Statistical Analysis Plan (SAP)

Trial: platelet-Rich plasma as a symptom- and disEaSe-modifying Treatment fOR knee ostEoarthritis - the RESTORE trial

Contents

Section 1. Administrative Information

1. Title

platelet-Rich plasma as a symptom- and disEaSe-modifying Treatment fOR knee ostEoarthritis - the RESTORE trial

2. Trial registration

Prospectively registered (Australian New Zealand Clinical Trials Registry Trial Id: ACTRN12617000853347, 09/06/2017)

3. SAP version

Version: 1.0 Date: 12/06/2020

4. Protocol Version

This document has been written based on information contained in the RESTORE study protocol version 1.5 dated 01/03/2018. The protocol was published as follows:

Paterson KL, Hunter D, Metcalf B, Eyles J, Duong V, Kasza J, Wang Y, Buchbinder R, Cicuttini F, Forbes A, Harris A, Yu S, Wang B, Connell D, Linklater J, Bennell K. Efficacy of intra-articular injections of platelet-rich plasma as a symptom- and disease-modifying treatment for knee osteoarthritis - the RESTORE trial protocol. *BMC Musculoskelet Disord*. 2018;19:272.

5. SAP Revisions

Not applicable

6. Names and affiliations

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Section 2: Introduction

7. Background and rationale

Osteoarthritis, of which the knee joint is the most commonly involved lower limb site, affects around 2 million Australians with conservative projections estimating a 58% increase by 2032 [1]. Knee OA causes substantial pain and physical dysfunction ultimately impairing quality-of-life. The total economic cost of OA in Australia in 2012 was $8.5 billion [1]. This includes $3.75 billion in direct costs, the majority being joint replacement surgery for advanced disease (80,000 Australians in 2012 and increasing at a rate of >5% per annum) [1] and knee arthroscopic surgery (~100,000 Australians annually). The societal and health care burden of OA will continue to rise given population ageing and escalation in obesity. In recognition of the burden, arthritis is a government priority health area.

There is no cure for knee OA and to date, most research has focused on treatments to alleviate pain and prevent functional decline. Recommended drug therapies (such as analgesics and anti-inflammatory agents) and non-drug therapies (such as exercise) have short-term clinical benefits but effect sizes are small to modest at best [2]. Furthermore, these drugs can have adverse events, while uptake and maintenance of exercise is often poor leading to lack of long-term benefit. Intra-articular therapies in clinical use for knee OA include hyaluronic acid (HA, a viscosupplement), and corticosteroids. However, HA is controversial with variable recommendations given across clinical guidelines [3][4]. Intra-articular steroids are generally recommended for short-term pain relief only given that benefits are limited to a few weeks [5, 6]. As knee OA is typically progressive, with both symptoms AND structural deterioration drivers for joint replacement, identifying efficacious safe treatments that address both is an important objective. Currently, however, there are no approved disease-modifying therapies.

One such biologic therapy is platelet-rich plasma (PRP), an autologous blood product that contains an elevated concentration of platelets. Activation of PRP releases an initial burst then a sustained release of growth factors and other molecules, including platelet-derived growth factor, transforming growth factor-β, type I insulin-like growth factor and vascular endothelial growth factor. These proteins are responsible for a range of critical tissue healing roles such as chondrocyte apoptosis inhibition, bone and vessel remodelling, inflammatory modulation, and importantly, collagen synthesis. Additionally, other bioactive molecules released by platelets, such as fibrin, act as a scaffold and chemo-attractant for further migration of stem and other cells to the damaged tissue. Given the limited repair capacity of articular cartilage, these roles offer a mechanism by which PRP may enhance tissue healing and cartilage regeneration in knee OA. There is limited randomised controlled trial (RCT) evidence suggesting short-term symptomatic benefits of PRP for knee OA but the published studies possess unclear risk for bias, and generally have small sample sizes and lack longer-term follow-up [7]. Furthermore, only two RCTs have investigated structural effects of PRP using MRI [8, 9] and these also possessed major methodological limitations. Additional high quality RCTs are needed to determine the effects of PRP on pain and joint structural change on MRI.

8. Objectives

Study objectives:

Primary objective: To determine if a series of injections of PRP into the knee joint lead to greater reduction in knee pain and less loss of medial tibial cartilage volume in the knee joint when compared to a series of placebo saline injections at 12 months.

Secondary objective: To determine if a series of injections of PRP into the knee joint will have greater benefits for other clinical (other pain measures, physical function, quality of life, global rating of change) and MRI structural (effusion, synovitis, cartilage morphology, bone marrow lesions, cartilage defects, meniscal morphology) outcomes compared to placebo injections at 2 (clinical) and 12 (clinical and MRI) months.

Research hypotheses:

Primary alternative hypotheses:
A series of injections of PRP into the knee joint will lead to greater reduction in knee pain when compared to a series of placebo saline injections at 12 months.

A series of injections of PRP into the knee joint will lead to less loss of medial tibial cartilage volume when compared to a series of placebo saline injections at 12 months.

Secondary alternative hypothesis: A series of injections of PRP into the knee joint will have greater benefits for other clinical (other pain measures, physical function, quality of life, global rating of change) and MRI structural (effusion, synovitis, cartilage morphology, bone marrow lesions, cartilage defects, meniscal morphology) outcomes compared to placebo injections at 2 (clinical) and 12 (clinical and MRI) months.

Interpretation of primary outcomes:

We will consider the PRP treatment to be effective for *symptoms* if there is found to be a difference in change between groups for the primary outcome of pain over 12 months favouring PRP.

We will consider the PRP treatment to be effective for *joint structure* if there is found to be a difference in change between groups for the primary outcome of medial tibial cartilage volume over 12 months favouring PRP.

Section 3: Trial Methods

9. Trial design

The RESTORE trial is designed as a two-group, superiority, randomized, placebo-controlled trial. Treatment allocation is a 1:1 ratio.

10. Randomisation

Participants will be randomly allocated to the platelet-rich plasma injection group or the placebo injection group using a randomization schedule prepared and stored by the National Health and Medical Research Council (NHMRC) Clinical Trial Centre and accessed by telephone. Randomization will occur according to a 1: 1 allocation and will be stratified in blocks with varying sizes of 6 or 10, stratified according to site (Melbourne or Sydney) and radiographic disease severity (KL grades 2 or 3). A research nurse at each site will telephone the NHMRC Clinical Trial centre just prior to administration of the first injection to reveal the participant's group allocation.

11. Sample size

Primary outcomes will be the 12-month change in (i) overall average knee pain over the last week measured using an 11-point numeric rating scale with terminal descriptors 'no pain' (score 0) and 'worst pain possible' (score 10); and (ii) medial tibial cartilage volume. The minimum clinically important difference to be detected in OA trials is a change in pain of 1.8 (out of 10 units) [10]. Using control group data from our 12-month RCT in mild to moderate knee OA, we assume a between-participant standard deviation (SD) of change in pain of 2.4 and baseline to 12-month correlation in scores of 0.29 [11]. We wish to find a 40% reduction in amount of cartilage loss with platelet rich plasma. Based on our data [12], slowing the rate of cartilage loss by this amount will delay need for knee replacement. Assuming that PRP reduces the rate of cartilage loss by 40%, this is likely to double the time to joint replacement. For example, if rates of cartilage loss are constant over time it can be estimated that patients treated with PRP will take approximately 30 years to progress from the earlier stages of knee OA (when 20% of cartilage is lost [13]) to end stage knee OA (when 60% of cartilage is lost [12]) compared

to controls (15 years). For medial tibial cartilage volume, we anticipate the control group will lose 2.8% (SD 3.5%) of cartilage volume in 12-months [11], with a conservative baseline to 12-month correlation in scores of 0.50. These assumptions, together with an analysis of covariance adjusted for baseline scores, indicates that 115 participants per arm will have 80% power to detect a 40% reduction in loss of cartilage volume with a two-sided significance level of 0.05. With this number of participants, we have >99% power to detect the minimum clinically important difference in pain. Allowing for 20% loss to follow-up, we will recruit 144 participants per arm - total 288 participants.

12. Framework

This trial uses a superiority hypothesis testing framework between groups for all outcomes.

13. Statistical Interim analyses and stopping guidance

Nil

14. Timing of final analysis

Final analysis will be performed after all participants have reached the 12-month timepoint and completed assessments.

15. Timing of outcome assessments

Table 4.6 in the study protocol details the timing of outcome assessments, the majority of which occur at baseline, 2- and 12-months.

Section 4: Statistical Principles

16. Level of statistical significance

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level.

17. Description of any planned adjustment for multiplicity, and if so, including how the type 1 error is to be controlled

We have two primary outcomes: one primary *symptomatic* outcome (knee pain) and one primary joint *structural* outcome (medial tibial cartilage volume from MRI). These two domains are important in assessing the effect of PRP on different outcomes in knee OA. We will therefore not adjust for dual outcomes but instead report all effect sizes, confidence intervals, and p values in order to let readers use their own judgment about the relative weight of the conclusions on the effect of PRP for symptoms and structure. This approach aligns with the usage of p-values favoured by the American Statistical Association [14].

18. Confidence intervals to be reported

All confidence intervals will be 95% confidence intervals.

19. Adherence and Protocol Deviations

The primary analysis will be based on the principle of intention-to-treat, whereby participants are included in the groups to which they were originally assigned, regardless of their adherence to their assigned treatments. Any protocol deviations (if they occur), including errors applying inclusion/exclusion criteria and/or administration of the wrong intervention will be summarised in trial results (patient flow diagram/text) by treatment group. Randomisation errors resulting from these errors will be handled according to recommendations [15].

In this trial, participants are required to receive 3 intra-articular injections of either PRP or saline. Participants will be classified as adherent (or not) based on whether they received all 3 injections. The proportions (number and percentage) of participants receiving 0, 1, 2 or 3 injections will be reported for each treatment group.

20. Analysis Populations

The primary analysis will be based on the principle of intention-to-treat, whereby participants are included in the groups to which they were originally randomised, regardless of their adherence to their assigned treatments.

Section 5: Trial Population

21. Screening Data

Screening data will be collected and summarized. A CONSORT flow diagram will be used [16]. The following summaries will be presented in text and/or flow diagram: time frame for recruitment, the number of patients screened, the number of patients recruited, the number of screened patients not recruited, and the reasons for non-recruitment.

22. Eligibility

Trial inclusion and exclusion criteria are described in section 6.2 of the trial protocol. Reasons for exclusion will be summarized in the CONSORT [16] flow diagram.

23. Recruitment

A CONSORT flow diagram [16] will be used to describe the number of people enrolled, randomized, allocated to each treatment group, lost to follow up (including reasons) and analysed.

24. Withdrawal/follow-up

If a participant withdraws from the study, the nature, timing of and reasons for withdrawal will be described (provided the participant responds to contact made by the research team). Any data provided up to the point of withdrawal will be analysed in accordance with intention to treat analyses, unless the participant specifically requests to withdraw their data from the study. Losses to follow-up (including reasons) will be summarised in the CONSORT flow diagram by treatment group.

25. Baseline characteristics

Baseline characteristics will be summarised by treatment group and presented in a table:

- Age
- Gender
- Height, body mass, body mass index
- Radiographic disease severity using the Kellgren & Lawrence scale
- Knee alignment (measured from x-ray)
- Current employment status
- Duration of knee OA symptoms
- Unilateral or bilateral knee symptoms
- Problems in other joints
- Current medication use
- Expectation of treatment outcome
- painDETECT category (neuropathic, nociceptive or unclear)
- Physical activity level (assessed via the PASE questionnaire)
- Medial tibial plateau cross-sectional area from baseline MRI
- Presence of knee effusion from baseline MRI

Baseline characteristics will be summarised as appropriate (means and standard deviations for continuous variables that appear to be distributed approximately symmetrically, medians and interquartile ranges for other continuous variables, counts and percentages for categorical variables). Tests of statistical significance will not be undertaken for comparing baseline characteristics of treatment groups; rather the clinical importance of any imbalance will be noted.

An appendix table will provide summaries of baseline characteristics and baseline levels of primary and secondary outcomes and compare these characteristics between two groups: those participants who provide both

primary outcomes at 12 months, and those participants who are missing one or both primary outcomes. T-tests will be used to compare continuous characteristics between these groups, and chi-squared tests will be used to compare categorical characteristics.

Section 6: Analysis

26. Outcome definitions

Co-primary outcomes:

- Change in severity of knee pain: Average overall knee pain in the past week is self-assessed using a 11-point numeric rating scale (NRS) with terminal descriptors of 'no pain' (score 0) and 'worst pain possible' (score 10). Change score at 2 months (secondary time point) and 12 months (primary time point) will be calculated as follow-up minus baseline.

- Change in medial tibial cartilage volume: An MRI is performed of the study knee using a 3T whole body system with dedicated extremity coil and a T1-weighted fat suppressed 3D gradient recall acquisition sequence. Medial tibial cartilage volume will be measured by manually drawing disarticulation contours around the cartilage edges, section by section. Change score at 12 months will be calculated as follow-up minus baseline.

Secondary outcome:

- Change in severity of knee pain while walking: Average overall knee pain while walking in the past week is self-assessed using a 11-point NRS with terminal descriptors of 'no pain' (score 0) and 'worst pain possible' (score 10). Change score at 2 months and 12 months will be calculated as follow-up minus baseline.

- Change in each of pain, other symptoms, function in daily living, function in sport and recreation and knee-related quality of life in the last week: The five subscales of the Knee Injury and Osteoarthritis Outcome Score (KOOS) are being measured including i) pain (9-items), ii) other symptoms (7-items), iii) function in daily living (17-items), iv) function in sport and recreation (5-items) and v) knee-related quality of life (4-items). Responses are provided on a 5-point scale. Scores will be calculated for each subscale and range from 0 to 100 with 0 indicating worst possible symptoms. Change scores at 2 and 12 months will be calculated as follow-up minus baseline.

- Global improvement at 2 and 12 months: Global improvement in a) pain, b) physical function and c) overall will be scored using a 7-point global rating of change Likert scale with response options ranging from "much worse" to "much better" when compared to baseline. Participants indicating they are "moderately better" or "much better" will be classified as improved. All other respondents will be classified as not improved.

- Change in health-related quality of life: The AQoL questionnaire (version AQoL-8D) measures health-related quality of life. This is a 35-item questionnaire and scores range from -0.04 to 1.00 with 1.00 indicating full health-related quality of life. Change scores at 2 and 12 months will be calculated as follow-up minus baseline.

- Change in severity of intermittent knee pain and constant knee pain at 2 and 12 months. The Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire is a self-report multi-dimensional, OA-specific measure of pain experience in people with knee OA. It is comprised of 5-items assessing constant knee pain in the previous week, and 6-items assessing intermittent knee pain in the previous week. Total scores range from 0 to 100, with higher scores indicating worse pain. Change scores at 2 and 12 months will be calculated as follow-up minus baseline.

- MRI osteoarthritis knee score (MOAKS): an OA-specific semi-quantitative tool evaluating multi-feature joint changes associated with OA. MOAKS includes 4 sub-scores, related to changes in a) meniscus morphology (any regions with worsening at 12 months compared to baseline; scored as yes or no), b) inter-condylar synovitis (worsening in inter-condylar synovitis at 12 months compared to baseline; scored as yes or no), c) cartilage morphology (number of areas with worsening in thickness at 12 months compared to baseline; categorised as 0, 1, 2, or 3+), and d) and whole knee effusion (change in whole knee effusion at 12 months compared to baseline; categorised as worsened, no change or improved).

- Bone marrow lesion size: assessed from the MRIs at baseline and 12-months using categorical scoring in the medial distal femur and the proximal tibia (range 0–3 per region, with higher scores indicating greater bone marrow lesion size). Progression of bone marrow lesions (yes/no) will be defined as an increase in score by at least 1 from baseline to follow-up in either the medial tibial or medial femoral compartment.

- Cartilage defects: score in the medial distal femur and the proximal tibia at baseline and 12- months using categorical scoring (range 0–4 per region, with higher scores indicating greater cartilage defects). Progression of medial cartilage defects (yes/no) will be defined as an increase in score by at least 1 from baseline to follow-up in either the medial tibial or medial femoral compartment.

27. Analysis methods

We will conduct an intention-to-treat analysis whereby all participants will be included in the analysis in the group to which they were randomised. Analysis will be conducted by a biostatistician blinded to treatment group, with two-sided hypothesis tests and p-values < 0.05 significant. If the proportion of missing data exceeds 5%, missing outcome data will be imputed using multiple imputation methodology, and sensitivity to the missing at random assumption will be investigated [17]. Changes from baseline will be presented for each group at each time point using the mean change and 95% confidence intervals.

For the primary symptomatic outcome of overall average knee pain (numeric rating scale), a longitudinal analysis will be conducted, with differences in mean change (follow-up minus baseline) compared between the groups using a mixed linear regression model with the baseline value of pain, stratifying variables (Kellgren and Lawrence grade and injecting site) and an interaction between month and treatment group as covariates, including random effects for participants [18]. This will include data from the primary time point of 12 months and the secondary time point.

For the primary structural outcome of medial tibial cartilage volume, differences in mean annual percentage change (follow-up minus baseline) at 12 months will be compared between the groups using linear regression models with the baseline medial tibial cartilage volume value and stratifying variables (Kellgren and Lawrence grade and injecting site) as covariates.

For secondary continuous outcomes (knee pain on walking, KOOS subscales, quality of life and ICOAP), longitudinal analyses will be conducted, with differences in mean change (follow-up minus baseline) compared between the groups using mixed linear regression models with the baseline value, stratifying variables (Kellgren and Lawrence grade and injecting site) and an interaction between month and treatment group as covariates, including random effects for participants [18]. These will include data from the primary time point of 12 months and the secondary time point.

The binary secondary outcome of global improvement will be compared between groups using risk differences calculated after fitting longitudinal regression models for binary outcomes, adjusted for stratification variables and accounting for clustering of measurements within participants. This will include data from the primary time point of 12 months and the secondary time point.

The binary secondary outcomes of progression of medial tibiofemoral compartment bone marrow lesion size and medial tibiofemoral compartment cartilage defects as well as MOAKS measurements of meniscal morphology and inter-condylar synovitis at 12 months will be compared between groups using risk differences and risk ratios calculated after fitting log-binomial regression models, adjusted for baseline scores and stratification variables. Should the log-binomial regression models fail to converge, logistic regression models adjusting for the same variables will be fit, with results reported as odds ratios, risk ratios and risk differences, calculated from fitted logistic regression models.

For the MOAKS measurements of cartilage morphology and whole knee effusion at 12 months, multinomial logistic regression models will be fit, adjusting for the baseline scores and stratification variables, with results

reported as relative-risk ratios with 95% confidence intervals.

The success of blinding will be assessed using the James Blinding Index [19].

28. Statistical Methods – adjustment for covariates

As described above, analyses will be conducted adjusting for covariates which include baseline values and the stratifying variables (Kellgren and Lawrence grade and injecting site). For the mixed linear regression models, an interaction between month and treatment group will also be included as a covariate, including random effects for participants.

If necessary, secondary analyses will additionally include baseline covariates that appear to be unbalanced between treatment groups (see sensitivity analyses below).

29. Statistical Methods – sensitivity analyses

Due to a change in centrifuge speed from 3500RPM to 3300RPM (equivalent to 1500g with the study centrifuge) at the Melbourne site, implemented on the 7th of December 2017, we plan to do a sensitivity analysis excluding participants randomized and treated before this date. By the 7th of December 2017, 31 participants across the two recruitment sites had been randomized.

A sensitivity analysis will estimate treatment effects on the primary outcomes at 12 months assuming full adherence to the assigned treatment (full adherence defined as three injections). Complier average causal effects will be estimated using an instrumental variables approach (where randomization is the instrument for adherence). Two-stage least squares models will be fit [20] with complier average causal effects reported with 95% confidence intervals and p-values.

If an imbalance is noted between groups for relevant baseline characteristics, sensitivity analyses will be conducted including these characteristics as covariates in the models assessing treatment effects.

30. Statistical Methods – subgroup analyses

We will also conduct planned exploratory analyses to investigate potential moderators that could influence response to treatment for the two primary outcomes at 12 months. Pre-identified potential moderators include KL grade, body mass index, knee effusion on MRI and knee alignment. To assess the moderation of the effect of randomised treatment group by binary potential moderators (KL grade and effusion), an interaction term between randomised group and the potential moderator, as well as terms for the randomised group and the potential moderator, will be included in outcome regression models. To assess the moderation of the effect of randomised treatment group by continuous potential moderators (body mass index and knee alignment), the multivariable fractional polynomial interaction approach described previously [21] will be applied. This approach allows for nonlinear functional forms of the continuous potential moderator to be included in the regression model for outcomes, with the potential for separate nonlinear functional forms in each treatment group.

The hypothesis for each moderator analysis is below:

- KL grade (2 or 3): the symptomatic and structural benefits of PRP compared with placebo will be greater in those with KL2 compared to KL3.

- BMI: The symptomatic and structural benefits of PRP compared with placebo will be greater in those with a lower BMI than those with a higher BMI.

- Presence of knee effusion (Graded from MRI using MOAKS with 0-1 categorised as absent and 2 and 3 as present): The symptomatic and structural benefits of PRP compared with placebo will be greater in those without a knee joint effusion compared with those with a knee joint effusion.

- Static knee alignment: The symptomatic and structural benefits of PRP compared with placebo will be greater in those with less malalignment than in those with greater malalignment.

31. Missing data reporting and assumptions/statistical methods to handle missing data

Baseline characteristics of participants with one or both primary outcomes missing at 12 months will be compared to those of participants with both primary outcomes, as outlined in Section 25. If more than 5% of participants have at least one primary outcome missing at 6 months, multiple imputation will be applied. The number of imputed datasets will be approximately equal to the proportion of participants with missing primary outcomes for the primary outcome with the most missing data. Missing baseline characteristics will be imputed using single mean imputation. Missing outcome values will be imputed separately by treatment group, using chained equations and predictive mean matching, using the five nearest neighbours. Imputation models will include baseline levels of outcomes and baseline characteristics that appear to be different between participants who provide complete follow up data and participants who do not. Initially imputation models for all outcomes will be chained together, with outcomes broken into subsets if imputation models do not converge. Imputed datasets will be compared to complete data using density plots for continuous outcomes and plots of proportions for binary outcomes.

To assess the potential impact of the violation of the missing-at-random assumption on conclusions for the primary outcomes, a pattern-mixture approach (as in White et al [22]) will be applied. We will explore the impact of the violation of the missing-at-random assumption if the assumption was violated in both groups, or in one group only.

32. Additional Analyses

A separate health economic evaluation will be performed if there is a demonstrated clinical benefit from PRP at 12 months. A demonstrated clinical benefit in this context will be defined as a clinically relevant difference in change between groups at 12 months favouring PRP for the primary pain outcome (≥1.8 units out of 10 [10]) or for the AQoL8D (≥0.06 points†). The cost effectiveness of PRP will be estimated by calculating the incremental average health care cost of those treated and the difference in health-related quality of life over the 12 months of the trial compared to the placebo group. The comparison will be reported as the incremental cost per additional quality adjusted life year, and the net benefit of treatment over 12 months. The quality adjusted life year will be calculated using the area under the curve for adjusted AQoL8D values at 2 months and 12 months. Net benefits will be calculated using a range of potential money values of a quality adjusted life year. Costs will include the cost of treatment and associated imaging as well as the downstream medical, pharmaceutical and hospital costs in each arm. Health care utilization data will be collected by questionnaire at each interview. Cost effectiveness will be calculated using a generalized linear regression model for costs and quality adjusted life years, adjusted for stratification, a time-treatment interaction and baseline quality of life. Predicted costs and outcomes will be used to calculate means for cost effectiveness ratios and net benefits with bootstrapped 95%CIs. In secondary economic analysis, the cost per change in pain over 12 months will be calculated using similar statistical models. The impact on employment and productivity at work will be calculated from data collected by questionnaire (World Health Organisation Health Performance Questionnaire).

† There is no reported minimal important difference for the AQoL-8D; however, there is a reported minimal important difference for the AQoL-4D which has the same scoring anchors [23].

33. Harms

The number (and percentage) of patients experiencing adverse events will be presented for each treatment group and the nature of the event(s) described. Adverse events are defined as any untoward medical occurrence in a trial participant which does not necessarily have a causal relationship with the treatment. These will be categorized into adverse events likely related to the treatment and those likely unrelated. Serious adverse events are defined as any untoward and unexpected medical occurrence that results in death, is life-threatening, requires hospitalisation or prolongation of existing inpatient's hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or any other important medical condition which may require medical or surgical intervention to prevent one of the outcomes listed.

34. Statistical Software

Stata v15 will be used (StataCorp. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC)

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