2. **Caregiver Eligibility Criteria**

Inclusion Criteria:
1. Relative or friend who is identified by the patient participant and lives with the patient or has contact with them at least twice per week.
2. The ability to read and respond to questions in English or Spanish
3. Age > 18 years

Exclusion Criteria:
Caregivers are excluded if:
1. They have cognitive or psychiatric conditions as determined by the treating oncologist to prohibit study consent or participation

4. Randomization

Patients from the 20 participating sites are registered on the study centrally by the MGH research team. Once the patient is registered, a member of the MGH research team (independent from study staff who recruit, enroll, and administer assessments to participants) performs randomization procedures using on a computer-generated block randomization schema, stratified by study site. Both the participating study clinicians and patients are aware of the study group assignments, since the modality of intervention visits precluded blinding PC clinicians or patients.

5. Intervention Delivery

The initial PC visit in both groups occurred in person within four weeks of enrollment in the outpatient clinic setting, with subsequent visits taking place every four weeks (either through telehealth or in person depending on group assignment). Patients who survive greater than 18 months are permitted to decrease the frequency of PC visits per their preference. After each study visit, PC clinicians document the encounter in the patient's health record. PC clinicians also complete an electronic survey to note the topics addressed during each study visit and whether a caregiver was present.

5.1. Telehealth PC Arm

After the initial in-person visit, subsequent visits take place in patients' homes (or the setting of their choice) through telehealth at least every four weeks until death. PC clinicians can see patients more frequently than every four weeks, at their discretion. Patients can be scheduled to meet with the PC clinician in the clinic if requested by the patient or a clinician. If a patient

has an in-person visit with the PC clinician, they are still scheduled for their telehealth visits every four weeks. The PC clinician is required to communicate with the attending oncology clinicians through e-mail, telephone, or in person after each patient encounter.

5.2. In-Person PC Arm

Patients randomized to in-person PC are scheduled for their first PC visit within four weeks of enrollment and then at least every four weeks thereafter until the patient is no longer able to come into the clinic or death. PC visits are scheduled on the same day as oncology visits unless the patient is agreeable to scheduling the PC visit on a different day. Joint visits with PC and oncology (i.e., both clinicians seeing the patient together in one visit) are recommended but not required. PC clinicians can see patients more often than every four weeks at their discretion. If a patient does not have a scheduled visit to the cancer center, the PC clinician contacts them through telephone within four weeks of their prior appointment to conduct the visit.

6. Modifications to Study Conduct during the COVID-19 Pandemic

The US health care response to COVID-19 was to rapidly minimize in-person care delivery in outpatient clinics, including oncology and palliative care. By March 10, 2020 nearly all health care systems were swiftly transitioning to predominantly telephone and video care models to minimize patient and clinician risk of COVID-19 infection. On March 15, 2020, study enrollment was closed to avoid significant contamination of the intervention delivery modality between study groups. From March 15, 2020 until May 2020, all REACH PC sites remained closed to enrollment. While REACH PC was closed to enrollment, all currently enrolled patients continued to complete patient-reported measures remotely, which was permitted as per the protocol prior to COVID-19, and to receive the intervention with monthly contact with a palliative care clinician. During this time, the majority of patients assigned to the in-person group received palliative care via telephone or video, which was closely documented in order to address such intervention contamination in the analytic plan.

7. Outcome Measures

The study outcome measures include a combination of participant self-report questionnaires and data from patients' electronic health records. The self-report measures are described in Table 1.

Name of Measure	Participant	Time points	Scoring
Sociodemographic Questionnaire	Pt & Cg	BL only	
SCQ	Pt only	BL only	Range: 0-36 (Higher score indicate worse medical condition)
FACT-L	Pt only	BL, 12, 24, 36, and 48 weeks	Total score range: 0-136 (Higher score indicates better quality of life)
Patient PTPQ	Pt only	BL, 12, 24, 36, and 48 weeks	

PHQ-9	Pt only	BL, 12, 24, 36, and 48 weeks	Range: 0-27 (Higher scores indicate more severe depression)
Brief Cope	Pt only	BL, 12, 24, 36, and 48 weeks	Range for each facet: 2-8 (Higher scores indicate more engagement in coping style)
Support Service Utilization	Pt only	24 weeks	
HADS	Pt & Cg	BL, 12, 24, 36, and 48 weeks	Range for each domain: 0-21 (Higher scores indicate more severe depression/anxiety)
Satisfaction with Care Delivery Questionnaire	Pt & Cg	12, 24, 36, and 48 weeks	
CARGOQOL	Cg only	BL, 12, 24, 36, and 48 weeks	Range is 0-100 (Higher scores indicate better quality of life)
Caregiver PTPQ	Cg only	BL, 12, 24, 36, and 48 weeks	
After Death Assessment	Cg only	3 months after patient death	

Pt (patient); Cg (caregiver); BL (Baseline); SCQ (Self-Administered Comorbidity Questionnaire); FACT-L (Functional Assessment of Cancer Therapy-Lung); PTPQ (Perception of Treatment and Prognosis questionnaire); PHQ-9 (Patient Health Questionnaire); HADS (Hospital Anxiety and Depression Scale); CARGOQOL (CareGiver Oncology Quality of Life)

The **primary outcome** is the patient-reported quality of life at 24 weeks from enrollment, as measured by the FACT-L.

The **secondary outcomes** are:

1. Patient report of patient-clinician communication about EOL care preference using the following item on the PTPQ: “Have you and your doctors discussed any particular wishes you have about the care you would want to receive if you were dying?” The patient’s final assessment will be used.
2. Patient length of stay in hospice (in days) among patients who die during the study, as documented in the EHR.
3. Caregiver attendance in PC visits, per PC clinician documentation in the post-visit electronic survey.
4. Patient satisfaction with care as measured by the Satisfaction with Care Delivery Questionnaire. The patient’s final assessment will be used.
5. Caregiver satisfaction with care as measured by the Satisfaction with Care Delivery Questionnaire. The caregiver’s final assessment will be used.

The **exploratory outcomes** are:

1. Rate of change in patient quality of life from baseline to week 48, as measured by the FACT-L.
2. Patient coping strategies at 24 weeks, as measured by the Brief-COPE Questionnaire
3. Rate of change in patient coping strategies across all study time points, as measured by the Brief-COPE Questionnaire.
4. Patient prognostic understanding within 24 weeks, based on the PTPQ items listed below. The patient's final post-baseline assessment within 24 weeks will be used.
    a. Patient's primary goal of current cancer care. Responses will be dichotomized based on whether the patient selected "to cure my cancer" versus any of the other options.
    b. Patient's endorsement of the statement "My cancer is curable," analyzed as "yes" versus "no."
5. Caregiver prognostic understanding within 24 weeks, based on the PTPQ items listed below. The caregiver's final post-baseline assessment within 24 weeks will be used.
    a. Caregiver's perception of the primary goal of the patient's current cancer care. Responses will be dichotomized based on whether the patient selected "to cure his/her cancer" versus any of the other options.
    b. Caregiver's endorsement of the statement "My loved ones' cancer is curable," analyzed as "yes" versus "no."
6. Caregiver QOL at 24 weeks, as assessed by the CARGOQOL.
7. Rate of change in caregiver QOL across all study time points, as assessed by the CARGOQOL.
8. Caregiver mood at 24 weeks, as measured by the HADS.
9. Rate of change in caregiver mood across all study time points, as measured by the HADS.
10. Patient mood at 24 weeks, as assessed by the HADS.
11. Rate of change in patient mood across all study time points, as measured by the HADS.
12. Patient depression symptoms at 24 weeks, as measured by the PHQ-9.
13. Rate of change in patient depression symptoms across all study time points, as measured by the PHQ-9.
14. Patient health care utilization at the end of life (i.e., during the 30 days prior to death) among patients who die during the study, including:
    a. Number of emergency department visits
    b. Number of hospitalizations
    c. Chemotherapy administration
15. Caregiver perceptions of patient death as assessed 3 months following the patient's death on the After Death Assessment. This outcome will only be evaluated among caregivers of patients who die during the study.

8. Sample Size and Power Calculation

Sample size calculations were performed to demonstrate equivalence with a margin of ±4 points on the FACT-L at week 24, assuming a standard deviation of 17.5 points and a between-group difference of 0 points. 469 patients per group would achieve 95% power at a 5% significance level using two one-sided, equal-variance t-tests. To account for an anticipated 33% missing data proportion at week 24 due to loss-to-follow-up, withdrawal, or death, enrollment of 625 per group (1250 total) was planned.

9. General Statistical Considerations

Statistical Software

All statistical analyses will be performed using SAS (SAS Institute Inc., NC, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

Analysis Population

The primary analyses will be conducted according to the intention-to-treat principle. All randomized patients will be included and analyzed in the group to which they were initially randomized, regardless of intervention adherence. To address intervention contamination introduced during the COVID-19 pandemic, sensitivity analyses will be conducted to ensure the validity of the study findings. These sensitivity analyses may include per-protocol analysis, contamination adjusted intention-to-treat analysis using instrumental variables, and inverse probability weighting analyses to provide robust statistical estimates for the primary and secondary outcomes in this trial.

Patient Disposition

The flow of patients through the study will be demonstrated using a flow diagram, consistent with the Consolidated Standards of Reporting Trials (CONSORT) statement. This diagram will display number of patients assessed for eligibility, the number of patients who enrolled and randomized in the study and the number of patients who were excluded or otherwise not enrolled. For enrolled patients, the study group allocation will be displayed, along with the number of patients who complete follow-up assessments at each time point. The number of patients in each group who were lost to follow-up or otherwise excluded from analysis will be displayed.

Baseline Characteristics

Baseline characteristics including demographic information, smoking status, cancer type, comorbidities, and baseline PROs score will be summarized by intervention group using descriptive statistics and visual displays. Descriptive statistics for continuous variables will include the number of subjects, mean, standard deviation, median, first and third quartiles, and minimum and maximum values for the observed value. Frequencies and percentages will be calculated for categorical variables.

Adjustment of the Intervention Effect

The primary analyses for all outcomes will be unadjusted except when adjustment for baseline outcome values is pre-specified. For the primary outcome, a sensitivity analysis will evaluate the impact of adjustment for study site, the randomization stratification variable (n=20 sites). Adjustment for study site via a main effect or random effect will be considered. Small strata will be combined as needed to ensure numeric stability of model estimates.

For all outcomes, sensitivity analyses will adjust for baseline characteristics that are imbalanced between treatment groups, if needed. Imbalanced characteristics will be identified *a priori* by examining the distributions of baseline characteristics known to be associated with the primary and secondary outcomes by intervention group. Characteristics that are imbalanced to an extent that is considered clinically meaningful will be included as main effects.

Significance Level and Multiplicity Adjustment

Statistical significance testing for equivalence of the primary outcome will use two one-sided tests, each with a type I error rate of 0.05. The Benjamini-Hochberg false discovery rate (FDR) control approach will be used to interpret results of significance tests of secondary outcomes with an FDR of 0.15. Analyses of exploratory outcomes will not be adjusted for multiple comparisons, and presented results will emphasize estimates and confidence intervals.

Scoring of Patient-Reported Outcomes

Total and subscale scores for patient-reported outcomes will be calculated for each patient/timepoint using published scoring algorithms. When scoring instructions specifically address how missing item responses should be handled in the score calculation, these instructions will be followed. If no specific guidance for handling missing item responses is provided, subscale scores (if applicable) or total scores (for unidimensional scales) will be calculated via single imputation of the mean of observed subscale values if >50% of the subscale items are non-missing. For scales with total scores derived from the sum or average of two or more subscales, the total score will not be calculated unless all subscale scores can be calculated.

Primary analyses of FACT-L scores will utilize the standard published scoring method. Secondary analyses will use an alternative scoring method for surveys that do not meet the above criteria for calculating the total score—i.e., those that have 50% or fewer non-missing responses on one or more subscales. The alternative scoring method allows calculation of the total score if >50% of all items (across all four subscales) are non-missing.

Missing Data

Primary analyses will include available data without imputation of missing data. The characteristics of patients who do versus do not complete the week 24 survey will be compared descriptively. Sensitivity analyses will explore how different assumptions about the missing data mechanisms affect estimated outcomes. These sensitivity analyses may include multiple imputation, terminal decline joint modeling, or partially conditional models, which provide estimates of the mean conditional on being alive and observed at each timepoint.

10. Statistical Analysis

Primary Outcome

The primary outcome is patient-reported quality of life at week 24, as measured by the FACT-L. The difference in week 24 means between intervention groups will be estimated using a linear regression model with group assignment (telehealth PC vs in-person PC) and baseline FACT-L score as main effects. Using the pre-specified equivalence margin of ±4 points, equivalence of telehealth PC will be established if the 90% confidence interval (CI) for the estimated difference in means is within the equivalence interval (-4, 4). The corresponding p-value for equivalence will be calculated as the larger of the two p-values from two one-sided tests of the estimated difference in means against null values of -4 and 4. Model-based estimates of the mean with 95% CI in each group, the difference in means between groups and its 90% CI, and the p-value will be reported.

To accompany the approach described above, we will also use a linear mixed effects regression model to estimate the difference in week 24 means between intervention groups. This model will

utilize FACT-L scores at baseline, week 12, and week 24, with estimation via maximum likelihood. The model will include fixed effects for group assignment (telehealth PC vs in-person PC), time from baseline (in weeks), and the time-by-group interaction, as well as random intercepts for each patient. A contrast will be used to estimate the difference in means at week 24, and this estimate will be evaluated for equivalence in the same manner described above. This will be reported as a sensitivity analysis for evaluating equivalence for the primary outcome.

Secondary Outcomes

The difference between groups in the proportion of patient-clinician communication about EOL care preference at the final follow-up assessment will be assessed using a generalized linear regression model specified with an identity link function and binomial response probability distribution. The model will include group assignment (telehealth PC vs in-person PC) as a main effect. Using the pre-specified equivalence margin of ±8%, the nominal p-value for equivalence will be calculated as the larger of the two p-values from two one-sided tests of the estimated difference in proportions against null values of -8% and 8%. Equivalence of in-person PC will be established if the nominal p-value is significant after application of the multiplicity adjustment procedure for secondary outcomes. Model-based estimates of the proportion with 95% CI in each group, the difference in proportions between groups and its 90% CI, the nominal p-value, and the multiplicity-adjusted p-value will be reported.

The difference between groups in the mean length of stay in hospice among patients who die during the study will be assessed using a linear regression model with a main effect for group assignment (telehealth PC vs in-person PC). Using the pre-specified equivalence margin of ±6 days, the nominal p-value for equivalence will be calculated as the larger of the two p-values from two one-sided tests of the estimated difference in means against null values of -6 and 6. Equivalence of telehealth PC will be established if the nominal p-value is significant after application of the multiplicity adjustment procedure for secondary outcomes. Model-based estimates of the mean with 95% CI in each group, the difference in means between groups and its 90% CI, the nominal p-value, and the multiplicity-adjusted p-value will be reported.

The proportion of caregiver attendance in PC visits will be compared between groups using a generalized linear mixed effects regression model specified with an identity link function and binomial response probability distribution. The model will include a main effect for group assignment (telehealth vs in-person) and random intercepts for each patient. Superiority of telehealth PC will be established if the nominal p-value for the difference in proportions (against a null value of 0) is significant in favor of telehealth PC after application of the multiplicity adjustment procedure for secondary outcomes. Model-based estimates of the proportion with 95% CI in each group, the difference in proportions between groups and its 95% CI, and the nominal p-value, and the multiplicity-adjusted p-value will be reported.

The difference between groups in the mean patient and caregiver satisfaction with care delivery will be assessed using a linear regression model with a main effect for group assignment (telehealth PC vs in-person PC), separately for patients and caregivers. Superiority of telehealth PC will be established if the nominal p-value for the difference in means (against a null value of 0) is significant in favor of telehealth PC after application of the multiplicity adjustment procedure for secondary outcomes. Model-based estimates of the mean with 95% CI in each group, the difference in means

between groups and its 95% CI, and the nominal p-value, and the multiplicity-adjusted p-value will be reported.

Exploratory Outcomes

The rate of change in quality of life from baseline to week 48 (assessed by the FACT-L) will be compared between groups using a linear mixed effects regression model. This model will utilize FACT-L scores at each timepoint, with estimation via maximum likelihood. The model will include fixed effects for group assignment (telehealth vs in-person PC), time from baseline (in weeks), and time-by-group interaction, as well as random intercepts for each patient. Model-based estimates of the slope with 95% CI in each group and the difference in slopes between groups and its 95% CI will be reported.

The following exploratory outcomes will be compared between intervention groups utilizing the same approach:

- Patient coping strategies, as measured by the Brief-COPE Questionnaire
- Caregiver QOL, as assessed by the CARGOQOL
- Caregiver mood, as measured by the HADS
- Patient mood, as measured by the HADS
- Patient depression symptoms, as measured by the PHQ-9

For each outcome, the difference in means at 24 weeks between intervention groups will be estimated using a linear regression model with group assignment (telehealth PC vs in-person PC) and baseline score as main effects. Model-based estimates of the mean with 95% CI in each group and the difference in means between groups and its 95% CI will be reported. In addition, for each outcome the rate of change across all study timepoints will be compared between groups using a linear mixed effects regression model with estimation via maximum likelihood. The model will include fixed effects for group assignment (telehealth vs in-person PC), time from baseline (in weeks), and time-by-group interaction, as well as random intercepts for each patient. Model-based estimates of the slope with 95% CI in each group and the difference in slopes between groups and its 95% CI will be reported.

Proportions of patient and caregiver prognostic understanding within 24 weeks, based on PTPQ items eliciting the goal of cancer care (“to cure my/my loved one’s cancer” vs any other option) and the assessment of curability (“yes” vs “no”) will be compared using generalized linear models specified with an identity link function and binomial response probability distribution. Model-based estimates of the proportion with 95% CI in each group and the difference in proportions between groups and its 95% CI will be reported.

Multiple metrics of healthcare utilization at the end of life will be compared between intervention groups among patients who die during the study. The number of emergency department visits and number of hospitalizations at the end of life will be compared using linear regression models or count regression models (e.g., Poisson, negative binomial) if the linear regression distributional assumptions are violated. The proportions of chemotherapy administration (any versus none) at the end of life will be compared using generalized linear models specified with an identity link function and binomial response probability distribution. Additionally, the occurrence of any emergency

department visit or any hospitalization at the end of life may be compared using these binomial models. Model-based estimates of the mean or proportion with 95% CI in each group and the difference in means or proportions between groups and its 95% CI will be reported.

Among caregivers of patients who die during the study, caregiver perceptions of patient death will be compared between intervention groups will be estimated using linear regression models with group assignment (telehealth PC vs in-person PC) as a main effect. Each of the three items on the After Death Assessment will be analyzed separately. Model-based estimates of the mean with 95% CI in each group and the difference in means between groups and its 95% CI will be reported.

Statistical Analysis Plan Addendum

This addendum to the REACH SAP includes detailed clarifications and required modifications that were made to the analysis plan after the SAP had been finalized and signed.

Index	Date	**Topic:** Description
1	2024-01-17	**Analysis method for the proportion of caregiver attendance in PC visits** Due to model convergence issues of the pre-specified generalized linear mixed effects model with identity link, we modify our analysis plan for this secondary outcome as follows: *The proportion of caregiver attendance in PC visits will be compared between groups using a binomial generalized estimating equation regression model with robust standard errors, the identity link function, a main effect for group assignment, and an independence working correlation structure.*
2	2024-01-31	**Week 24 analysis time point for three secondary outcomes:** To align with the primary outcome (evaluated at 24 weeks), we will evaluate secondary outcomes #3, #4, and #5 in the SAP <u>through week 24:</u> 3. *Caregiver attendance in PC visits, per PC clinician documentation in the post-visit electronic survey **through week 24**.* 4. *Patient satisfaction with care as measured by the Satisfaction with Care Delivery Questionnaire. The patient's final assessment **through week 24** will be used.* 5. *Caregiver satisfaction with care as measured by the Satisfaction with Care Delivery Questionnaire. The caregiver's final assessment **through week 24** will be used.*
3	2024-02-06 (A) 2024-04-17 (B)	**Multiplicity adjustment for secondary outcomes:** ***(A)*** Given ongoing data collection efforts that pertain to secondary outcomes #1 and #2 in the SAP (which require 48-week follow-up), and our intention to analyze and report results for secondary outcomes #3, #4, and #5 alongside the primary outcome (which require only 24-week follow-up) before 48-week follow-up is complete, we modify our plan for multiplicity adjustment of secondary outcomes as follows: *Given our pre-specified false discovery rate (FDR) of 0.15 across all 5 secondary outcomes, but our intention to analyze and report secondary outcomes at two different points in time, we'll split FDR evenly as follows:* • *We will use Benjamini-Hochberg with FDR control at 0.03 x 3 = 0.09 for secondary outcomes 3-5 in the SAP.*

		• *We will use Benjamini-Hochberg with FDR control at 0.03 x 2 = 0.06 for secondary outcomes 1-2 in the SAP.* ***(B)*** Given concerns raised during peer review that FDR of 0.15 is not stringent enough for addressing multiple secondary outcomes in confirmatory randomized trials, we modify our plan for multiplicity adjustment of secondary outcomes as follows: *A Bonferroni correction will be used to interpret results of significance tests of secondary outcomes with an overall family-wise error rate (FWER) of 0.05.*