PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The effect of tart cherry juice on risk of gout attacks: protocol for a randomised controlled trial
AUTHORS	Lamb, Kirstie; Lynn, Anthony; Russell, Jean; Barker, Margo

VERSION 1 – REVIEW

REVIEWER	Richard Day St Vincent's Hospital and University of New South Wales, Sydney, Australia
REVIEW RETURNED	15-Nov-2019

GENERAL COMMENTS	The rationale for this RCT of tart cherry juice v matched placebo is reasonable and clear, the power of the study is based on a quite ambitious effect size and the study has a comprehensive list of outcomes beyond the primary outcome of reduction of the frequency of attacks. Primary outcome is stated to be 'frequency and intensity' of attacks. Power is calculated on reduction of frequency of attacks to a quarter. Perhaps the primary outcome should be noted to be frequency alone? It is not clear whether the primary outcome will be at 6 or 12 months or both. Presumably this will be at 12 months but it is not clear. Markers of inflammation, eg CRP, will rise a lot during attacks. May this not interfere with background CRP levels that it seems the study focusses upon (sampling at baseline, 6 and 12 months) It is unclear what is meant by a 'dietary intervention period' that all participants will be exposed to? Is this to assure comparable diets for each group? Clarity of purpose around this aspect is needed. The test treatment is described as 'tart' - is the placebo similarly 'tart'? Be good to be reassured on this point and note that in the protocol. re compliance, a lot of bottles will need to be collected at 6 and 12 months. Is this realistic?

REVIEWER	Keith R. Martin University of Memphis
REVIEW RETURNED	03-Dec-2019

GENERAL COMMENTS	The proposed protocol for a randomized controlled trial by Lamb et al. entitled "The effect of tart cherry juice on risk of gout attacks" describes a 12-month, double-blind, two armed, parallel RCT study in adults with diagnosed gout. There are several points of clarification regarding the details relating to the methods. Did clinical diagnosis of gout include both serum uric acid (and creatinine) and joint aspirate for sodium urate crystals? Has medication, both prescribed and over-the-counter, e.g., NSAIDS including each dose been captured since medical professionals and/or individuals may prescribe or take an initially high dose followed by lower doses. Regarding medication use and functional status, is the use of dietary supplements being monitored? In the abstract, it is mentioned that those who have experienced a gout flare will be included. Are these flares self-reported and/or validated clinically? The amounts of tart cherry juice and placebo (volume) being consumed are implied. Is this single-strength juice at 11-16 Brix? Is this 250 mL each day? In the exclusion criteria, the recruiting practitioner may deem the patient unsuitable to participate. Could this statement be qualified to indicate what reasons and/or objective parameters are being used to exclude respondents to avoid potential unintended bias? Were participants asked to dilute the concentrate or were pre-prepared bottles of placebo or tart cherry juice provided? Regarding the placebo beverage, how did the authors obtain the cherry flavor, match sedimentation, match astringency, etc.? Under dietary intervention, it is stated that participants are advised to not consume cherries. Did or are any of the participants displaying altered dietary patterns with increased (beyond normal dietary pattern) consumption of other darkly pigmented fruits?

VERSION 1 – AUTHOR RESPONSE

Reviewers' comments to Author:

1. Primary outcome is stated to be 'frequency and intensity' of attacks. Power is calculated on reduction of frequency of attacks to a quarter. Perhaps the primary outcome should be noted to be frequency alone?
2. It is not clear whether the primary outcome will be at 6 or 12 months or both. Presumably this will be at 12 months but it is not clear.

Statements referring to the primary outcome have been corrected to refer to only the frequency of flares, whilst 'intensity' of attacks has been designated a secondary outcome measure. We have also explicitly stated that this primary outcome of change in frequency of gout flares will be assessed at 12 months:

Abstract, methods and analysis: *'The primary study outcome is change in frequency of self-reported gout attacks.'*
Aims and Objectives: *'The primary objective of this trial is to assess if a daily supplement of tart cherry juice influences the frequency of gout attacks over 12 months relative to a daily supplement of a placebo drink'.*
Hypotheses: *'In patients diagnosed with gout, a dietary intervention of a daily tart cherry concentrate drink for a 12-m period will reduce the frequency of gout flares compared with a placebo drink.'*
Study design and setting: *'The primary outcome measure will be between-group difference in the frequency of gout flares from baseline to 12 months. Secondary outcome measures will be between-group differences in gout flare pain, serum urate concentration…'*
Statistical analysis: *'Independent generalised mixed model analyses of variance will be performed to test for changes in frequency of flares from baseline to 12 months between treatments (cherry versus placebo)'*

3. Markers of inflammation, eg CRP, will rise a lot during attacks. May this not interfere with background CRP levels that it seems the study focusses upon (sampling at baseline, 6 and 12 months)

Thank you for this useful comment. We agree that markers of inflammation will rise substantially during a gout attack but would then be expected to subside as the gout flare resolves. As we are interested in exploring the sustained effect of tart cherry on background inflammation over the 12-months of the study rather than acute effects during a gout flare, we will re-schedule appointments for any participant that is experiencing a gout flare until after the flare has resolved. This information has been added to the **'Study design and setting'** section of the manuscript.

4. It is unclear what is meant by a 'dietary intervention period' that all participants will be exposed to? Is this to assure comparable diets for each group? Clarity of purpose around this aspect is needed.

The 'dietary intervention period' is referring to the 12-month period of cherry juice/placebo drink supplementation. We have reworded references to 'dietary intervention period' to make this clearer:
Study design and setting: '*Each participant will be enrolled onto the study for 12 months.'*
Self-reported data, gout flares: *'A gout flare diary will be completed by participants over the 12-month supplementation period to assess gout flares.'*

5. The test treatment is described as 'tart' - is the placebo similarly 'tart'? Be good to be reassured on this point and note that in the protocol.

The placebo drink has been made similar to the cherry concentrate through the addition of citric acid. We have now provided more information on the composition of the placebo drink in the **Dietary Intervention** section of the manuscript: '*the placebo drink has been constituted to have a similar colour, taste and tartness as the cherry concentrate through the addition of blue and red food colourings, red and black cherry flavourings and citric acid to a low-fruit cordial (summer fruits flavour)'.*

6. re compliance, a lot of bottles will need to be collected at 6 and 12 months. Is this realistic?

Participants receive only 1 bottle of undiluted concentrate (~940 ml) per month. Nevertheless, storage of empty bottles over a 6-month period may be a practical issue for some households. Therefore, we have decided against this measure of compliance.
The text in the **Compliance** section of the paper has been changed accordingly: *'A daily calendar will be completed to record adherence to the intervention. Routine monthly telephone contact and face-to-face contact when delivering the drinks will be used to encourage compliance.'*

7. Did clinical diagnosis of gout include both serum uric acid (and creatinine) and joint aspirate for sodium urate crystals?

In the UK, clinical diagnosis of gout is typically based on clinical examination, assessment of reported symptoms (e.g. pain, swelling and redness) and elevated serum uric acid. Joint aspiration is not usually carried out (NICE CKS, 2018).
Additional information has been added to the following section to reflect this:
Participants and recruitment: *'At each PIC, computerised patient records will be searched to identify eligible individuals that have a clinical diagnosis of gout. Diagnosis is typically based on clinical examination, assessment of reported symptoms and elevated serum urate.'*

8. Has medication, both prescribed and over-the-counter, e.g., NSAIDS including each dose been captured since medical professionals and/or individuals may prescribe or take an initially high dose followed by lower doses. Regarding medication use and functional status, is the use of dietary supplements being monitored?

Information on the use of all medication including NSAIDS and dietary supplements is collected at baseline. Participants will be asked to inform the study team of any changes, as these occur. The use of medication and dietary supplements is also recorded in detail at 6- and 12-month time points. Additionally, participants record details of all medications used during a flare in their gout flare diary.
The following section has been amended to include this information:
Medication use and functional status: *'Medication use (contemporary and historical) will be recorded at baseline and monitored closely throughout the study. This record includes both prescribed and over-the-counter medication. Any changes to medication use, for example dosing changes or new prescriptions will be recorded in participants' medication log. Dietary supplement use will also be recorded at baseline, 6 and 12 months.'*

9. In the abstract, it is mentioned that those who have experienced a gout flare will be included. Are these flares self-reported and/or validated clinically?

We used the CART approach outlined by Gaffo et al. (2018) to identify gout flares. This is based on a self-report of a gout flare combined with a pain at rest score of > 3 on a 10 point scale. This method has been used in a previous diet intervention study (Dalbeth et al. 2012) and has been reported to have a good level of accuracy (Teoh et al. 2019).

The abstract been amended to state that flares are self-reported

Abstract, methods and analysis: *'This 12-month, parallel, double-blind, randomised, placebo-controlled trial will recruit 120 individuals (aged 18-80 years) with a clinical diagnosis of gout who have self-reported a gout flare in the previous year.'*

We have also emphasised that gout flares will be self-reported in the following sections:

Study design and setting: '*The study is a 12-month, double-blind, two-armed, parallel RCT performed in adults aged 18 to 80 years, with an existing clinical diagnosis of gout and who have reported at least one gout flare in the last 12 months.'*

Inclusion criteria: *'At least one self-reported gout flare with a pain score >3 (on a 0-10 numerical rating scale) in the past 12 months.'*

Self-reported data, gout flares: '*Information on gout flares experienced by participants in the preceding 12 months will be collected at baseline. This information covers frequency, duration, location, pain severity (0-10 numerical rating scale) and treatment. During the 12-month supplementation period participants will keep a diary to record all instances of gouty pain, again*

covering duration, location, pain severity and treatment. A gout flare will be recorded if self-reported pain at rest is >3.[40]'

10. The amounts of tart cherry juice and placebo (volume) being consumed are implied. Is this single-strength juice at 11-16 Brix? Is this 250 mL each day?

Participants are instructed to add 220 ml of water to 30 mL of the provided concentrate (either tart cherry concentrate or cherry-flavoured placebo), totalling **250 ml** daily. The tart cherry concentrate is 68 Brix and is diluted 8.3-fold by participants. We have now included the Brix value of the undiluted concentrate in our manuscript and emphasised that the total volume consumed per day of *diluted* drink is 250 ml.
The **dietary intervention** section now states*: 'Participants will be provided monthly with either Montmorency tart cherry 68 Brix concentrate (King Orchards, Michigan, USA) or a low-phenol, cherry-flavoured placebo concentrate. Both drinks will be diluted with water by participants before consumption (30 mL of concentrate with 220 mL of water, totalling 250ml daily).'*

11. In the exclusion criteria, the recruiting practitioner may deem the patient unsuitable to participate. Could this statement be qualified to indicate what reasons and/or objective parameters are being used to exclude respondents to avoid potential unintended bias?

Reasons for deeming a patient unsuitable are frailty, dementia and terminal medical conditions.
The **exclusion criteria** section now states: *'Recruiting practitioner deems that the patient is unsuitable to participate (frailty, dementia and terminal medical conditions).'*

12. Were participants asked to dilute the concentrate or were pre-prepared bottles of placebo or tart cherry juice provided?

Participants were asked to make up each 250 ml drink serving daily by diluting the concentrate provided with cold tap water (30 ml concentrate with 220 ml water, totalling 250 ml per day). Participants are provided with graduated cups with clear 30 ml and 250 ml volume markings.
This information has been added to the **dietary intervention** section as follows*: 'Both drinks will be diluted with water by participants daily before consumption (30 mL of concentrate with 220 mL of water, totalling 250ml daily). Graduated cups with clear markings indicating required volumes of concentrate and water will be provided to participants.'*

13. Regarding the placebo beverage, how did the authors obtain the cherry flavor, match sedimentation, match astringency, etc.?

Small amounts of black and red cherry flavouring have been added to the fruit-flavoured placebo drink (low-fruit cordial) to increase cherry flavour. The total phenolic and anthocyanin content of the placebo drink was analysed in our laboratory and has been shown to be minimal. Citric acid has also been added to increase the tartness of the placebo drink. Colours were matched through the addition of red and blue food colourings.
The following information has been included in the **Dietary Intervention** section of the protocol paper: '*the placebo drink has been constituted to have a similar colour, taste and tartness as the cherry concentrate through the addition of blue and red food colourings, red and black cherry flavourings and citric acid to a low-fruit cordial (summer fruits flavour)'.*

Drinks have not been matched for sedimentation. However, the parallel design renders comparison between drinks by participants unlikely.

14. Under dietary intervention, it is stated that participants are advised to not consume cherries. Did

or are any of the participants displaying altered dietary patterns with increased (beyond normal dietary pattern) consumption of other darkly pigmented fruits?

At present we only have baseline dietary information from a small number of participants. We will assess any changes in consumption of darkly pigmented fruit through 6- and 12-month diet diaries.

Supporting References:

Dalbeth, N., Ames, R., Gamble, G. D., Horne, A., Wong, S., Kuhn-Sherlock, B., ... & Palmano, K. (2012). Effects of skim milk powder enriched with glycomacropeptide and G600 milk fat extract on frequency of gout flares: a proof-of-concept randomised controlled trial. *Annals of the rheumatic diseases*, *71*(6), 929-934.

Gaffo, A. L., Dalbeth, N., Saag, K. G., Singh, J. A., Rahn, E. J., Mudano, A. S., ... & Vazquez-Mellado, J. (2018). Brief report: validation of a definition of flare in patients with established gout. *Arthritis & Rheumatology*, *70*(3), 462-467.

Teoh, N., Gamble, G. D., Horne, A., Taylor, W. J., Palmano, K., & Dalbeth, N. (2019). The challenges of gout flare reporting: mapping flares during a randomized controlled trial. *BMC rheumatology*, *3*(1), 27.

VERSION 2 – REVIEW

REVIEWER	Richard Day St Vincent's Clinicial School, UNSW Medicine and St Vincent's Hospital Sydney
REVIEW RETURNED	07-Jan-2020

GENERAL COMMENTS	Questions and suggestions dealt with well

REVIEWER	Keith R. Martin Center for Nutraceutical & Dietary Supplement Research, School of Health Studies, University of Memphis, Memphis, TN, USA
REVIEW RETURNED	30-Jan-2020

GENERAL COMMENTS	The manuscript has been effectively modified and clarified. This reviewer has no further comments.