


# BMJ Open Targeting the reduction of inflammatory risk associated with cardiovascular disease by treating periodontitis either alone or in combination with a systemic anti-inflammatory agent: protocol for a pilot, parallel group, randomised controlled trial

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## ABSTRACT

**Introduction** Cardiovascular disease (CVD) is associated with systemic inflammation. Colchicine, an anti-inflammatory drug, reduces the incidence of CVD events. Periodontitis, a chronic localised inflammatory disease of the tissues supporting the teeth, triggers systemic inflammation and contributes to inflammatory risk. Treatment for periodontitis reduces markers of inflammation, however, there is no evidence on whether an anti-inflammatory medication in combination with periodontal treatment can reduce the inflammatory risk. The aim of this trial is to investigate the effect of periodontal treatment either alone or in combination with an anti-inflammatory agent on inflammation in patients with periodontitis and CVD at 8 weeks.

**Methods and analysis** 60 participants with moderate-to-severe periodontitis, coronary artery disease and an increased inflammatory risk (>2 mg/L high sensitivity C reactive protein (hsCRP) levels) will be recruited from a tertiary referral hospital in Australia in a parallel design, single blind, randomised controlled trial. Baseline hsCRP levels, lipid profile and periodontal assessment will be completed for each participant before they are randomised in a 1:1:1:1 ratio to one of 4 arms as follows: (group A) periodontal treatment and colchicine; (group B) periodontal treatment only; (group C) colchicine only or (group D) control/delayed periodontal treatment. Periodontal treatment will be provided over three treatment visits, 0.5 mg of colchicine will be provided as a daily tablet. Participants will be followed up at 8 weeks to measure primary and secondary outcomes and complete a follow-up questionnaire. The primary outcome is the difference in hsCRP levels, the secondary outcomes are differences in lipid levels and periodontal parameters and the feasibility measures of recruitment conversion rate, completion rate and the safety and tolerability of the trial.

**Ethics and dissemination** The study has been approved by the Western Sydney Local Health District Human Ethics Committee (protocol number 2019/ETH00200). Results will

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is the first study to investigate changes in a systemic inflammatory marker in patients with cardiovascular disease using anti-infective and anti-inflammatory treatment (treatment of gum disease) either alone or in combination with a systemic anti-inflammatory medication.
- ⇒ The suitability of a self-report questionnaire for recruiting participants with periodontitis from a cardiology ward will be tested and will provide a blueprint for a future multicentre study.
- ⇒ The feasibility of the recruitment conversion rate and study completion rate will be established using prespecified feasibility targets.
- ⇒ The design of a pilot study implies that findings cannot be used to make conclusions about the effectiveness of the interventions on reducing systemic inflammation.
- ⇒ Due to the nature of the clinical intervention, it is not possible to blind those delivering or receiving the intervention.

be published in peer-reviewed journals and presented at conferences.

**Trial registration number** ACTRN12619001573145.

## INTRODUCTION

### Periodontitis

Periodontitis is a chronic microbial infection of the soft and hard tissues supporting the teeth.<sup>1</sup> The prevalence of periodontitis ranges from 30% to 55%, increases with age and peaks in the fifth and sixth decades of life.<sup>2,3</sup> The chronic inflammatory response in periodontitis is triggered by persisting subgingival bacterial deposits, is slowly progressive



and in most cases painless.<sup>4</sup> Untreated, periodontitis can result in the loss of supporting bone and connective tissue around the teeth leading to the loosening of teeth and eventually tooth loss.<sup>4</sup> The consequences of periodontitis may impair the quality of life and may cause psychological distress due to compromised aesthetics, and reduced chewing function.<sup>5</sup>

### Coronary artery disease and inflammation

The pathophysiology of atherosclerosis was traditionally attributed to an increase in lipid deposits on the surface of artery walls resulting in a decrease or complete occlusion of blood flow triggering a cardiovascular incident such as a myocardial or cerebral infarction.<sup>6</sup> There is growing evidence that inflammation plays a key role in all stages of atherosclerosis, from the formation of the early lesion through to thromboembolism.<sup>7</sup> The elevation of inflammatory markers, in particular C reactive protein (CRP), is associated with an increased risk of atherosclerosis,<sup>8</sup> and in survivors of myocardial infarction (MI) an increased risk of recurrent infarction and death due to coronary heart disease (CHD).<sup>9</sup> Therefore, reducing this inflammatory risk is integral to improving cardiovascular disease (CVD) related outcomes.

### Reducing systemic inflammation

The Canakinumab Anti-inflammatory Thrombosis Outcome Study demonstrated that targeting inflammation, via direct inhibition of interleukin-1 $\beta$  in survivors of acute MI with elevated CRP levels  $\geq 2$  mg/L, resulted in a modest reduction in major adverse CVD events.<sup>10</sup> However, canakinumab is not a cost-effective treatment and serious adverse events (SAEs) such as sepsis and fatal injection were reported in this trial.<sup>10</sup> Another anti-inflammatory medication to reduce CVD events is colchicine, an anti-tubulin drug commonly used in the treatment of gout. Colchicine has a broader mechanism of action compared with canakinumab and includes inhibition of tubulin polymerisation, resulting in downregulation of inflammatory pathways and alteration of leucocyte responsiveness.<sup>11</sup> Colchicine has been specifically shown to reduce levels of high sensitivity CRP (hsCRP),<sup>12</sup> which is an established marker for future CVD events.<sup>13</sup> In addition, randomised controlled trials (RCTs) of low-dose colchicine (0.5 mg) in patients with chronic coronary artery disease in the Low-Dose Colchicine trial and the Colchicine Cardiovascular Outcomes trial have shown that although colchicine reduces the overall risk of cardiovascular events in MI survivors, a significant effect on death from cardiovascular causes or MI was not shown.<sup>14 15</sup> Interestingly, non-specific anti-inflammatory treatment with methotrexate in the cardiovascular inflammation reduction trial has been shown to have no effect on cardiovascular outcomes or reduce inflammatory markers.<sup>16</sup> The evidence, therefore, does not yet support routine administration of anti-inflammatory medications as secondary prevention for CVD and raises the question

about whether an intervention further upstream maybe warranted.<sup>17</sup>

Although the impact of colchicine on hsCRP is well established, the impact on lipids is inconclusive. A study on short term exposure (30 days) to colchicine failed to demonstrate a significant impact on lipid levels in patients with chronic coronary artery disease.<sup>18</sup> However, in a rodent model of diet induced hyperlipidaemia, 5 weeks of colchicine treatment has been shown to reduce plasma lipids.<sup>19</sup> There is therefore a need for further clinical research.

Periodontal therapy is aimed at reducing inflammation and there is moderate evidence to support the reduction of serum inflammatory markers such as CRP following treatment for periodontitis.<sup>20</sup> Although the evidence to date does not suggest that periodontal therapy reduces plasma lipids.<sup>20</sup> Periodontitis has been shown to be associated with dyslipidaemia, therefore, further clinical studies on the impact of periodontal treatment on plasma lipids is indicated.<sup>21</sup>

### Biological mechanisms linking periodontitis and coronary artery disease

Periodontitis, a localised chronic inflammatory response in the oral cavity, is associated with an increased risk of atherosclerosis and an increase in systemic inflammatory markers.<sup>22</sup> Oral bacteria enter the blood stream directly as a result of a transient bacteraemia arising during normal daily activities such as eating, tooth brushing or flossing<sup>23</sup> and may lodge on artery walls triggering atherogenesis.<sup>24</sup> In animal models, pathogenic oral bacteria associated with periodontitis have been identified in atherothrombotic tissues and have been shown to induce endothelial dysfunction.<sup>25</sup> In addition, some pathogenic oral bacteria are able to invade host phagocytes, allowing the bacteria to be transported to distant organs causing atheroma formation in these sites once they are deposited by the phagocyte.<sup>26</sup> Finally, periodontitis has been shown to trigger an acute phase response leading to the systemic release of inflammatory markers, including CRP.<sup>24</sup>

### Periodontal treatment studies

Observational studies have demonstrated that periodontitis is consistently associated with a moderately increased risk for coronary artery disease<sup>27–29</sup> and that this association is dose-dependent, with more severe forms of periodontitis associated with an increased risk for CVD.<sup>28</sup> Systematic reviews of interventional studies in 2014<sup>22</sup> and 2018<sup>30</sup> have confirmed the impact of periodontal treatment on reducing inflammatory markers including CRP. Furthermore, a recent narrative review reported that multiple RCTs have demonstrated that periodontal treatment, or periodontal treatment with adjunctive aids such as antibiotics reduce inflammatory markers and circulating lipids.<sup>31</sup>

With the increasing interest for the treatment of CVD by anti-inflammatory medications and the well-documented positive effect of periodontitis treatment

on systemic hsCRP levels, there is interest in comparing the effect of both dental and oral anti-inflammatory treatment on CRP levels. The fact that periodontitis treatment has no adverse systemic side effects, compared with those reported for canakinumab or colchicine makes it an attractive treatment option for reducing the systemic inflammatory burden. To prepare for a novel randomised clinical trial using combined endpoints of CVD this feasibility study is essential to test recruitment, establish sample size and trial safety for a definitive study investigating how periodontitis treatment alone or in combination with a systemic anti-inflammatory drug reduces systemic CRP levels.

The primary objectives of this pilot RCT are to determine the changes in hsCRP levels, between baseline and the 8-week follow-up. In addition, this study will determine changes in lipids and periodontal parameters between baseline and 8-week follow-up and will evaluate the feasibility of recruitment conversion, trial completion, and the safety and tolerability of trial interventions.

For the future RCT, we hypothesise that periodontitis is an upstream source of inflammatory risk, and that, non-surgical periodontal treatment is an upstream approach that can reduce systemic inflammation and the combined events of CVD. In addition, we hypothesise that periodontal treatment in combination with colchicine will result in a greater decrease in hsCRP than either treatment modality on its own.

## METHODS AND ANALYSIS

### Study design and setting

This study is a parallel design, single blinded, pilot RCT with an 8-week follow-up investigating the effect of periodontal treatment and colchicine therapy on reducing systemic inflammation (hsCRP). The study will be conducted at Westmead Hospital and the Westmead Centre for Oral Health, both of which are a part of the Western Sydney Local Health District in New South Wales, Australia. The design and methods of this trial comply with the Consolidated Standards of Reporting Trials statement for RCTs.<sup>32</sup> Participants will be recruited from the cardiology ward at Westmead Hospital and periodontal treatment (three dental visits over a 2-week period) will be provided in a general practice dental clinic at the Westmead Centre for Oral Health. The first participant for this study was recruited on 23 June 2022 and we expect the study to be completed in 12 months.

### Study population

A total of 60 participants will be recruited from a cardiology ward within a tertiary teaching hospital in Sydney, Australia. Participants will be screened by staff in the cardiology ward for medical eligibility (adult ( $\geq 18$  years), have acute coronary syndrome/stable angina as documented in the medical record, currently on statin therapy and have hsCRP  $>2$  mg/L). Screening for dental eligibility criteria will be a two-step process, the first part will be

**Table 1** Inclusion and exclusion criteria

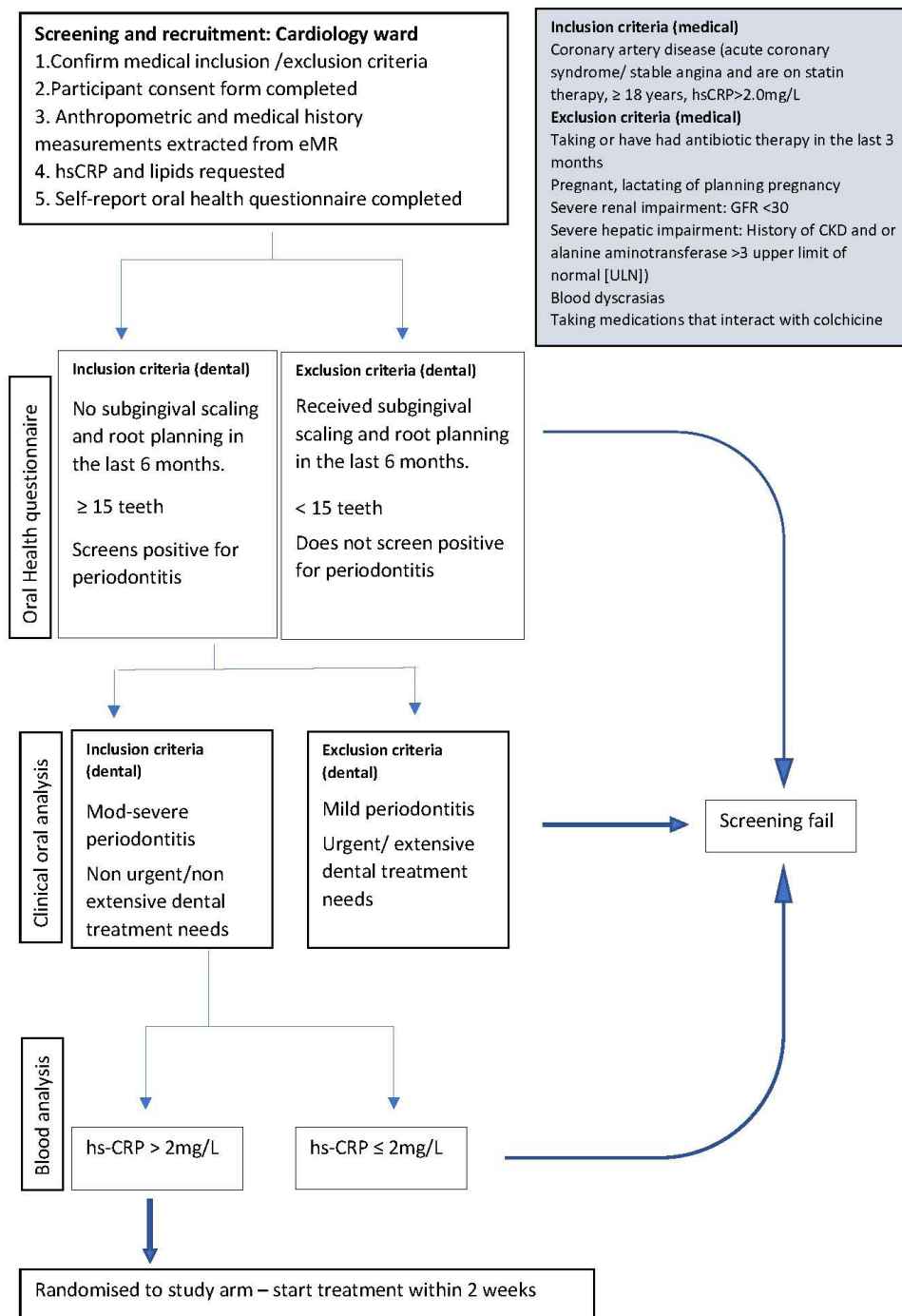
Inclusion criteria	Medical	<ul style="list-style-type: none"> <li>▶ <math>\geq 18</math> years.</li> <li>▶ Coronary artery disease (acute coronary syndrome/stable angina documented in medical records).</li> <li>▶ Current statin therapy.</li> <li>▶ hsCRP <math>&gt;2</math> mg/L.</li> </ul>
	Dental	<ul style="list-style-type: none"> <li>▶ <math>\geq 15</math> teeth.</li> <li>▶ Not treated for gum disease (subgingival scaling and root planning) in the last 6 months.</li> <li>▶ Moderate to severe periodontitis.<sup>34</sup></li> </ul>
Exclusion criteria	Medical	<ul style="list-style-type: none"> <li>▶ Current or recent antibiotic therapy in the (last 3 months).</li> <li>▶ Pregnant, lactating or planning pregnancy.</li> <li>▶ Severe renal impairment: Glomerular filtration rate (GFR) <math>&lt;30</math>.</li> <li>▶ Severe hepatic impairment: History of CKD and/or alanine aminotransferase <math>&gt;3</math> upper limit of normal.</li> <li>▶ Blood dyscrasias.</li> <li>▶ Taking medications that interact with colchicine.</li> </ul>

hsCRP, high sensitivity C reactive protein.

performed in the cardiology ward using a self-report oral health related questionnaire.<sup>33</sup> Participants are eligible if they have  $\geq 15$  teeth, have not received treatment for their gums (subgingival scaling and root planning) in the last 6 months and have moderate to severe periodontitis ( $\geq 20$  periodontal pockets with probing pocket depths of  $>4$  mm and marginal alveolar bone loss of  $>30\%$ ).<sup>34</sup> A study researcher will ensure that eligibility criteria are satisfied before the participant is invited for a clinical periodontal analysis, which will determine the periodontal diagnosis and thereby complete the screening process and form part of the baseline assessment. Table 1 provides a summary of the eligibility criteria. A sequence of the recruitment process is provided in figure 1.

### Randomisation

Randomisation will be stratified by age, gender and periodontal status as measured by the Periodontal Screening and Recording index (PSR). A randomisation allocation table will be computer generated and Research Electronic Data Capture (REDCap), a secure web-based password protected software platform will be used for allocation of participants to each group. Participants will be contacted by an email, which will be automated and sent through REDCap to advise them when to attend their treatment visit. Participants will be randomised in a 1:1:1:1 ratio into one of four arms of the trial. Allocation will occur after baseline assessment and the researcher conducting both the baseline and follow-up assessment will be blinded to group allocation. It is not possible to blind the participant or the treating dentist due to the nature of the dental treatment.

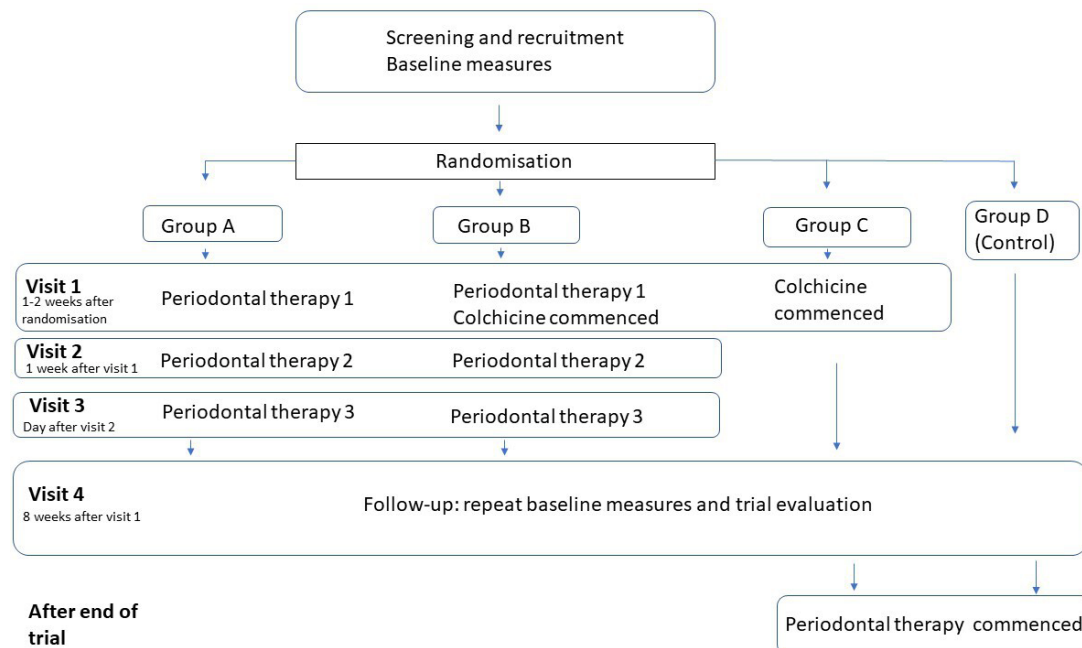


**Figure 1** Summary of the recruitment process. Participants are screened in the cardiology ward to ensure they meet the medical inclusion/exclusion criteria, informed consent is signed prior to the completion of the self-report oral health questionnaire. If the questionnaire indicates a risk for periodontitis the participant will be invited to attend a baseline assessment which will include an oral examination, anthropometric and medical history measures will be recorded and blood tests will be arranged. If the participant satisfies the dental inclusion/exclusion criteria they will be randomised to the treatment arms. High sensitivity C reactive protein (hsCRP), glomerular filtration rate (GFR), chronic kidney disease (CKD), electronic medical record (eMR).

## Interventions

Participants will be randomised into one of four arms as follows: (group A) periodontal treatment and colchicine; (group B) periodontal treatment only; (group C) colchicine only or (group D) control/delayed periodontal treatment. Treatment for the periodontal treatment

groups (groups A and B) will be initiated within 2 weeks from randomisation and will be provided by a dentist over three treatment visits during weeks 1 and 2 of the study period. Similarly, colchicine treatment for the colchicine treatment groups (groups A and C) will be provided as a 0.5 mg daily tablet for 8 weeks of the study period. The



**Figure 2** Study flow chart.

control group and colchicine only group (groups C and D) will receive periodontal treatment after the 8-week follow-up (figure 2). A single calibrated and trained oral health therapist, blinded to the treatment allocations will perform the baseline and 8-week follow-up assessments.

#### Non-surgical periodontal treatment

Periodontal treatment will be provided as three treatment visits. Visit 1 will include oral hygiene motivation and instruction and supragingival plaque removal. Visit 2 will occur 1 week after visit 1 and will include subgingival instrumentation on one side of the mouth. Subgingival treatment will be provided under local analgesia and will involve a combination of powered ultrasonic and hand instrumentation with no limit set to the duration of the session. Visit 3 will occur on the following day, as per the two-stage (within 24 hours) full-mouth protocol<sup>35</sup> and will include subgingival instrumentation on the other side of the mouth. A final follow-up visit will be completed 8 weeks after visit 1 to repeat the baseline measures. Participants who fail to attend a treatment visit will be followed up by phone and the reason for non-attendance will be documented. All non-surgical periodontal treatment will be provided by trained dental professionals following standard treatment guidelines and standardised operating procedures.<sup>35</sup>

#### Anti-inflammatory treatment

Colchicine treatment will be provided to participants as a 0.5 mg tablet to be taken orally once/day for 8 weeks. A study designated doctor will prescribe the colchicine and the drug will be dispensed free of charge by a private pharmacy located within Westmead Hospital according to the study protocol. Participants

will be asked to keep a logbook to record daily intake. Compliance will be ascertained through a pill count by the number of tablets that are returned to the pharmacy at the end of the study period.

#### Study outcomes and data collection

Participants will be followed up at 8 weeks to measure primary and secondary outcomes. The primary outcome of this pilot trial is the difference in hsCRP measures. Secondary outcomes are the differences in lipid levels and periodontal parameters and the feasibility measures. The trial has been designed to estimate the proportion of patients who meet our feasibility criteria with reasonable confidence.<sup>36 37</sup> The study would proceed to a definitive trial without modification if these prespecified feasibility criteria are met, including recruitment conversion rate and completion rate. In addition, the trial will report time to recruitment and safety and tolerability of the trial.

#### Assessment of physical measures

Physical and anthropometric measurements will be recorded by the nursing staff in the morning before the participants' first meal and will include weight (kg), height (cm), heart rate (beats/minute) and blood pressure (mm Hg). Weight measurements will be taken using electronic scales, the participant will be required to wear minimal clothing and remove their shoes. Height measures will be taken using a stadiometer with shoes removed. Heart rate and blood pressure measures will be recorded with an automated machine by trained nursing staff while the participant is seated and rested. Body mass index will be calculated using the measures of height and weight.

**Table 2** Clinical parameters for periodontal analysis

Clinical parameter	Description
Recession	Distance in mm from the cemento enamel junction to the gingival margin.
Probing pocket depth	Distance in mm from the gingival margin to the base of the sulcus or pocket.
Clinical attachment level	Distance in mm from the cemento enamel junction to the base of the sulcus or pocket.
Bleeding on probing	The presence of bleeding expressed as yes/no at each site (30 s after probing).
Plaque and bleeding index	The presence of plaque deposits and gingival bleeding will scored using established indices. <sup>46 47</sup>

### Assessment of inflammatory burden: change in hsCRP and lipid profile

Two fasted 10 mL venous blood samples will be collected from the antecubital vein by a registered nurse from participants at baseline and follow-up. The blood samples will be sent for analysis of hsCRP to a laboratory at the Royal Prince Alfred Hospital, Sydney and for lipid profile analysis (total cholesterol, triglycerides, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol) to a laboratory at Westmead Hospital. The hsCRP analyses will be conducted on a Cobas 8000, modular analyser and the lipid profile will be analysed on a Siemens Atellica immunoassay and clinical chemistry analyzer.

### Assessment of clinical oral health measures: change in periodontal parameters

All clinical parameters will be recorded at six sites per tooth (distobuccal, mid-buccal, mesiobuccal, distopalatal, mid-palatal, mesiopalatal) using a Florida probe<sup>38</sup> (table 2).

For each participant the following information will be reported: (A) number of teeth, (B) mean periodontal pocket depth, (C) mean clinical attachment level, (D) the percentage of sites with probing pocket depths of 1–3 mm, 4–6 mm and >7 mm, (E) the percentage of sites with BOP, (F) periodontal stage and grade, (G) plaque and bleeding indices and (H) tooth brushing and interdental cleaning frequency.

### Assessment of feasibility measures

The proportion of participants successfully recruited to the trial and the proportion of participants successfully completing the trial will be compared with our prespecified feasibility criteria.

In addition, we will report the percentage of participants lost as screening failures and the reasons for screening failure will be identified. The time taken for recruitment will also be provided. The percentage of participants starting treatment within 1–2 weeks of randomisation will be reported, and a breakdown of the proportion of participants completing each treatment visit along with reasons for non-completion provided.

### Assessment of participant safety and tolerability of the trial

At the end of the 8-week period, participants will be invited to complete a structured questionnaire of a series of Likert responses and open-ended questions on their experiences in the trial. Participants will be asked to rate the acceptability of the study procedures, how likely they are to recommend the trial to others and for details of any AEs following treatment interventions including the severity of any post-treatment complications.

### Process evaluation

A screening log will be kept in order to record reasons for non-participation for individuals who are either ineligible or who decline to participate. The screening log will also record the number of participants recruited each week and the time taken to complete recruitment. A treatment log will be kept in order to record timing of first treatment visit following randomisation and any reasons for delays, missed treatment visits and reasons for any non-attendance of treatment visits or non-compliance with medications. To assess the safety of the trial, data on AEs and SAEs will be collected at treatment visits and at the final 8-week follow-up visit as part of the treatment log. Participants will be asked non-leading questions to determine whether they have developed a new medical or dental condition or have an exacerbation of an existing medical or dental condition.

### Statistical analysis plan

The statistical plan for this study will be determined prior to study completion. Analysis of the difference in hsCRP, lipids and periodontal parameters will be according to the intention-to-treat principle where participants are analysed in the arm they have been allocated. The level of statistical significance will be set at  $p < 0.05$ . The primary analysis will be an adjusted analysis performed to assess differences between groups for hsCRP, lipid profile and periodontal parameters between baseline and follow-up using log binomial for binary (categorical) outcomes and an analysis of variance for continuous outcomes. Covariates used for adjusted analyses will include age, sex, PSR code, smoking status, periodontal stage and number of teeth. Outcome measures available at baseline (hsCRP, lipid profile and periodontal parameters) will also be included in the statistical model. An unadjusted analysis will be performed to assess differences between groups using a  $X^2$  test for binary (categorical) outcomes and independent sample t-tests for continuous outcomes.

The feasibility measures will be presented as percentages, and means and SD, as is appropriate. The outcomes will be compared with the predetermined feasibility criteria to determine whether changes to the protocol are required before proceeding with the multicentre trial.

### Sample size

This pilot study is not powered to determine the impact of periodontal treatment and/or colchicine treatment on systemic inflammation, this question will be answered in

a larger definitive trial. The sample size of 15 per arm for this study has been chosen based on pilot study recommendations when no prior studies exist on which to base the sample size calculation and includes provision for a 20% attrition rate.<sup>39</sup> The data from this study will be used to estimate variance to enable sample size calculation for the main trial.

The feasibility criteria for this study have been designed as follows:

1. Recruitment conversion rate—we estimate that as the prevalence of periodontitis in a cardiovascular population can be as high as 97%<sup>40</sup> and that over 40% of patients with CHD have been shown to have elevated hsCRP levels.<sup>41</sup> We estimate a rate of 40% successful screening, therefore a sample size of 60 has a 95% CI of (32.2% to 47.8%).
2. Completion rate—based on colchicine related side effects, which has led to 10%–15% of patients withdrawing from a previous trial<sup>42</sup> and approximately 15% of participants failing to comply with multiple treatment visits in a periodontal therapy trial,<sup>43</sup> for an estimated completion rate of 70%, a sample size of 60 has a 95% CI of (58.41% to 81.59%).

### Data management

Study data will be collected and stored using REDCap tools hosted at the University of Sydney.<sup>44 45</sup> Access to the REDCap data base will be controlled by the principal investigator and will require institutional log in credentials. For data analysis, data files will be stored on the University of Sydney Research Data Store, which is a secure platform hosted by the University for research data storage. Access to these data files will be controlled by the principal investigator and will require institutional log in credentials. Deidentified data will be used for any analyses and publications and data will be retained for a period of 5 years following study completion.

### Patient and public involvement

Participant feedback from the trial evaluation survey and information collected in relation to the safety and tolerability of the trial will provide important patient involvement in the design of a future trial multicentre trial.

## ETHICS AND DISSEMINATION

### Ethical approval

The study sponsor is the Western Sydney Local Health District. The design and conduct of this trial will be overseen by a study team (authors) from the University of Sydney's Westmead Applied Research Centre. The sponsor will not be involved in collection, management or analysis of the data. The study will comply with the National Health and Medical Research Council ethical guidelines for human research. Ethical approval for this trial has been obtained from the Western Sydney Local Health District Human Research Ethics Committee (protocol number: 2019/ETH00200), protocol version

7 dated 19 July 2022. Written informed consent will be obtained from all participants (online supplemental material 1) before any data collection or intervention occurs. Study findings are intended to inform the design of a larger, definitive trial. The trial registration number is ACTRN12619001573145 and has been registered prospectively (14/11/2019) with the Australian and New Zealand Clinical Trials Registry (ANZCTR) (refer to online supplemental material 2) for trial data set). A clinical trials notification (CTN) for this study has been obtained from the Therapeutic Goods Administration (CT-2021-CTN-03 319-1 v1). The study has been funded Internally by the University of Sydney.

### Dissemination

The results from this study will be published in peer-reviewed journals and presented nationally and internationally at both oral health and cardiology conferences. Individual participant data will be made available after deidentification, beginning 9 months and ending 5 years after publication of the results, to researchers who provide a methodologically sound proposal. The outcomes from this pilot trial will be used to refine the study protocol, establish a sample size and will allow for planning of a larger multicentre trial.

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