Statistical Analysis Plan (SAP)

Trial: the COPE trial

Contents

Section 1. Administrative Information

1. Title

Effects of a self-directed online yoga program in people with knee osteoarthritis: randomised controlled trial (COPE)

2. Trial registration

Prospectively registered (Australian New Zealand Clinical Trials Registry Trial Id: ACTRN12620000012976, 13/01/2020)

3. SAP version

Version: 1.0 Date: 16/11/2020

4. Protocol Version

This document has been written based on information contained in the COPE study protocol version 7 dated 19/10/2020.

5. SAP Revisions

Not applicable

6. Names and affiliations

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Section 2: Introduction

7. Background and rationale

Knee osteoarthritis (OA) is a major contributor to global disability (Cross et al., 2014). Pain and impaired function, together with co-morbidities including depression and anxiety, are commonly reported by patients with knee OA (Johnson et al., 2014; Murphy et al., 2012). With an aging global population, identifying effective conservative treatments that are widely accessible and help people self-manage their knee OA is an important research priority (Cross et al., 2014; Hoy et al., 2014).

Previous research has established that people with lower limb OA demonstrate impairments in strength, mobility and balance (Hassan et al., 2001; Hinman et al., 2002) and an increased risk of falls (Deandrea et al., 2010; Pandya et al., 2005). Exercise can reduce pain and improve function and quality of life in people with knee OA (Cross et al., 2014; Fransen et al., 2015; Hochberg et al., 2012; McAlindon et al., 2014; Zhang et al., 2010) and is recommended by clinical guidelines ((RAGCP), 2018; Bannuru et al., 2019; Kolasinski et al., 2020). Yoga is one type of exercise that is shown to improve balance, mobility, and range of motion in older adults (Amin et al., 2014; Ebnezar et al., 2012; Youkhana et al., 2016). Further, mindfulness-based stress-reduction programs may help people with chronic pain conditions manage their symptoms (Bennell et al., 2016; Bennell et al., 2017a; Bennell et al., 2018; Rosenzweig et al., 2010). Yoga combines physical exercise in the form of static and dynamic postures with mindfulness strategies such as deep breathing and relaxation. This combination may be useful for people living with knee OA by addressing both physical and psychological aspects of the condition.

While limited, research on yoga for knee OA to date has shown positive results with regards to pain, function, and quality of life, suggesting that yoga may be a useful adjunct therapy for OA management (Brenneman et al., 2015; Cheung et al., 2017; Cheung et al., 2016; Ghasemi et al., 2013; Kolasinski et al., 2005; Kuntz et al., 2018; Park et al., 2017). Specifically, in-person group yoga classes have been found to be an effective treatment for people with knee OA (Cramer et al., 2015; Posadzki et al., 2011; Sharma, 2014; Wang et al., 2018). Indeed, recent guidelines from the Royal Australian College of General Practitioners (RACGP) published in 2018 conditionally recommended Hatha yoga for knee OA (RACGP, 2018). However, in-person group yoga classes may be difficult or inconvenient for many patients to access and involve a cost. Increasingly, people are accessing health and exercise resources online (Australian Bureau of Statistics., 2018), given that 94% of Australian households have a computer, and 86% with internet access (Australian Bureau of Statistics., 2018). Importantly, 79% of older Australians (aged 65 or above) are accessing the internet (Australian Communications and Media Authority, 2016). Online interventions for healthcare and exercise have the potential to reach a wide audience regardless of location at a lesser cost. An internet search of "yoga" and "joint pain" yields numerous online resources and programs. However, to our knowledge, the efficacy of an online yoga program for people with knee OA has not been tested. Studies of online yoga interventions for other populations such as adult caregivers, people with myeloproliferative neoplasm, cancer, or mood disorders have been conducted on a limited scale with generally positive results (Candow, 2019; Huberty et al., 2018; Uebelacker et al., 2018; Zernicke et al., 2014).

8. Objectives

Study objectives:

Primary objective: To evaluate the effects of a self-directed 12-week online yoga program plus online

education on self-reported pain and function in people with knee OA when compared to a control intervention consisting of online education-only at 12 weeks.

Secondary objectives:
To investigate the effects of a self-directed 12-week online yoga program plus online education on self-reported pain and function in people with knee OA when compared to a control intervention consisting of online education-only, at 24 weeks.

To investigate the effects of a self-directed 12-week online yoga program plus online education on other self-reported outcomes (outcomes namely other measures of knee pain, stiffness, depression, anxiety, stress, global change, health-related quality of life, self-efficacy, fear of movement, and activities-specific balance confidence) in people with knee OA when compared to a control intervention consisting of online education-only, at 12 and 24 weeks.

Research hypotheses:

Primary alternative hypothesis: A self-directed twelve-week online yoga program plus online education will improve self-reported pain and function in people with knee OA when compared to a control intervention consisting of online education-only at 12 weeks.

Secondary alternative hypotheses:
A self-directed twelve-week online yoga program plus online education will improve self-reported pain and function in people with knee OA when compared to a control intervention consisting of online education-only at 24 weeks.

A self-directed twelve-week online yoga program plus online education will improve other self-reported outcomes (outcomes namely other measures of knee pain, stiffness, depression, anxiety, stress, global change, health-related quality of life, self-efficacy, fear of movement, and activities-specific balance confidence) in people with knee OA when compared to a control intervention consisting of online education-only, at 12 and 24 weeks.

Interpretation of primary outcomes:

We will consider the yoga program to be effective if benefits are shown on either or both of the two primary outcomes (self-reported pain and function) at 12-weeks.

Section 3: Trial Methods

9. Trial design

The COPE trial is designed as an assessor-blinded, two-arm, pragmatic-superiority parallel-design randomized controlled trial. Treatment allocation is a 1:1 ratio.

10. Randomisation

Participants will undergo 1:1 randomisation into one of two groups: i) control group: online education only; or ii) intervention group: online education plus online yoga program. Computer-generated randomisation was prepared by an independent biostatistician using permuted blocks of varying sizes. The randomisation schedule is stored on a password-protected website (REDCapTM) at the University of Melbourne and maintained by a researcher not involved in participant recruitment or assessment. Group allocation is revealed to the participant by this same researcher after baseline assessment has been completed.

11. Sample size

Primary outcomes will be the 12-week change in i) average knee pain on walking in the last week measured using an 11-point numeric rating scale (0= 'no pain', 10= 'worst pain possible'); and ii) physical functioning based on the physical function subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Bellamy, 1997), measured with a 5-point Likert scale (0 = 'no difficulty', 4= 'extreme difficulty') with a total score of 0-68. We aim to detect an effect size of 0.4 (appropriate effect size for exercise interventions in knee OA (Fransen et al 2015) meaning we can detect a minimum between-group difference in change of 0.92 units for pain and 4.68 units for function, assuming a standard deviation of 2.3 and 11.7, respectively) with a conservative correlation between baseline to final assessment of 0.3 (based on our previous studies, Bennell et al, 2017b; Bennell et al, 2020) and using an ANCOVA adjusted for baseline scores. To do so, we need 90 participants per treatment arm to achieve 80% power and using a significance level of 0.05. Allowing for 15% attrition, we will recruit 106 participants per arm (212 in total).

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 24-week 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, 12- and 24-weeks.

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 for the analysis of the primary outcomes.

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 (knee pain and physical function). These two domains are both important in assessing the effect of a self-directed twelve-week online yoga program plus online education on different self-reported outcomes in knee OA. As such, we will consider a 5% significance level for each of the primary outcomes, although emphasis will be placed on the clinical meaning of effect sizes and confidence intervals when interpreting the results. We also have multiple secondary outcomes (other measures of knee pain, stiffness, depression, anxiety, stress, global change, health-related quality of life, self-efficacy, fear of movement, and activities-specific balance confidence). We will not adjust for multiplicity in the analysis of exploratory secondary outcomes but instead report all effect sizes, confidence intervals, and p values in order to let readers use their own judgement about the relative weight of the conclusions on the effect of an online yoga program for knee symptoms. This approach aligns with the usage of p-values favoured by the American Statistical Association (Wasserstein et al., 2019).

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.

In this trial, participants are required to access either online education plus online yoga program or online education only. A number of adherence measures are being collected as outlined below. Data from all adherence measures will be reported using means, standard deviations and proportions (number and percentage) as appropriate for each treatment group:

Adherence	Description	Scale	Time points
Number of yoga sessions undertaken (Yoga group)	Obtained from weekly participant logbooks	Range 0-3 per week for 12 weeks. If a participant does not provide all logbooks, number of yoga sessions undertaken will be calculated using the available completed logbooks.	12 weeks
Number of times yoga website accessed (Yoga	Obtained from website analytic data	Number	Throughout 24 weeks

group)			
Duration of yoga website sessions	Obtained from website analytic data	Reported in minutes	Throughout 24 weeks
Number of yoga sessions in the last week (Yoga group)	Self-reported. Scored on a 4-point Likert scale (0 – no sessions completed in the last week to 3 – 3 or more sessions completed in the last week).	Range 0-3 with a higher score indicating more exercise sessions	12 weeks, 24 weeks
Number of participants classified as adherent	Calculated from the self-reported number of yoga session in the last week	Dichotomous – adherent (2-3) and not adherent (0-1) and reported in number and percentage	12 weeks
Exercise Adherence Rating Scale (EARS) Section B (Yoga group) (Meade et al., 2018)	Section B - Scored from 6 questions regarding exercise adherence. Rated on a 5-point Likert scale (0 - completely agree to 4 - completely disagree)	Ranges from 0 and 24. A higher score indicates better adherence.	12 weeks, 24 weeks
Number of times control website accessed (control group)	Obtained from website analytic data	Number	Throughout 24 weeks
Duration of control website sessions (control group)	Obtained from website analytic data	Reported in minutes	Throughout 24 weeks

While adherence to the yoga sessions is measured via several variables as shown in the Table above, we will use the self-reported 'number of yoga sessions in the last week' to classify 'acceptable' adherence at 12 weeks for the complier average causal effects analysis. Based on this outcome, participants in the yoga group will be classified as 'adherent' if they report 2 or more yoga sessions in the past week, and all other participants in the yoga group will be classified as 'non-adherent'. Where this outcome is missing, logbooks at week 12, where available, will be used as a secondary data source to determine if the participant will be classified as 'adherent'.

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 groups. A complier average causal effects analysis will also be undertaken in a sensitivity analysis to determine the effect among those that received the intervention according to protocol, considering adherence to the yoga intervention (as defined in Section 19).

Section 5: Trial Population

21. Screening Data

Screening data will be collected and summarized. A CONSORT flow diagram will be used (Moher et al., 2012). The following summaries will be presented in text and/or flow diagram: time frame for recruitment, the number of participants screened, the number of participants recruited, the number of screened participants not recruited, and the reasons for non-recruitment.

22. Eligibility

Inclusion criteria for participants are: i) meet National Institute for Health and Care Excellence clinical criteria for diagnosing OA (aged ≥ 45 years, report activity-related knee pain and any knee-related morning stiffness lasting no longer than 30 minutes) (National Clinical Guideline Centre, 2014); ii) report knee pain on most days of the past month; iii) experience knee pain for three months or more; iv) report a minimum average walking pain score of 4 on an 11-point numeric rating scale (NRS) over the previous week (NRS 0= 'no pain', 10= 'worst pain possible'); v) have access to the internet; and vi) pass the Exercise and Sports Science Australia stage 1 pre-exercise screening questions (Exercise and Sports Science Australia, 2012).

Participants are excluded from the study if they: i) are unable to speak English; ii) have knee surgery/joint injection in the past 6 months or currently have a scheduled appointment with orthopaedic surgeon, or planned surgery in the next 6 months; iii) have a previous knee replacement on the affected side; iv) have systemic/inflammatory arthritic conditions; v) are undertaking regular (at least weekly) exercise (i.e. independently completing home-based leg strengthening exercises or attending gym or group exercise classes at least weekly) for the past 3 months; vi) unable to commit 6 months to the study; or vii) unable to walk unaided (without use of a frame or walking stick).

Any participant who i) reports a fall in the past 12 months or is house-bound due to immobility; or ii) fails the Exercise and Sports Science Australia stage 1 pre-exercise screening questions is required to obtain a written clearance from a general practitioner to participate. In cases where an eligible participant reports bilateral knee pain, the most painful knee is considered the study knee. However, if both knees are equally painful, the right knee will be selected as the focus of evaluation.

Reasons for exclusion will be summarized in the CONSORT (Moher et al., 2012) flow diagram.

23. Recruitment

A CONSORT flow diagram (Moher et al., 2012) will be used to describe the number of people enrolled, randomized, allocated to each 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 intervention group.

25. Baseline characteristics

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

- Age
- Gender
- Height, weight, body mass index
- Country of birth
- Current employment status
- Most painful knee
- Laterality of symptoms
- Duration of knee symptoms
- Pain in other parts of the body
- Average spine pain
- Average hip pain
- Number of participants with at least 1 of the listed co-morbidities and number of participants with each type of co-morbidity.
- Non-pharmacological treatments in last 3 months
- Current pain medication use
- Physical activity level (assessed via IPEQ-W)
- Expectation of treatment outcome
- Beliefs about effectiveness of yoga
- Self-efficacy when using computer (assessed via Modified Computer Self-Efficacy Scale)

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 to compare baseline characteristics of intervention 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 weeks, and those participants who are missing one or both primary outcomes.

Section 6: Analysis

26. Outcome definitions

Co-primary outcomes:

- Change in average knee pain on walking in the last week: Average knee pain on walking in the last week is self-assessed via an 11-point NRS (0= 'no pain', 10= 'worst pain possible'). Change score at 12 weeks (primary time point) and 24 weeks (secondary time point) will be calculated as follow-up minus baseline.
- Change in the Physical Function Subscale score of the WOMAC: The Physical Function Subscale contains 17 questions on knee function over the past 48 hours, with Likert response options ranging from 0 ('no difficulty') to 4 ('extreme difficulty'). Total score ranges from 0 to 68, with higher scores indicating poorer function. Change of the score at 12 weeks (primary time point) and 24 weeks (secondary time point) will be calculated as follow-up minus baseline.

Secondary outcome:

- Change in average knee pain in the past week: Average knee pain in the past week is self-assessed using a 11-point NRS (0= 'no pain', 10= 'worst pain possible'). Change score at 12 weeks (primary time point) and 24 weeks (secondary time point) will be calculated as follow-up minus baseline.
- Change in knee pain and stiffness: Responses to the Pain (5-item) and Stiffness (2-item) Subscales of the WOMAC are provided on a 5-point Likert scale (0= 'no difficulty', 4= 'extreme difficulty') and scores range from 0-20 and 0-8 for Pain and Stiffness Subscales respectively, where higher scores represent poorer outcomes. Change of the score for each subscale at 12 weeks (primary time point) and 24 weeks (secondary time point) will be calculated as follow-up minus baseline.
- Change in anxiety, depression, and stress: Responses to the Anxiety (7-item), Depression (7-item), and Stress (7-item) Subscales of the DASS-21 are provided on a 4-point Likert scale (0= 'did not apply to me at all', 3= 'applied to me very much or most of the time') and total score for each subscale ranges from 0-42 with higher scores indicating higher levels of anxiety, depression, and/or stress. Change of the score for each subscale at 12 weeks (primary time point) and 24 weeks (secondary time point) will be calculated as follow-up minus baseline.
- Overall global change to the study knee at 12 and 24 weeks: Overall global change to the study knee will be scored using a 7-point Likert scale. The terminal descriptors are 'much worse' to 'much better'. Participants reporting that 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-6D comprises 20 items that assess independent living, mental health, relationships, pain, coping and senses. Scores range from -0.04 to 1.00 with higher scores indicating better quality of life. Change score at 12 weeks (primary time point) and 24 weeks (secondary time point) will be calculated as follow-up minus baseline.
- Change in self-efficacy: Responses to the Self-Efficacy Pain (5-items) and Other-Symptoms (6-items) Scales of the Arthritis Self-Efficacy Scale are provided on a 10-point Likert scale (1= 'very uncertain', 10= 'very certain'). Total scores are an average of the total items per scale, ranging from 1 to 10, with higher scores indicating higher self-efficacy. Change score at 12 weeks (primary time point) and 24 weeks (secondary time point) will be calculated as follow-up minus baseline.

- Change in fear of movement: Responses to the Brief Fear of Movement Scale for OA (6-item) are provided on a 4-point Likert scale from 'strongly agree' to 'strongly disagree', with score range 6-24 with higher scores indicating higher fear of movement. Change score at 12 weeks (primary time point) and 24 weeks (secondary time point) will be calculated as follow-up minus baseline.
- Change in balance confidence: The ABC Scale contains 16-items, and scores are reported as a percentage with higher percentage indicating higher balance confidence. Change score at 12 weeks (primary time point) and 24 weeks (secondary time point) will be calculated as follow-up minus baseline.

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. If the proportion of missing data in either of the primary outcomes exceeds 5% at the primary timepoint of 12 weeks, missing outcome data will be imputed using multiple imputation methodology. For continuous outcomes, baseline, 12- and 24- week outcomes as well as changes from baseline (12-weeks and/or 24-weeks minus baseline) will be summarised for each group as means with standard deviations. To aid clinical interpretation, the primary outcomes will also each be dichotomized into those who do and do not achieve the minimal clinically important difference (MCID) in improvement in pain (1.8 NRS units) and function (6 WOMAC units). Counts and percentages of participants experiencing improvements based on global change scores and of participants achieving the MCID in improvement in pain (1.8 NRS units) and function (6 WOMAC units) will be reported in each treatment group at 12- and 24-weeks.

For the primary outcomes, a longitudinal analysis will be conducted, with differences in mean change (follow-up minus baseline) compared between the groups using a mixed-effects linear regression model adjusted for the baseline value of the outcome. A term for week and an interaction between week and treatment group will also be included as fixed effects, with random effects for participants to account for the longitudinal nature of the data (Fitzmaurice et al., 2011). This model will include data from the primary time point of 12-weeks and the 24-week secondary time point. Results will be presented as mean differences in change between groups with 95% confidence intervals, and p-values will also be reported.

Similar analyses will be conducted for continuous secondary outcomes. The binary secondary outcome of global change and the dichotomized primary outcomes, the achievement of the MCID in improvement in pain (1.8 NRS units) and function (6 WOMAC units), will each be compared between groups using risk differences and risk ratios calculated from a logistic regression model fit using generalized estimating equations, including a term for week and an interaction between week and treatment group as covariates. This model will include data from the primary time point of 12-weeks and the 24-week secondary time point. For all between-group comparisons, 95% confidence intervals and p-values will be reported.

If multiple imputation is required to handle missing data, complete-case analyses will also be conducted in sensitivity analyses. Standard diagnostic plots will be used to check model assumptions.

28. Statistical Methods – adjustment for covariates

As described above, analyses for all continuous variables will be conducted adjusting for baseline value

as a covariate. A term for week and an interaction between week and treatment group will also be included as covariates, and random effects will be included for participants. For the binary outcome, a term for week and an interaction between week and treatment group will be included as covariates.

29. Statistical Methods – sensitivity analyses

A sensitivity analysis will estimate treatment effects on the primary outcomes at 12 weeks assuming 'acceptable' adherence to the yoga intervention ('acceptable' adherence defined as in Section 19 as participant self-reporting 2 or more yoga sessions in the last week at 12 weeks). 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 (Stuart et al., 2008) with complier average causal effects reported with 95% confidence intervals and p-values.

30. Statistical Methods – subgroup analyses

Pre-identified potential moderators include age, pain self-efficacy, expectation of treatment effects, body mass index, and fear of movement. Expectation of treatment effects will be dichotomized into "Benefit"=Moderate improvement, Large improvement and Complete recovery and "No benefit"= No effect at all and Minimal improvement. To assess the moderation of the effect of randomised treatment group on the primary outcomes by the potential moderators, 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. Results will be calculated as the estimated mean effect on each of the primary outcomes of a one-unit increase in age, pain self-efficacy, body mass index or fear of movement for each group at 12 weeks and the estimated mean effect on each of the primary outcomes of an expectation of "benefit" for each group at 12 weeks.

The hypothesis for each moderator analysis is found in Table 1 in the Protocol Appendix.

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

An appendix table will provide summaries of baseline characteristics and baseline levels of primary and secondary outcomes where measured between two groups: those participants who provide both primary outcomes at 12 weeks, and those participants who are missing either or both primary outcomes. If more than 5% of participants have at least one primary outcome missing at 12-weeks, multiple imputation will be applied. The number of imputed datasets will be approximately equal to the proportion of participants missing the most primary outcome data, whichever primary outcome this is, with a minimum of 10 imputations conducted. 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, age, gender, body mass index, current employment status, laterality of symptoms, duration of knee symptoms, pain in other parts of the body, average spine pain, average hip pain, number and type of co-morbidities, pain medication use, physical activity level (assessed via IPEQ-W), expectation of treatment outcome, beliefs about effectiveness of yoga and self-efficacy when using computer (assessed via Modified Computer Self-Efficacy Scale). Initially imputation models will include all primary and secondary outcomes 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 descriptive tabulations for the binary outcome.

32. Additional Analyses

No additional analyses will be performed.

33. Harms

The number (and percentage) of participants experiencing adverse events will be presented for each treatment group and the nature of the event(s) described. Adverse events are defined as any problem experienced as a result of the study intervention, in the study knee or elsewhere in the body, lasting for 2 days or longer, and/or requiring cessation of the study intervention and/or seeking treatment from a healthcare professional.

34. Statistical Software

Stata v16.1 will be used (StataCorp. 2020. Stata Statistical Software: Release 16.1. College Station, TX: StataCorp LLC).

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