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Protocol (BMJ Open)

# The effect of tart cherry juice on risk of gout attacks: protocol for a randomised controlled trial

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## ABSTRACT

**Introduction:** Gout is a painful form of inflammatory arthritis associated with several comorbidities, particularly cardiovascular disease. Cherries, which are rich in anti-inflammatory and anti-oxidative bioactive compounds, are proposed to be efficacious in preventing and treating gout, but recommendations to patients are conflicting. Cherry consumption has been demonstrated to lower serum urate levels and inflammation in several small studies. One observational case-crossover study reported that cherry consumption was associated with reduced risk of recurrent gout attacks. This preliminary evidence requires substantiation. The proposed randomised clinical trial aims to test the effect of consumption of tart cherry juice on risk of gout attacks.

**Methods and analysis:** This 12-month, parallel, double-blind, randomised, placebo-controlled trial will recruit 120 individuals (aged 18-80 years) with a confirmed diagnosis of gout and who have experienced a flare in the last year. Participants will be randomly assigned to an intervention group, which will receive Montmorency tart cherry juice daily for a 12-m period, or a corresponding placebo group, which will receive a cherry-flavoured placebo drink. The primary study outcome is change in frequency and intensity of self-reported gout attacks. Secondary outcome measures include serum urate concentration, fractional excretion of uric acid, biomarkers of inflammation, blood lipids and other markers of cardiovascular risk. Other secondary outcome measures will be changes in physical activity and functional status. Statistical analysis will be conducted on an intention-to-treat basis.

**Ethics and dissemination:** This study has been granted ethical approval by the National Research Ethics Service, Yorkshire and The Humber - Leeds West Research Ethics Committee (ref: 18/SW/0262). Results of the trial will be submitted for publication in a peer-reviewed journal.

**Trial registration number:** NCT03621215.


## Strengths and limitations of this study

- This study will be the first randomised, double-blind, placebo-controlled trial to examine the effectiveness of tart cherry juice to reduce risk of recurrent gout flares.
- Primary and secondary outcomes are central to treatment of gout and its co-morbidities.
- This study will investigate mechanisms whereby tart cherry juice may reduce risk of recurrent gout flares and co-morbidities.
- The study design addresses the temporal risk of gout flares by assessing patients over a 12-month period and retention of participants may be challenging.

## INTRODUCTION

Gout is a debilitating and common type of inflammatory arthritis exerting a significant health burden.[1,2] The proportion of people afflicted with gout in the UK is substantial; around 3% of adults were affected in 2012, representing approximately 1.9 million people.[3] Men are typically at greater risk of developing gout than women and risk increases with age for both genders.[3] Gout is associated with numerous co-morbidities, including cardiovascular disease (CVD), obesity and hypertension.[3–5]

Acute recurrent attacks of arthritis are a defining feature of gout.[6] The underlying cause is a build-up of monosodium urate crystalline deposits in the joints, particularly those of the lower limbs causing acute pain, redness and inflammation.[7,8] Gout attacks are intermittent and may last from several days to up to several weeks. Usually only one joint is affected. Sustained hyperuricaemia, which most commonly occurs secondary to reduced fractional uric acid clearance, is recognised as the most important risk factor for gout.[9,10] Consumption of purine- or fructose-rich food and drink, including seafood, red meat, beer and sugar-sweetened beverages have been associated with increased uric acid levels and risk of gout flares.[11–16]

Early case reports from the 1950s suggested that consumption of cherries had a role to play in alleviating gouty pain and inflammation.[17] More recently cherries and cherry products have been shown to acutely lower serum urate after consumption in healthy people, while a daily supplement of cherry juice was associated with lower serum urate in a placebo-controlled crossover study of overweight and obese men and women.[18–20] It is unclear which bioactive component in cherries may be responsible for the effect; Bell et al proposed that anthocyanins and/or other phenolic compounds present in cherry may be important.[18]

There are very few studies in gout patients. In a case-crossover study of 633 gout sufferers, cherry consumption was associated with a 35% lower risk of gout flares.[21] This study was predicated on an acute temporal relationship between cherry consumption and likelihood of gout flares and did not evaluate the habitual effect of cherry consumption. Furthermore being observational in design, causality cannot be assumed.[21] While there have been two intervention studies that have addressed the potential for cherry to reduce risk of gout, these were both feasibility studies with limited sample size, lack of an appropriate placebo and within-group statistical comparison.[22,23]

In addition to lowering serum urate, cherry consumption may be of benefit in gout prophylaxis because cherries contain a variety of polyphenolic compounds with anti-inflammatory properties. These compounds may ameliorate the inflammatory response induced by monosodium urate crystals.[18,21] Indeed, cherry consumption has been shown to lower a recognised biomarker of inflammation C-reactive protein (CRP) in both healthy [18,24–26] and arthritic people.[27,28]

Despite the limited scientific evidence base, leading medical societies and charities (for example, British Society for Rheumatology, European League against Rheumatism, National Institute for Clinical Excellence, Arthritis Research UK, Mayo Clinic, UK Gout Society) endorse cherry consumption as a therapeutic aid for gout.[1,29–33] Contrastingly, the Food and Drug Administration in the United States has warned cherry juice growers and processers against making preventive disease claims.[34] A content analysis of US and UK newspapers reported that 25% of articles discussing dietary management of gout advised cherry consumption.[35] Notably, the UK's National Health Service health information website dismissed newspaper claims that advocated cherry consumption for gout.[36] There is a clear need for definitive evidence from a randomised controlled trial.

The proposed study is a 12-month RCT designed to provide superior evidence as to whether tart cherries are a useful adjuvant therapy for treatment of gout. The study will also elucidate possible mechanisms of effect through the measurement of serum urate, fractional urinary urate excretion, biomarkers of inflammation and oxidative stress. As participants are likely to be at increased risk of CVD, secondary study outcomes will be measures of arterial stiffness and blood lipids.

## AIM AND OBJECTIVES

The aim of this study is to evaluate the effects of a daily intervention of tart cherry juice over a 12-month period compared with a placebo drink on risk of gout attacks.

The primary objective of this trial is to assess if a daily supplement of tart cherry juice influences the frequency and intensity of gout attacks relative to a daily supplement of a placebo drink.

Its secondary objectives are to:

- assess if tart cherry juice supplementation impacts on risk factors for cardiovascular disease
- identify the effects of tart cherry juice supplementation on putative biological mediators of risk of gout

### 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 and intensity of gout flares compared with a placebo drink.
- In patients diagnosed with gout, a dietary intervention of a daily tart cherry concentrate drink for a 12-m period will lower markers of cardiovascular risk (arterial stiffness, blood pressure and blood lipids) compared with a placebo drink.

## METHODS AND ANALYSIS

Described according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[37]

### 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 experienced at least one gout flare in the last 12 months. The intervention group will receive a daily supplement of tart cherry juice and the placebo group will receive a cherry-flavoured drink. The primary outcome measure will be between-group difference in the frequency and intensity of gout flares. Secondary outcome measures will be between-group differences in serum urate concentration, fractional excretion of uric acid, blood lipids and recognised markers of inflammation (CRP, interleukin-6, tumour necrosis factor alpha), oxidative stress and vascular function (blood pressure, arterial stiffness). Changes in physical activity, perceived health and pain will also be secondary outcomes. Non-efficacy outcomes will include dietary intake measures, for example total energy, total sugars and consumption of gout trigger foods. Each participant will be enrolled for a 12-month dietary intervention period; physical and vascular measurements and fasted blood and 24-hour urine samples collected at 0, 6 and 12 months. These measurements will be made at Sheffield Hallam University's Food and Nutrition Research Laboratories in Sheffield, United Kingdom. An overview of the study

design and timeline is given in Figure 1. The study opened recruitment in June 2019 and is ongoing.

## Participants and recruitment

Participants will mainly be recruited from primary care practices in the English city of Sheffield and surrounding areas. The Clinical Research Network of Yorkshire and Humber, which provides localised infrastructure to support delivery of research, will select practices to act as Participant Identification Centres (PICs). At each PIC, computerised patient records will be searched to identify eligible individuals that have a diagnosis of gout. A general practitioner will screen the list of patients generated from this search for suitability to participate (for example, people who are frail or suffer from dementia would not be recruited). People who are eligible will be sent an invitation to participate; interested individuals will be encouraged to contact the research team for further study information. Such participants will be invited to attend an information, screening and enrolment meeting at Sheffield Hallam University. Written informed consent will be obtained from those willing to take part by the study coordinator (KL).

Recruitment from PICs will be augmented by poster advertising at local primary care practices and across the university campus, advertising on the UK Gout Society website and at local large-scale workplaces. Participants' general practitioner will be contacted to verify their eligibility.

### Inclusion criteria

- Aged between 18 and 80 years.
- Clinical diagnosis of gout.
- Have experienced at least one gout flare in the past 12 months.
- Participant is able to give informed consent.

### Exclusion criteria

- Allergy to cherries.
- Habitual consumption of cherries and/or cherry products.
- Severe renal impairment (glomerular filtration rate <30 mg/L).
- Type 1 or type 2 diabetes.
- Recruiting practitioner deems that the patient is unsuitable to participate.

## Dietary Intervention

Participants will be provided monthly with either Montmorency tart cherry concentrate (King Orchards, Michigan, USA) or a low-phenol, cherry-flavoured placebo concentrate. Both drinks will be diluted with water before consumption (30 mL of concentrate with 220 mL of water). Participants will be advised to consume their drink with breakfast and to keep the concentrate refrigerated. Consumption will be recorded daily on a calendar. Advice will be given to maintain usual dietary habits throughout the course of the intervention and to avoid cherry consumption.

Each daily serving of tart cherry has been estimated to provide: 80 kcal, 20 g carbohydrate, 870 mg phenolics and 14 mg of anthocyanins. Each serving of the placebo drink will provide: 2.9 kcal, 0.3 g carbohydrate, 13 mg phenolics and 0.2 mg anthocyanins. The placebo drink has been constituted to have similar colour and flavour as the cherry drink. It was not possible to match the drinks for energy content because the addition of sugars to the placebo drink would have jeopardised its shelf life. Furthermore, the addition of sucrose (comprising 50% fructose) has the potential to raise serum urate.[38]

## Data collection

### Laboratory visit data

#### *Anthropometric measurements*

Anthropometric measures of height and weight will be used to calculate Body Mass Index (weight (kg)/height (m)$^2$). Height without shoes will be measured to the nearest 0.1 cm using a stadiometer (Seca, Hamburg, Germany). Weight will be measured in light clothing to the nearest 0.1 kg using calibrated weighing scales (Seca 899, Hamburg, Germany).

#### *Fasting blood sample*

Fasted venous blood samples will be collected. These will be analysed for: serum inflammatory markers (CRP, IL-6 and TNF-α), serum urate and blood lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triacylglycerol). Oxidative DNA damage and antioxidant status will also be measured in lymphocytes using the Comet assay (single cell electrophoresis).

### *Urine samples*

Prior to each visit, participants will carry out a 24-hour urine collection. These samples will be used to calculate 24-hour urinary uric acid excretion. A further spot urine sample will be collected alongside the fasting blood sample to calculate fractional excretion of uric acid.

### *Arterial stiffness*

A Vicorder™ device (SMT Medical, Germany) will be used to measure brachial BP, central BP, carotid-femoral pulse wave velocity and augmentation index.

### *Medication use and functional status*

Medication use (contemporary and historical) will be recorded. Assessment of functional status covering pain, interference with daily activities and perceived health will be collected through interview using questions from a validated scale.[39]

## Self-reported data

### *Gout flare frequency and intensity*

A gout flare diary will be completed by participants over the intervention period to assess gout flares. Participants will record detail of all flares, including duration, location, pain severity (0-10 numerical rating scale) and any medication used to treat the flare.

### *Assessment of diet and physical activity levels*

Participants will complete a 4-day food diary using estimated household measures, and record physical activity in a diary over a 4-d period in the week preceding each laboratory visit.

### *Compliance*

A daily calendar will be completed to record adherence to the intervention. Used drinks bottles will be collected at 6 and 12 months to further assess compliance. Routine telephone contact will be used to encourage compliance.

### *Retention*

Participants may withdraw from the study at any time without giving any reason. Reasons for discontinuing the study will be recorded. Participants who decide to discontinue the intervention will be invited to return for follow-up visits to assess outcome measures.

### *Adverse events (AEs)*

All AEs will be recorded and reported, where applicable, following Good Clinical Practice and Health Research Authority guidelines. Participants will be advised to report all serious or

non-serious AEs to the research team; these data will be recorded. Additionally, the incidence of adverse events will be logged at laboratory visits and via telephone contact.

## Data management

The collection and storage of data will adhere to the standard requirements of the EU General Data Protection Regulation 2016/679. Data will be entered onto electronic spreadsheets, which will be stored on a secure University server. All data will be treated confidentially and anonymised for evaluation. Hard copies of data and documents will be kept in a locked and secure cabinet for the duration of the study. Following completion of the study, data will be transferred to Sheffield Hallam University's Research Data Archive (SHURDA), where it will be kept for 10 years. Hard copies will be disposed of confidentially and electronic data deleted after this period of time.

## Randomisation, allocation and blinding

All consenting participants will be block randomised (block size 4) in a 1:1 allocation to either a tart cherry juice group or a placebo cherry-flavoured drink group with stratification by sex and smoking status. Allocation sequence will be generated using a computer random number generator by an investigator not involved in participant enrolment and data collection (AL) and concealed from research personnel until the completion of the trial. The study coordinator (KL) who will be responsible for participant enrolment, distribution of intervention drinks and data collection will be blinded to treatment allocation until results have been analysed. Drinks will be provided to participants in identical bottles and labelled with participant identification number only to ensure that both study coordinator and participants are blinded to drink allocation throughout the study.

## Sample size

The power calculation was based on the potential impact of tart cherry supplementation on the primary outcome measure. Using data on gout occurrence in UK patients, the chance of a recurrence of at least one gout flare over a 12-month period is 11%.[40] It is predicted that cherry juice treatment will reduce this recurrence to one quarter of the rate of the actual recurrence (from 11% to 2.7%). Based on these data, it is estimated that 94 participants would provide 95% power at a significance level of 0.05. A sample of 120 participants will allow for an attrition rate of approximately 20%.

## Statistical analysis

Continuous variables will be presented as mean and confidence intervals. Statistical significance will be set at $p < 0.05$. Descriptive analysis of all baseline variables will be conducted to compare the two groups. All analyses will be performed using intention-to-treat analysis; all randomised participants will be included in the final analysis as far as data collected will allow. Independent generalised mixed model analyses of variance will be performed to test for changes in frequency of flares per month between treatments (cherry *versus* placebo); baseline, 6 months and 12 months times will be used for secondary outcomes. Analysis will be performed using IBM SPSS Statistics for Windows (New York, USA).

## Patient and public involvement

Gout patients were not directly involved in development of the research question or study design. We consulted with retired people from a local church group (Christ Church Fulwood, Sheffield, England) as to their understanding of written participant information and questionnaires. This group also provided feedback on the acceptability of the schedule of visits, study measures and intervention.

## Ethics and dissemination

The trial has been approved by Leeds West NHS Research Ethics Committee (18/SW/0262) and the HRA and Health and Care Research Wales (HCRW). It is registered at ClinicalTrials.gov (NCT03621215). Any protocol modifications will be sent for review by the research ethics committee and will be amended at the trial registry. Participants will be sent a summary of the trial findings when all data have been analysed. Dissemination of the study findings of this study will be through publication in a leading peer-reviewed journal and presentation at national and international conferences.

### Author affiliations

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## Contributors

AL and MEB designed the study and secured the funding. KL prepared study documents and coordinated the HRA and ethics applications. MEB and TL are joint principal investigators. KL is the study coordinator and co-investigator. KL drafted the manuscript for publication, with input from TL, JMR and MEB. JMR advised on the study design, power calculation and statistical analysis.

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Patient recruitment to the study is supported by Yorkshire and Humber National Institute for Health Research CRN.

## Competing interests

The authors declare that they have no competing interests.

## Ethics approval

The study protocol (version 2.0, January 2019) was reviewed and approved by Yorkshire and The Humber Leeds West REC (Ref: 18/SW/0262).

## Provenance and peer review

Not commissioned; externally peer reviewed.



**Figure 1**. Participant flow through the study. PA; physical activity

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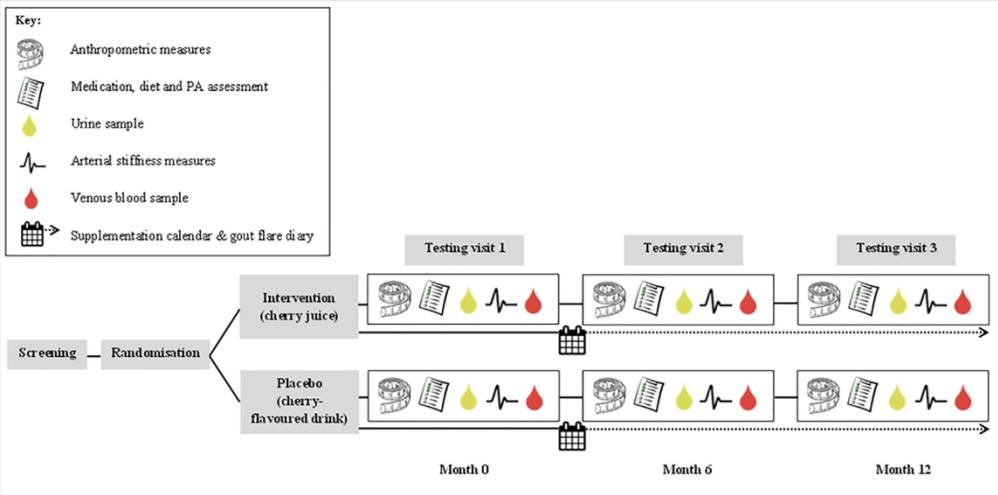


**Figure 1**. Participant flow through the study. PA; physical activity

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| | | Reporting Item | Page Number |
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| **Administrative information** | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | n/a |
| Protocol version | #3 | Date and version identifier | 11 |
| Funding | #4 | Sources and types of financial, material, and other support | 10-11 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 1, 10 |

| | | | |
|---|---|---|---|
| Roles and responsibilities: sponsor contact information | #5b | Name and contact information for the trial sponsor | 10 |
| Roles and responsibilities: sponsor and funder | #5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 10-11 |
| Roles and responsibilities: committees | #5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | n/a |
| **Introduction** | | | |
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| Background and rationale: choice of comparators | #6b | Explanation for choice of comparators | 7 |
| Objectives | #7 | Specific objectives or hypotheses | 4-5 |
| Trial design | #8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory) | 5 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | #9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be | 5 |

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| | | obtained | |
| Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 6 |
| Interventions: description | #11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 6-7 |
| Interventions: modifications | #11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease) | n/a |
| Interventions: adherance | #11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) | 8 |
| Interventions: concomitant care | #11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 7 |
| Outcomes | #12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 5, 7-8 |
| Participant timeline | #13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 5-6 |
| Sample size | #14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 9 |
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| Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 9 |
| Blinding (masking): emergency unblinding | #17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the | 7-8 |

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| Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 9-10 |
| Statistics: additional analyses | #20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | n/a |
| Statistics: analysis population and missing data | #20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 9 |
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| Data monitoring: formal committee | #21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | n/a |
| Data monitoring: interim analysis | #21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a |
| Harms | #22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 8 |
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| | | any, and whether the process will be independent from investigators and the sponsor | |
| **Ethics and dissemination** | | | |
| Research ethics approval | #24 | Plans for seeking research ethics committee / institutional review board (REC / IRB) approval | 10 |
| Protocol amendments | #25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators) | 10 |
| Consent or assent | #26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 6 |
| Consent or assent: ancillary studies | #26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| Confidentiality | #27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 8-9 |
| Declaration of interests | #28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 11 |
| Data access | #29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 11 |
| Ancillary and post trial care | #30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | n/a |
| Dissemination policy: trial results | #31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 10 |
| Dissemination policy: | #31b | Authorship eligibility guidelines and any intended use of | n/a |

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|---|---|---|---|
| authorship | | professional writers | |
| Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | n/a |
| **Appendices** | | | |
| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | n/a |
| Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |

BMJ Open

# The effect of tart cherry juice on risk of gout attacks: protocol for a randomised controlled trial



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Protocol (BMJ Open)

# The effect of tart cherry juice on risk of gout attacks: protocol for a randomised controlled trial

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## ABSTRACT

**Introduction:** Gout is a painful form of inflammatory arthritis associated with several comorbidities, particularly cardiovascular disease. Cherries, which are rich in anti-inflammatory and anti-oxidative bioactive compounds, are proposed to be efficacious in preventing and treating gout, but recommendations to patients are conflicting. Cherry consumption has been demonstrated to lower serum urate levels and inflammation in several small studies. One observational case-crossover study reported that cherry consumption was associated with reduced risk of recurrent gout attacks. This preliminary evidence requires substantiation. The proposed randomised clinical trial aims to test the effect of consumption of tart cherry juice on risk of gout attacks.

**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. Participants will be randomly assigned to an intervention group, which will receive Montmorency tart cherry juice daily for a 12-m period, or a corresponding placebo group, which will receive a cherry-flavoured placebo drink. The primary study outcome is change in frequency of self-reported gout attacks. Secondary outcome measures include attack intensity, serum urate concentration, fractional excretion of uric acid, biomarkers of inflammation, blood lipids and other markers of cardiovascular risk. Other secondary outcome measures will be changes in physical activity and functional status. Statistical analysis will be conducted on an intention-to-treat basis.

**Ethics and dissemination:** This study has been granted ethical approval by the National Research Ethics Service, Yorkshire and The Humber - Leeds West Research Ethics Committee (ref: 18/SW/0262). Results of the trial will be submitted for publication in a peer-reviewed journal.

**Trial registration number:** NCT03621215.


### Strengths and limitations of this study

- This study will be the first randomised, double-blind, placebo-controlled trial to examine the effectiveness of tart cherry juice to reduce risk of recurrent gout flares.
- Primary and secondary outcomes are central to treatment of gout and its co-morbidities.
- This study will investigate mechanisms whereby tart cherry juice may reduce risk of recurrent gout flares and co-morbidities.
- The study design addresses the temporal risk of gout flares by assessing patients over a 12-month period and retention of participants may be challenging.

## INTRODUCTION

Gout is a debilitating and common type of inflammatory arthritis exerting a significant health burden.[1,2] The proportion of people afflicted with gout in the UK is substantial; around 3% of adults were affected in 2012, representing approximately 1.9 million people.[3] Men are typically at greater risk of developing gout than women and risk increases with age for both genders.[3] Gout is associated with numerous co-morbidities, including cardiovascular disease (CVD), obesity and hypertension.[3–5]

Acute recurrent attacks of arthritis, also known as flares, are a defining feature of gout.[6] The underlying cause is a build-up of monosodium urate crystalline deposits in the joints, particularly those of the lower limbs causing acute pain, redness and inflammation.[7,8] Gout attacks are intermittent and may last from several days to up to several weeks. Usually only one joint is affected. Sustained hyperuricaemia, which most commonly occurs secondary to reduced fractional uric acid clearance, is recognised as the most important risk factor for gout.[9,10] Consumption of purine- or fructose-rich food and drink, including seafood, red meat, beer and sugar-sweetened beverages have been associated with increased uric acid levels and risk of gout flares.[11–16]

Early case reports from the 1950s suggested that consumption of cherries had a role to play in alleviating gouty pain and inflammation.[17] More recently cherries and cherry products have been shown to acutely lower serum urate after consumption in healthy people, while a daily supplement of cherry juice was associated with lower serum urate in a placebo-controlled crossover study of overweight and obese men and women.[18–20] It is unclear which bioactive component in cherries may be responsible for the effect; Bell et al proposed that anthocyanins and/or other phenolic compounds present in cherry may be important.[18]

There are very few studies in gout patients. In a case-crossover study of 633 gout sufferers, cherry consumption was associated with a 35% lower risk of gout flares.[21] This study was predicated on an acute temporal relationship between cherry consumption and likelihood of gout flares and did not evaluate the habitual effect of cherry consumption. Furthermore being observational in design, causality cannot be assumed.[21] While there have been two intervention studies that have addressed the potential for cherry to reduce risk of gout, these were both feasibility studies with limited sample size, lack of an appropriate placebo and within-group statistical comparison.[22,23]

In addition to lowering serum urate, cherry consumption may be of benefit in gout prophylaxis because cherries contain a variety of polyphenolic compounds with anti-inflammatory properties. These compounds may ameliorate the inflammatory response induced by monosodium urate crystals.[18,21] Indeed, cherry consumption has been shown to lower a recognised biomarker of inflammation C-reactive protein (CRP) in both healthy [18,24–26] and arthritic people.[27,28]

Despite the limited scientific evidence base, leading medical societies and charities (for example, British Society for Rheumatology, European League against Rheumatism, National Institute for Clinical Excellence, Arthritis Research UK, Mayo Clinic, UK Gout Society) endorse cherry consumption as a therapeutic aid for gout.[1,29–33] Contrastingly, the Food and Drug Administration in the United States has warned cherry juice growers and processers against making preventive disease claims.[34] A content analysis of US and UK newspapers reported that 25% of articles discussing dietary management of gout advised cherry consumption.[35] Notably, the UK's National Health Service health information website dismissed newspaper claims that advocated cherry consumption for gout.[36] There is a clear need for definitive evidence from a randomised controlled trial.

The proposed study is a 12-month RCT designed to provide superior evidence as to whether tart cherries are a useful adjuvant therapy for treatment of gout. The study will also elucidate possible mechanisms of effect through the measurement of serum urate, fractional urinary urate excretion, biomarkers of inflammation and oxidative stress. As participants are likely to be at increased risk of CVD, secondary study outcomes will be measures of arterial stiffness and blood lipids.

## AIM AND OBJECTIVES

The aim of this study is to evaluate the effects of a daily intervention of tart cherry juice over a 12-month period compared with a placebo drink on risk of gout attacks.

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.

Its secondary objectives are to:

- assess if tart cherry juice supplementation impacts on risk factors for cardiovascular disease
- identify the effects of tart cherry juice supplementation on putative biological mediators of risk of gout

### 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.
- In patients diagnosed with gout, a dietary intervention of a daily tart cherry concentrate drink for a 12-m period will lower markers of cardiovascular risk (arterial stiffness, blood pressure and blood lipids) compared with a placebo drink.

## METHODS AND ANALYSIS

Described according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[37]

### 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. The intervention group will receive a daily supplement of tart cherry juice and the placebo group will receive a cherry-flavoured drink. 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, fractional excretion of uric acid, blood lipids and recognised markers of inflammation (CRP, interleukin-6, tumour necrosis factor alpha), oxidative stress and vascular function (blood pressure, arterial stiffness). Changes in physical activity, perceived health and pain will also be secondary outcomes. Non-efficacy outcomes will include dietary intake measures, for example total energy, total sugars and consumption of gout trigger foods. Each participant will be enrolled onto the study for 12 months; physical and vascular measurements and fasted blood and 24-hour urine samples collected at 0, 6 and 12 months. These measurements will be made at Sheffield Hallam University's Food and Nutrition Research Laboratories in Sheffield, United Kingdom. Laboratory visits will be postponed for any participant that is experiencing a gout flare until after the flare has resolved. An overview

of the study design and timeline is given in Figure 1. The study opened recruitment in June 2019 and is ongoing.

## Participants and recruitment

Participants will mainly be recruited from primary care practices in the English city of Sheffield and surrounding areas. The Clinical Research Network of Yorkshire and Humber, which provides localised infrastructure to support delivery of research, will select practices to act as Participant Identification Centres (PICs). 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. A general practitioner will screen the list of patients generated from this search for suitability to participate (for example, people who are frail or suffer from dementia would not be recruited). People who are eligible will be sent an invitation to participate; interested individuals will be encouraged to contact the research team for further study information. Such participants will be invited to attend an information, screening and enrolment meeting at Sheffield Hallam University. Written informed consent will be obtained from those willing to take part by the study coordinator (KL).

Recruitment from PICs will be augmented by poster advertising at local primary care practices and across the university campus, advertising on the UK Gout Society website and at local large-scale workplaces. Participants' general practitioner will be contacted to verify their eligibility.

### Inclusion criteria

- Aged between 18 and 80 years.
- Clinical diagnosis of gout.
- At least one self-reported gout flare with a pain score >3 (on a 0-10 numerical rating scale) in the past 12 months.
- Participant is able to give informed consent.

### Exclusion criteria

- Allergy to cherries.
- Habitual consumption of cherries and/or cherry products.
- Severe renal impairment (glomerular filtration rate <30 mg/L).
- Type 1 or type 2 diabetes.

- Recruiting practitioner deems that the patient is unsuitable to participate (frailty, dementia and terminal medical conditions).

## Dietary Intervention

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 250 ml daily). Graduated cups with clear markings indicating required volumes of concentrate and water will be provided to participants. Participants will be advised to consume their drink with breakfast and to keep the concentrate refrigerated. Consumption will be recorded daily on a calendar. Advice will be given to maintain usual dietary habits throughout the course of the intervention and to avoid cherry consumption.

Each daily serving of tart cherry has been estimated to provide: 80 kcal, 20 g carbohydrate, 870 mg phenolics and 14 mg of anthocyanins. Each serving of the placebo drink will provide: 2.9 kcal, 0.3 g carbohydrate, 13 mg phenolics and 0.2 mg anthocyanins. The placebo drink has been constituted to have 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). It was not possible to match the drinks for energy content because the addition of sugars to the placebo drink would have jeopardised its shelf life. Furthermore, the addition of sucrose (comprising 50% fructose) has the potential to raise serum urate.[38]

## Data collection

### Laboratory visit data

#### *Anthropometric measurements*

Anthropometric measures of height and weight will be used to calculate Body Mass Index (weight (kg)/height $(m)^2$). Height without shoes will be measured to the nearest 0.1 cm using a stadiometer (Seca, Hamburg, Germany). Weight will be measured in light clothing to the nearest 0.1 kg using calibrated weighing scales (Seca 899, Hamburg, Germany).

#### *Fasting blood sample*

Fasted venous blood samples will be collected. These will be analysed for: serum inflammatory markers (CRP, IL-6 and TNF-α), serum urate and blood lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triacylglycerol). Oxidative

DNA damage and antioxidant status will also be measured in lymphocytes using the Comet assay (single cell electrophoresis).

### *Urine samples*

Prior to each visit, participants will carry out a 24-hour urine collection. These samples will be used to calculate 24-hour urinary uric acid excretion. A further spot urine sample will be collected alongside the fasting blood sample to calculate fractional excretion of uric acid.

### *Arterial stiffness*

A Vicorder™ device (SMT Medical, Germany) will be used to measure brachial BP, central BP, carotid-femoral pulse wave velocity and augmentation index.

### *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 the participant's medication log. Dietary supplement use will also be recorded at baseline, 6 and 12 months. Assessment of functional status covering pain, interference with daily activities and perceived health will be collected through interview using questions from a validated scale.[39]

## 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]

### *Assessment of diet and physical activity levels*

Participants will complete a 4-day food diary using estimated household measures and record physical activity in a diary over a 4-d period in the week preceding each laboratory visit.

### *Compliance*

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.

### *Retention*

Participants may withdraw from the study at any time without giving any reason. Reasons for discontinuing the study will be recorded. Participants who decide to discontinue the intervention will be invited to return for follow-up visits to assess outcome measures.

### *Adverse events (AEs)*

All AEs will be recorded and reported, where applicable, following Good Clinical Practice and Health Research Authority guidelines. Participants will be advised to report all serious or non-serious AEs to the research team; these data will be recorded. Additionally, the incidence of adverse events will be logged at laboratory visits and via telephone contact.

## Data management

The collection and storage of data will adhere to the standard requirements of the EU General Data Protection Regulation 2016/679. Data will be entered onto electronic spreadsheets, which will be stored on a secure University server. All data will be treated confidentially and anonymised for evaluation. Hard copies of data and documents will be kept in a locked and secure cabinet for the duration of the study. Following completion of the study, data will be transferred to Sheffield Hallam University's Research Data Archive (SHURDA), where it will be kept for 10 years. Hard copies will be disposed of confidentially and electronic data deleted after this period of time.

## Randomisation, allocation and blinding

All consenting participants will be block randomised (block size 4) in a 1:1 allocation to either a tart cherry juice group or a placebo cherry-flavoured drink group with stratification by sex and smoking status. Allocation sequence will be generated using a computer random number generator by an investigator not involved in participant enrolment and data collection (AL) and concealed from research personnel until the completion of the trial. The study coordinator (KL) who will be responsible for participant enrolment, distribution of intervention drinks and data collection will be blinded to treatment allocation until results have been analysed. Drinks will be provided to participants in identical bottles and labelled with participant identification number only to ensure that both study coordinator and participants are blinded to drink allocation throughout the study.

## Sample size

The power calculation was based on the potential impact of tart cherry supplementation on the primary outcome measure. Using data on gout occurrence in UK patients, the chance of a

recurrence of at least one gout flare over a 12-month period is 11%.[41] It is predicted that cherry juice treatment will reduce this recurrence to one quarter of the rate of the actual recurrence (from 11% to 2.7%). Based on these data, it is estimated that 94 participants would provide 95% power at a significance level of 0.05. A sample of 120 participants will allow for an attrition rate of approximately 20%.

## Statistical analysis

Continuous variables will be presented as mean and confidence intervals. Statistical significance will be set at $p < 0.05$. Descriptive analysis of all baseline variables will be conducted to compare the two groups. All analyses will be performed using intention-to-treat analysis; all randomised participants will be included in the final analysis as far as data collected will allow. 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); baseline, 6 months and 12 months times will be used for secondary outcomes. Analysis will be performed using IBM SPSS Statistics for Windows (New York, USA).

## Patient and public involvement

Gout patients were not directly involved in development of the research question or study design. We consulted with retired people from a local church group (Christ Church Fulwood, Sheffield, England) as to their understanding of written participant information and questionnaires. This group also provided feedback on the acceptability of the schedule of visits, study measures and intervention.

## Ethics and dissemination

The trial has been approved by Leeds West NHS Research Ethics Committee (18/SW/0262) and the HRA and Health and Care Research Wales (HCRW). It is registered at ClinicalTrials.gov (NCT03621215). Any protocol modifications will be sent for review by the research ethics committee and will be amended at the trial registry. Participants will be sent a summary of the trial findings when all data have been analysed. Dissemination of the study findings of this study will be through publication in a leading peer-reviewed journal and presentation at national and international conferences.

### Author affiliations

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## Acknowledgements

We acknowledge the input of Dr Tim Tait, Consultant Rheumatologist, United Lincolnshire Hospitals NHS Trust, Lincoln, England for his guidance about clinical aspects of the study protocol. We are grateful to Dr Caroline Mitchell and Dr Helen Twohig from the Academic Unit of Primary Medical Care, University of Sheffield for their helpful advice.

## Contributors

AL and MEB designed the study and secured the funding. KL prepared study documents and coordinated the HRA and ethics applications. MEB and AL are joint principal investigators. KL is the study coordinator and co-investigator. KL drafted the manuscript for publication, with input from AL, JMR and MEB. JMR advised on the study design, power calculation and statistical analysis.

## Funding

The sponsor of this research is Sheffield Hallam University, UK. This work is supported by the Cherry Marketing Institute (CMI), Michigan, US. CMI did not have any input into the design of the study or writing of this manuscript and will not play any role in the collection, analysis and interpretation of data. The protocol was initiated and designed by the investigators who have no personal financial relationships with CMI.

Patient recruitment to the study is supported by Yorkshire and Humber National Institute for Health Research CRN.

## Competing interests

MEB and AL are the joint recipients of a research grant from the CMI, Michigan, US. None of the authors have any personal financial relationships with CMI.

## Ethics approval

The study protocol (version 2.0, January 2019) was reviewed and approved by Yorkshire and The Humber Leeds West REC (Ref: 18/SW/0262).

## Provenance and peer review

Not commissioned; externally peer reviewed.

**Figure 1**. Participant flow through the study. PA; physical activity

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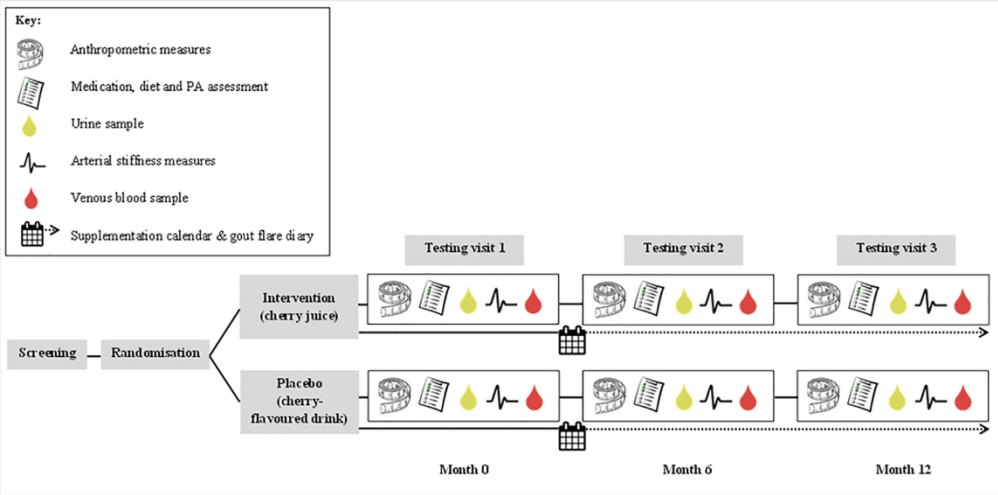


**Figure 1**. Participant flow through the study. PA; physical activity

209x104mm (300 x 300 DPI)

# Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

| | | Reporting Item | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | n/a |
| Protocol version | #3 | Date and version identifier | 11 |
| Funding | #4 | Sources and types of financial, material, and other support | 10-11 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 1, 10 |

| | | | |
|---|---|---|---|
| Roles and responsibilities: sponsor contact information | #5b | Name and contact information for the trial sponsor | 10 |
| Roles and responsibilities: sponsor and funder | #5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | 10-11 |
| Roles and responsibilities: committees | #5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | n/a |
| **Introduction** | | | |
| Background and rationale | #6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 3 |
| Background and rationale: choice of comparators | #6b | Explanation for choice of comparators | 7 |
| Objectives | #7 | Specific objectives or hypotheses | 4-5 |
| Trial design | #8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory) | 5 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | #9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be | 5 |

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| | | obtained | |
| Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 6 |
| Interventions: description | #11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 6-7 |
| Interventions: modifications | #11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease) | n/a |
| Interventions: adherance | #11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) | 8 |
| Interventions: concomitant care | #11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 7 |
| Outcomes | #12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 5, 7-8 |
| Participant timeline | #13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 5-6 |
| Sample size | #14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 9 |
| Recruitment | #15 | Strategies for achieving adequate participant enrolment to reach target sample size | 6 |

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| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: sequence generation | #16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 9 |
| Allocation concealment mechanism | #16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 9 |
| Allocation: implementation | #16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 9 |
| Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 9 |
| Blinding (masking): emergency unblinding | #17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the | 7-8 |

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| | | protocol | |
| Data collection plan: retention | #18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 8 |
| Data management | #19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 8-9 |
| Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 9-10 |
| Statistics: additional analyses | #20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | n/a |
| Statistics: analysis population and missing data | #20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | 9 |
| **Methods: Monitoring** | | | |
| Data monitoring: formal committee | #21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | n/a |
| Data monitoring: interim analysis | #21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a |
| Harms | #22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 8 |
| Auditing | #23 | Frequency and procedures for auditing trial conduct, if | n/a |

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| | | any, and whether the process will be independent from investigators and the sponsor | |
| **Ethics and dissemination** | | | |
| Research ethics approval | #24 | Plans for seeking research ethics committee / institutional review board (REC / IRB) approval | 10 |
| Protocol amendments | #25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators) | 10 |
| Consent or assent | #26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 6 |
| Consent or assent: ancillary studies | #26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| Confidentiality | #27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 8-9 |
| Declaration of interests | #28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 11 |
| Data access | #29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 11 |
| Ancillary and post trial care | #30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | n/a |
| Dissemination policy: trial results | #31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 10 |
| Dissemination policy: | #31b | Authorship eligibility guidelines and any intended use of | n/a |

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| authorship | | professional writers | |
| Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | n/a |
| **Appendices** | | | |
| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | n/a |
| Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |