COlchicine in Patients with Acute Coronary Syndromes – the COPS trial

A multicentre, double-blind, randomised, placebo-controlled trial to assess the impact of low-dose colchicine on long-term cardiovascular outcomes in patients presenting with acute coronary syndromes.

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Literature review

Introduction:

Cardiovascular disease remains the leading cause of mortality and morbidity globally.[1,2] In fact, recent data shows an alarming 40% increase in cardiovascular mortality globally over the last two decades.[3] Despite recent advances in medical therapy and high percutaneous coronary intervention (PCI) success rates, long term mortality and cardiac event rates remain high in patients presenting with acute coronary syndromes (ACS).[4-7] This is highlighted in a study comparing intensive lipid lowering strategy to optimal medical therapy whereby a quarter of ACS patients in the treatment arm had a major adverse cardiac event (MACE) by 2 years.[8]

Over the last decade, it has become apparent that inflammation plays a pivotal role in all stages of atherosclerosis, from initiation through progression and ultimately thrombotic complications of acute coronary sydnromes.[9-13] Amidst various anti-inflammatory therapies, colchicine has recently emerged as a promising novel therapeutic option for cardiovascular disease owing to its potent anti-inflammatory properties. Data from large randomised trials of colchicine for treatment of cardiovascular disease are lacking. To date, no prospective large studies have been performed to determine the effect of colchicine on long-term cardiovascular outcomes in ACS patients.

Background/Rationale:

Atherosclerosis is a diffuse process and patients presenting with ACS frequently (30-40%) harbour multivessel coronary disease, which is a major risk factor for increased cardiovascular morbidity and mortality.[14-16] On the other hand, ACS represents a generalized inflammatory phenomenon that affects not only coronary vessels but also

other vascular beds.[17-19] The atherosclerotic plaques residing in the intimal layer of vascular walls are predisposed to various injurious forces that might render them vulnerable. Neutrophil infiltration of atherosclerotic lesions as a response to local injury or systemic inflammation can further aggravate the inflammatory cascades upon exposure to the plaque contents, hence inciting plaque instability or rupture. Histopathological studies had identified neutrophil infiltration to be actively associated with acute coronary events with high number of neutrophils seen in ruptured plaques.[20] Moreover, widespread activation of neutrophils across the coronary vascular bed has been reported in patients with unstable angina regardless of the location of the culprit lesion.[21] These observations fuel the speculation that colchicine, which has an anti-tubulin effect that inhibits neutrophil function, is capable of alleviating the inflammatory process involved in the clinical manifestation of coronary artery disease (CAD).

Extending the support for the role of inflammation in the culmination of CAD, statins have been shown to reduce recurrent ischaemic events due to their anti-inflammatory effects in addition to their known lipid-lowering capabilities.[22,23] Data from the GRACE study showed notable improvement in cardiovascular outcomes in ACS patients who had previous or early in-hospital statin therapy, indicating that statin therapy may modulate early pathophysiologic processes in ACS.[24] On the contrary, early cessation of statins has been associated with poorer outcomes in ACS. [25,26] To attest the inflammatory hypothesis of atherothrombosis, several large-scale trials are currently underway to assess the effectiveness of targeted anti-inflammatory therapies (such as canakimumab and methotrexate) on cardiovascular events.[27,28]

Colchicine, a "natural" (an alkaloid derived from the plant of Lily family *Colchicum autumnale*) and ancient (used as a powerful purgative by ancient Greeks more than 2000 years ago) drug,[29] has been widely used today for the treatment of inflammatory conditions such as acute gout,[30] pseudogout,[31] familial Mediterranean fever (FMF)[32] and pericariditis.[33,34] It has a narrow therapeutic-toxicity window and a marked pharmacokinetic variability between individuals.[35] Despite the common adverse effects of gastrointestinal symptoms, the long-term use of colchicine at doses of 1-2mg daily has been documented to be safe and well tolerated such as in patients with FMF.[36] Rare side effects of chronic colchicine administration including bone marrow suppression, liver failure and rhabdomyolysis.[37]

The inflammatory-modulating effects of colchicine are likely due to the disruption of microtubules – the important filamentous intracellular structures that are involved in cell division, signal transduction, regulation of gene expression, migration and secretion.[38] At low concentrations, colchicine inhibits the formation of microtubules while at high concentrations it promotes their depolymerisation.[38] Colchicine has also been shown to impede adhesion of neutrophils to the vascular endothelium,[39] as well as downregulating the release of inflammatory mediators.[35]

Recent human studies suggest that colchicine is useful in a wide spectrum of cardiovascular disease. The benefits of colchicine in the management of acute and recurrent idiopathic pericarditis were demonstrated previously,[40-42] leading to the endorsement and wide acceptance of colchicine as a treatment option in pericardial inflammation.[33,43,44] In addition, colchicine has been shown to reduce postoperative atrial fibrillation (AF) in patients undergoing cardiac surgery.[45] In another prospective

randomized study, the administration of colchicine as a monotherapy for 3 months after pulmonary vein isolation was associated with lower AF recurrences.[46]

Not until recently, has colchicine been recognised as a potential novel therapy in coronary artery disease. A pilot study involving 200 patients with stable CAD demonstrated that low-dose colchicine can effectively reduce levels of high-sensitivity C-reactive protein (hs-CRP)[47] – a known negative prognostic marker of cardiovascular outcomes.[48-50] Subsequently, the LoDoCo trial demonstrated a significant reduction in cardiovascular outcomes (ACS, out-of-hospital cardiac arrest, non-cardioembolic ischemic stroke) in stable CAD patients who received low-dose (0.5mg/day) colchicine in addition to standard medical therapy compared to standard medical therapy alone (4.5% versus 16.0%; hazard ratio 0.29).[51]

To date, there is only one published small pilot study that examined the effects of colchicine in ACS population.[52] A total of 80 ACS and/or ischaemic stroke patients were recruited, randomised to colchicine or placebo, and followed up for 30 days. Despite a moderate dose of colchicine (1mg/day) used, no difference was shown in platelet function or hsCRP levels. This study, however, failed to examine hard clinical end points due to the small sample size and was not specific for ACS.

An interesting observation from animal data suggested that colchicine works synergistically when combined with atorvastatin in ameliorating inflammation and improving endothelial function.[53] This concept of synergism is important in the conceptual design of our study as the beneficial effects of colchicine might become evident when combined with statin therapy.

Intriguingly, retrospective observations indicated that continuous use of colchicine was associated with a lower than expected risk of myocardial infarction in patients with FMF[54] and gout,[55] hence indirectly support the beneficial effect of colchicine on cardiovascular disease. Another randomized study evaluated the role of colchicine in preventing in-stent restenosis (ISR) after PCI in diabetic patients.[56] At 6 months, colchicine was associated with less neointimal hyperplasia and a significant reduction in angiographic ISR rate (16% in the colchicine group versus 33% in the control group). Similar benefits in terms of lumen area loss as determined by intravascular ultrasound were also seen in colchicine-treated patients.

This study will seek to evaluate the effects of low-dose colchicine on long-term cardiovascular outcomes in ACS population who are treated medically and/or with PCI. In this study, all participants will receive high-intensity statin therapy as recommended by the current ACC/AHA guideline for secondary prevention of cardiovascular disease.[57] A moderate-intensity statin regime will be considered if subjects develop statin-associated adverse effects. Patients enrolled in the study will receive dual antiplatelet therapy as per current ACS guidelines.[58,59] On the other hand, the dose of colchicine chosen in this study is relatively low compared to the usual dosage administered for other inflammatory conditions. The chosen dose is also comparable to the dosage used in previous cardiovascular trials which has been proven to be safe and relatively well tolerated.[47,51,52]

Hypothesis

We postulate that the addition of colchicine to standard secondary prevention therapy, which includes a statin and dual antiplatelet therapy, will reduce major adverse cardiac events and improve health-related quality of life at 12 months in patients presenting with ACS.

Aims

The primary aim is to determine the effect of low-dose colchicine in addition to standard medical therapy on long-term cardiovascular outcomes in ACS populations. The secondary aim is to evaluate the impact of colchicine on health-related quality of life.

Methodology

Trial design

The COPS trial will adopt a double-blind, randomised, placebo-controlled design. Both the research team members and the patients will be blinded to the treatment allocation. The study aims to compare the outcomes in ACS patients who receive standard medical therapy (placebo group) versus those who receive colchicine in addition to standard medical therapy (intervention group). Participants will be followed up for 12 months for predefined cardiovascular outcomes.

Study population

All ACS patients who are admitted to the hospital will be screened for eligibility after coronary angiography, which is deemed an appropriate management strategy according to the treating team. Patients will be eligible for the study if they meet the following inclusion and exclusion criteria:

Inclusion criteria:

- Age between 18 to 85 years old
- Written informed consent
- Acute coronary syndromes (ACS)[1] – defined by ischaemic symptoms with elevated troponin or ECG changes
- Presence of coronary artery disease – defined by ≥30% luminal stenosis in epicardial vessel of ≥2.5mm luminal diameter on visual angiographic assessment
- Coronary artery disease which is managed with PCI or medical therapy at the discretion of the treating team

Exclusion criteria:

- Coronary artery disease requiring surgical revascularization
- Pre-existing long-term colchicine use for other medical conditions
- Pre-existing, or plan for, administration of other immunosuppressant therapy
- Severe liver impairment – defined by elevated serum ALT and/or AST levels twice the upper limit of normal AND total serum bilirubin level twice the upper limit of normal OR coagulopathy (INR>1.5)
- Severe renal insufficiency – defined by eGFR<30mL/min/1.73m^2
- Pre-existing use of strong CYP3A4 or P-glycoprotein inhibitors[2] (eg. cyclosporine, antiretroviral drugs, antifungals, erythromycin and clarithromycin) and no other alternative medical therapy can be used
- Known active malignancy
- Known allergy or hypersensitivity to colchicine
- Pregnant and lactating woman or woman with childbearing potential without effective birth control methods

[1] Appendix 1
[2] List of CYP3A4 and P-glycoprotein inhibitors in Appendix 2

Conception, pregnancy and breast-feeding

At present, there is no evidence to suggest that the use of colchicine causes infertility in both men and women.[60] Although there is no evidence that colchicine is teratogenic or associated with miscarriage and stillbirth in pregnant women, due to lack of evidence in human studies, we will not be including pregnant women in this study. Therefore, women of child-bearing potential must have a negative serum pregnancy test and/or urine pregnancy test prior to commencement of colchicine. Female participant who becomes pregnant whilst receiving colchicine will need to contact the study investigators immediately, have the medication ceased immediately, and have follow up with local obstetric team to discuss pregnancy plan.

Recruitment and randomisation of participants

Study sites

We plan to recruit participants from a number of sites across Australia, which include (1) St Vincent's Hospital Melbourne, (2) Frankston Hospital, (3) Northern Hospital, (4) Barwon Health – University Hospital Geelong, (5) Box Hill Hospital, (6) Monash Medical Centre, (7) Royal Hobart Hospital, (8) The Royal Melbourne Hospital, (9) Gold Coast University Hospital, (10) Bankstown-Lidcombe Hospital, (11) Concord Repatriation General Hospital, (12) The Royal North Shore Hospital, (13) John Hunter Hospital, (14) Wollongong Hospital, (15) Ballarat Base Hospital, (16) SJOG Ballarat Hospital and (17) Western Health – Footscray and Sunshine Hospitals.

Enrolment/Randomisation

Eligible participants who meet the inclusion and exclusion criteria will be approached by the research team after coronary angiography ± angioplasty. Written informed consent

will be obtained. A research team member will record the participant's baseline variables, biochemistry and haematology results, and medical history[3]. The participant's estimated left ventricular systolic function will be obtained from either left ventriculogram or transthoracic echocardiogram. The principal investigators or associate investigators at each site will register the participant on a web-based database. Following the registration, stratified permuted-block randomisation that is concealed from the investigators will be performed via a web-based service. Both the researcher and the participant will be blinded to the treatment allocation. The randomisation system will advise the study team whether the participant is randomised to receive Drug A or Drug B.

Trial treatment

All participants will be commenced on high-intensity statin therapy and dual antiplatelet therapy. A moderate-intensity statin dose can be prescribed if the participants are unable to tolerate the high-intensity dose due to adverse effects. Patients will be randomised to receive either colchicine (intervention group) or placebo (control group) in addition to other standard secondary prevention therapies as per current ACS management guidelines. Patients in the intervention group will receive 0.5mg twice daily oral colchicine for the first month, followed by 0.5mg daily for another 11 months (total 12 months of colchicine). Patients in the control group will receive placebo tablets. Participants will be supplied with three months of study drug when they are discharged from the hospital. Subsequent medications will be mailed to the participants by the research team via registered post. A letter[4] containing important details of the study will be posted or faxed to their general practitioners.

[3] Refer to data collection form in Appendix 3
[4] Letter to general practitioner in Appendix 4

Dose adjustment

If the participant develops severe gastrointestinal symptoms within the first month of treatment, the dose of study medication can be reduced to once daily.

Treatment suspension

If the participant develops medical conditions that require colchicine therapy such as gout or pericarditis, study medication can be suspended for the entire duration of colchicine therapy and be recommenced after the participant completes the course of colchicine treatment. The duration of treatment suspension will be recorded.

Emergency unblinding

To main the overall quality and legitimacy of the clinical trial, unblinding of treatment allocation is permissible in exceptional circumstances when knowledge of the actual treatment is essential for further management of the patient. The investigator/medical staff is encouraged to discuss with the lead principal investigators if he/she believes that unblinding is necessary.

The investigator is encouraged to maintain the blind as far as possible. The actual allocation should not be disclosed to the patient and/or other study personnel; nor should there be any written or verbal disclosure of the code and treatment allocation in any of the corresponding patient documents. The investigator must report all treatment unblinding (with reason) on the corresponding care report form (CRF) page.

Unblinding is not necessarily a reason for study drug discontinuation.

Adverse effects and discontinuation of colchicine

Participants will be asked specifically regarding the adverse reactions of colchicine during the scheduled telephone interviews at 1, 6 and 12 months. All colchicine-related adverse events will be classified according to the Common Terminology Criteria for Adverse Events (CTCAE).[61] The severity of adverse event will be assessed[5] and all serious adverse events (SAE) will be reported to the Research Governance Unit at St Vincent's Hospital Melbourne (the sponsor) as well as Therapeutic Goods Administration (TGA) Australia. If the participants discontinue the study drug, the date and reason for discontinuation will be recorded. These participants will be followed up in the usual manner and included in the primary intention-to-treat analysis.

Medication compliance and dispensing

Medication adherence will be assessed by prescription refills and pill counts. Participants will be asked to count the number of pills remain in their medication bottles during scheduled interviews and at the end of treatment period. Participants will return all unused medications to the trial team at the end of study. Rate of adherence will be reported as the percentage of prescribed doses of the medication actually taken by the patient over the 12-month treatment period.

The study drug (colchicine) will be provided by Aspen Pharmacare Australia and stored in a secured/locked cupboard in the cardiology research department at lead study sites. Participants will receive a phone call every 3 months to confirm refill requirement. A medical doctor of the study team will dispense the medications and crosschecked by

[5] Safety reporting assessment flowchart in Appendix 5

another doctor. The medications (either placebo or colchicine) will be mailed to the participants every 3 months via registered post.

End points

Primary outcome

The primary outcome for this study will be the rate of major adverse cardiovascular events (MACE) at 1 year. MACE[6] is defined as a composite of:

(a) Acute coronary syndrome

(b) Ischaemic-driven revascularization

(c) Death from any cause

(d) Non-cardioembolic ischaemic stroke

Secondary outcomes

(a) Individual components of the primary outcome which include acute coronary syndrome, ischaemic-driven revascularization, death from any cause, and non-cardioembolic ischaemic stroke.

(b) Death due to cardiovascular disease

(c) Health-related quality of life assessed using EuroQol 5-Dimensions 5-Level (EQ-5D-5L) and Seattle Angina questionnaires[7]

(d) Hospital presentation or readmission with troponin negative chest pain

Follow up

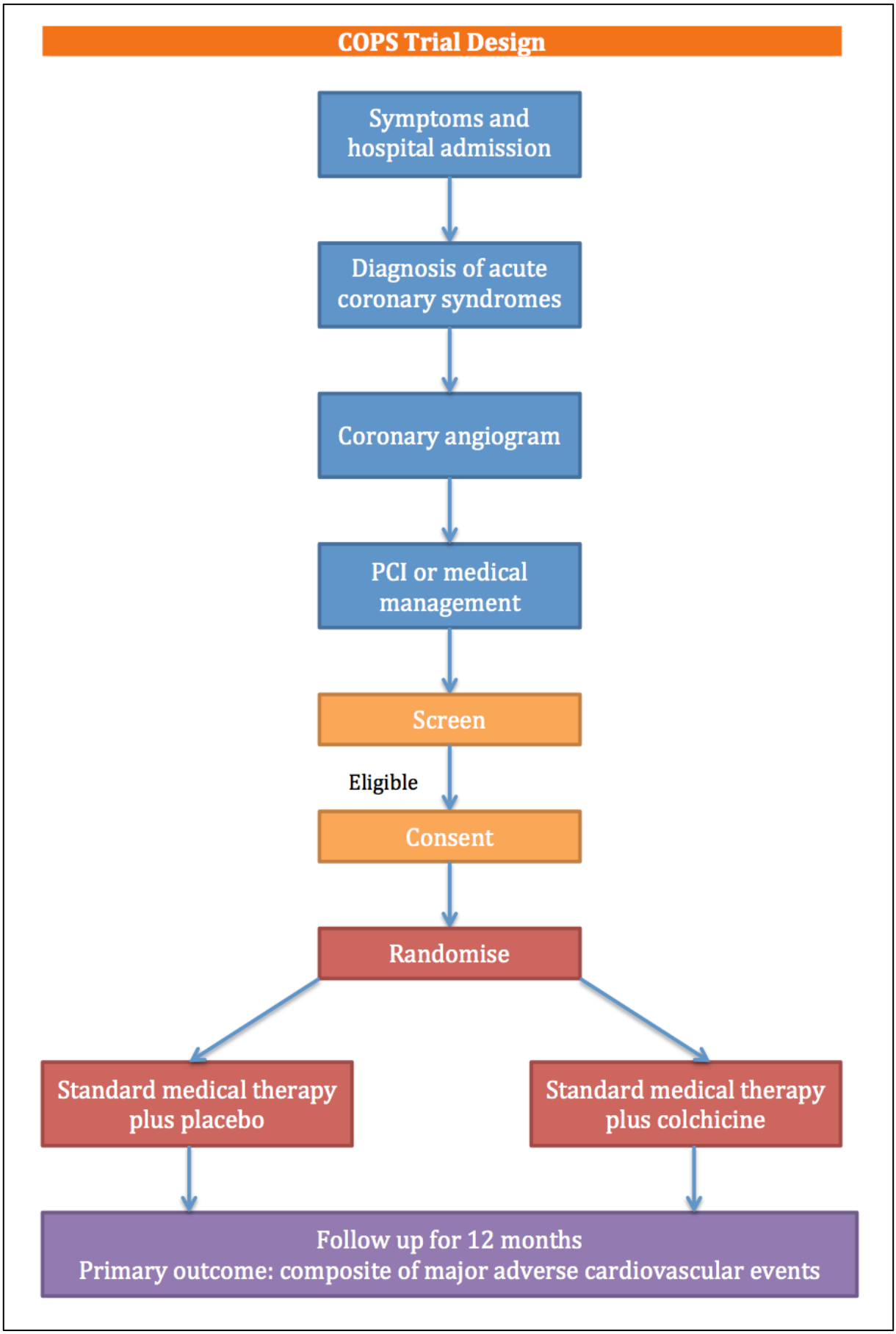
Participants will be followed up by telephone interviews at 1, 6 and 12 months. Outcome, patient's compliance with treatment and medication safety data will be collected.

[6] Definitions of outcome/clinical events in Appendix 1
[7] Appendix 7-8

Participants will also be interviewed for quality of life measures (Seattle Angina and EQ-5D questionnaires) at baseline and at 12 months. The pre-specified study duration will be follow-up of 12 months in all patients.

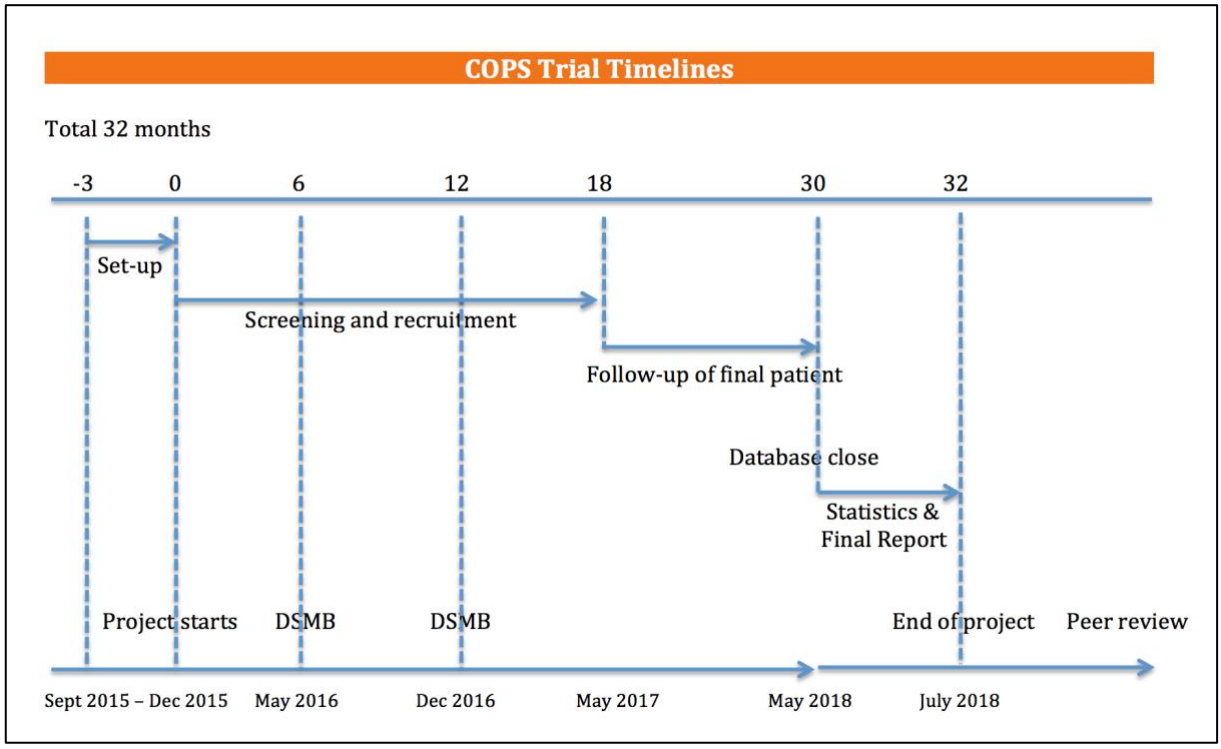
MACE (type of event and date) will be adjudicated by a Clinical Event Committee (CEC) comprised of two cardiologists who are independent of the trial and are blinded to the treatment allocations. Information on serious adverse events (SAEs) during the follow-up will be obtained by contacting the patients via scheduled telephone interviews and by reviewing their primary and secondary care records. This information will be de-identified and relayed to the CEC in the format of hard copy paperwork and/or electronic file.

Data collection	Baseline	1 month	6 months	12 months
Clinical characteristics	X			
Angiographic characteristics	X			
Transthoracic echo	X			
Discharge medications	X			
Quality of life questionnaires	X			X
Outcome data	X	X	X	X
Adverse reactions to medications		X	X	X


COPS Trial Design
Symptoms and hospital admission
Diagnosis of acute coronary syndromes
Coronary angiogram
PCI or medical management
Screen
Eligible
Consent
Randomise
Standard medical therapy plus placebo
Standard medical therapy plus colchicine
Follow up for 12 months
Primary outcome: composite of major adverse cardiovascular events

Timelines

We expect recruitment to commence in Sept 2015 and continue for a total duration of 18 months with follow-up of final patient to complete 12 months later. A final report will be prepared within 2 months after the completion of the study. It is anticipated that the results of this study will be published in a peer-reviewed journal.



Data analysis and statistical methods

Summary statistics including mean and standard deviation will be calculated for all baseline characteristics by treatment group. All time-to-event outcomes will be calculated from the date of randomization to the date of the first documented event. If a patient has not experienced an event at the cut-off date for the statistical analysis, the outcome data will be censored at the cut-off date. If the patient has been deemed lost-to-follow-up or has withdrawn from the study, the analysis will include the last date of patient's assessment. Outcomes for patients that provide no follow-up will be imputed using

multiple imputation (refer to *Statistical method for the primary endpoint*). The cut-off date or study censor date will be determined after the database has been locked for the analysis.

The primary efficacy analysis will be based on the intention-to-treat principle. Each patient will be followed up for a minimum duration of 12 months. A secondary pre-specified on-treatment analysis will also be performed based on patients who are both tolerant and compliant to therapy beyond the first month of randomisation.

Analysis sets

There are three data analysis sets in this study:

(1) Full Analysis Set (FAS) which consists of all patients randomised to the study. Analyses will be performed according to treatment arm and the strata utilized at randomization

(2) Per Protocol Set (PPS) which excludes a subset of FAS patients with major protocol deviations (MPDs). Examples of MPDs include but not limited to: study treatment received is different from treatment assigned by randomisation; or stratum assigned by randomisation is different from stratum reported by the investigator. Any other MPDs leading to exclusion from the FAS will be detailed and justified in the final report of the study.

(3) Safety Set (SS) which includes all patients who received at least one dose of study drug.

Statistical method for the primary endpoint

The primary outcome, will be analysed by time-to-first event survival analysis (log rank test). The primary analysis will be on an intention-to-treat basis of all randomised

patients according to treatment group. Outcomes for participants that provide no follow-up data will be imputed using multiple imputation, redrawing 50 samples. Imputations will be inferred from the following baseline variables: age, diabetes, previous myocardial infarction, previous PCI/CABG, and cardiac biomarkers. The treatment effect will be reported as a hazard ratio, together with a 95% confidence interval. Kaplan-Meier estimates of the MACE at 1, 6 and 12 months, as well as 95% confidence intervals, will be reported in a table by treatment group and also displayed graphically.

A sensitivity analysis of the primary endpoint will also be performed on the PPS using the same methods as described above for the primary analysis.

In addition, supplementary analyses performed on the FAS, Cox Proportional Hazards models incorporating the following covariates: gender, age, hypertension, diabetes, hypercholesterolaemia, smoking history, family history of coronary artery disease, previous myocardial infarction, previous PCI/CABG, previous stroke, and peripheral vascular disease; and their possible interactions with the treatment arms, will be evaluated. The proportional hazards assumption will be checked for all models.

Statistical methods for the secondary endpoints

Fine and Gray[62] competing risks regression will be used to compare the effects of treatment arms for the following competing risks:

- Acute coronary syndrome
- Ischaemic-driven revascularization
- Non-cardioembolic ischaemic stroke
- Death from any cause

- Death due to cardiovascular disease

Cumulative incidences, and their 95% confidence intervals will be reported.

Health-related quality of life will be compared between groups using baseline-adjusted linear regression.

Sample size justification

We postulate that the control group will have a combined event rate of approximately 20% over 3 years in the control group versus 10% in the treatment group based on previous literature.[63-66] The 20% and 10% per 3 year event rate translates to 3.45% and 7.16% annual event rates. On this basis we estimate that a sample size of 1009 patients provides 80% power at 5% significance to detect this difference, using a log-rank test. We expect to see 49 events in the cohort. This corresponds to a hazard ratio of 2.1170 and assumes participant attrition of 10% over the period of the study.

Safety

The assessment of safety will be based on the frequency of adverse events. All safety data will be available in listings as required. The Safety Set will be used for all listings and summaries.

Adverse Events (AE)

All adverse events recorded during the study (i.e. newly occurring or worsening since randomization) will be summarized by treatment arm. The incidence of adverse events will be summarized by body system, severity (worst grade based on CTCAE grades), type

of adverse event and relationship to study drug. Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and type of adverse event.

Adverse events will be summarized, by treatment arm, by presenting the number and percentage of patients having any adverse event in each body system and having each individual adverse event.

Tolerability

The percentage of patients who discontinue protocol treatment in the first 12 months of the study will be summarised by reason for discontinuation and treatment arm.

Trial governance

The trial will be conducted in line with Guidelines for Good Clinical Practice (GCP) in Clinical Trials. The sponsor of the trial is St Vincent's Hospital Melbourne. The Trial Steering Committee will be chaired by an independent cardiologist. The Clinical Event Committee (CEC) will consist of two cardiologists who are independent of the trial and blinded to the treatment allocations. The independent Data and Safety Monitoring Board (DSMB) will review confidential reports of relevant analyses of trial data every 6 months and will use specified statistical criteria to guide its assessment of whether the existing trial protocol should be stopped or undergo modification.

Protocol modification or early termination of the trial will be considered in the event of any of the following:

(a) Inadequate recruitment: less than 100 patients per year once a consistent accrual rate has been established

(b) Unacceptable toxicity as assessed by the DSMB

(c) Evidence becoming available during the accrual phase of the trial which clearly demonstrates that it is unethical to randomise patients to one or both of the trial arms

References

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 2015;131:e29-322.
2. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation 2001;104:2746-53.
3. Roth GA, Forouzanfar MH, Moran AE, et al. Demographic and epidemiologic drivers of global cardiovascular mortality. The New England journal of medicine 2015;372:1333-41.
4. Lloyd-Jones DM, Camargo CA, Allen LA, Giugliano RP, O'Donnell CJ. Predictors of long-term mortality after hospitalization for primary unstable angina pectoris and non-ST-elevation myocardial infarction. The American journal of cardiology 2003;92:1155-9.
5. Mauri L, Silbaugh TS, Garg P, et al. Drug-eluting or bare-metal stents for acute myocardial infarction. The New England journal of medicine 2008;359:1330-42.
6. Malenka DJ, Kaplan AV, Lucas FL, Sharp SM, Skinner JS. Outcomes following coronary stenting in the era of bare-metal vs the era of drug-eluting stents. Jama 2008;299:2868-76.
7. Furman MI, Dauerman HL, Goldberg RJ, Yarzebski J, Lessard D, Gore JM. Twenty-two year (1975 to 1997) trends in the incidence, in-hospital and long-term case fatality rates from initial Q-wave and non-Q-wave myocardial infarction: a multi-hospital, community-wide perspective. Journal of the American College of Cardiology 2001;37:1571-80.
8. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. The New England journal of medicine 2004;350:1495-504.
9. Croce K, Libby P. Intertwining of thrombosis and inflammation in atherosclerosis. Curr Opin Hematol 2007;14:55-61.
10. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. The New England journal of medicine 2005;352:1685-95.
11. Mulvihill NT, Foley JB. Inflammation in acute coronary syndromes. Heart 2002;87:201-4.
12. Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: from pathophysiology to practice. Journal of the American College of Cardiology 2009;54:2129-38.
13. Libby P. Mechanisms of acute coronary syndromes. The New England journal of medicine 2013;369:883-4.
14. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. The New England journal of medicine 2000;343:915-22.
15. Jaski BE, Cohen JD, Trausch J, et al. Outcome of urgent percutaneous transluminal coronary angioplasty in acute myocardial infarction: comparison of single-vessel versus multivessel coronary artery disease. American heart journal 1992;124:1427-33.
16. Muller DW, Topol EJ, Ellis SG, Sigmon KN, Lee K, Califf RM. Multivessel coronary artery disease: a key predictor of short-term prognosis after reperfusion therapy for acute myocardial infarction. Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Study Group. American heart journal 1991;121:1042-9.
17. Mauriello A, Sangiorgi G, Fratoni S, et al. Diffuse and active inflammation occurs in both vulnerable and stable plaques of the entire coronary tree: a histopathologic

study of patients dying of acute myocardial infarction. Journal of the American College of Cardiology 2005;45:1585-93.
18. Rioufol G, Finet G, Ginon I, et al. Multiple atherosclerotic plaque rupture in acute coronary syndrome: a three-vessel intravascular ultrasound study. Circulation 2002;106:804-8.
19. Lombardo A, Rizzello V, Natale L, et al. Magnetic resonance imaging of carotid plaque inflammation in acute coronary syndromes: a sign of multisite plaque activation. Int J Cardiol 2009;136:103-5.
20. Naruko T, Ueda M, Haze K, et al. Neutrophil infiltration of culprit lesions in acute coronary syndromes. Circulation 2002;106:2894-900.
21. Buffon A, Biasucci LM, Liuzzo G, D'Onofrio G, Crea F, Maseri A. Widespread coronary inflammation in unstable angina. The New England journal of medicine 2002;347:5-12.
22. Antonopoulos AS, Margaritis M, Lee R, Channon K, Antoniades C. Statins as anti-inflammatory agents in atherogenesis: molecular mechanisms and lessons from the recent clinical trials. Curr Pharm Des 2012;18:1519-30.
23. Bu DX, Griffin G, Lichtman AH. Mechanisms for the anti-inflammatory effects of statins. Curr Opin Lipidol 2011;22:165-70.
24. Spencer FA, Allegrone J, Goldberg RJ, et al. Association of statin therapy with outcomes of acute coronary syndromes: the GRACE study. Ann Intern Med 2004;140:857-66.
25. Saab FA, Eagle KA, Kline-Rogers E, Fang J, Otten R, Mukherjee D. Comparison of outcomes in acute coronary syndrome in patients receiving statins within 24 hours of onset versus at later times. The American journal of cardiology 2004;94:1166-8.
26. Heeschen C, Hamm CW, Laufs U, Snapinn S, Bohm M, White HD. Withdrawal of statins increases event rates in patients with acute coronary syndromes. Circulation 2002;105:1446-52.
27. Mampuya WM, Frid D, Rocco M, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. American heart journal 2013;166:597-603.
28. Ridker PM. Testing the inflammatory hypothesis of atherothrombosis: scientific rationale for the cardiovascular inflammation reduction trial (CIRT). J Thromb Haemost 2009;7 Suppl 1:332-9.
29. Nuki G, Simkin PA. A concise history of gout and hyperuricemia and their treatment. Arthritis Res Ther 2006;8 Suppl 1:S1.
30. Underwood M. Gout. BMJ Clin Evid 2015;2015.
31. Rosenthal AK, Ryan LM. Nonpharmacologic and pharmacologic management of CPP crystal arthritis and BCP arthropathy and periarticular syndromes. Rheum Dis Clin North Am 2014;40:343-56.
32. Lidar M, Livneh A. Familial Mediterranean fever: clinical, molecular and management advancements. Neth J Med 2007;65:318-24.
33. Imazio M. Contemporary management of pericardial diseases. Curr Opin Cardiol 2012;27:308-17.
34. Imazio M. Evaluation and management of pericarditis. Expert Rev Cardiovasc Ther 2011;9:1221-33.
35. Terkeltaub RA. Colchicine update: 2008. Semin Arthritis Rheum 2009;38:411-9.
36. Kallinich T, Haffner D, Niehues T, et al. Colchicine use in children and adolescents with familial Mediterranean fever: literature review and consensus statement. Pediatrics 2007;119:e474-83.

37. Putterman C, Ben-Chetrit E, Caraco Y, Levy M. Colchicine intoxication: clinical pharmacology, risk factors, features, and management. Semin Arthritis Rheum 1991;21:143-55.
38. Bhattacharyya B, Panda D, Gupta S, Banerjee M. Anti-mitotic activity of colchicine and the structural basis for its interaction with tubulin. Med Res Rev 2008;28:155-83.
39. Cronstein BN, Molad Y, Reibman J, Balakhane E, Levin RI, Weissmann G. Colchicine alters the quantitative and qualitative display of selectins on endothelial cells and neutrophils. J Clin Invest 1995;96:994-1002.
40. Imazio M, Bobbio M, Cecchi E, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the COlchicine for acute PEricarditis (COPE) trial. Circulation 2005;112:2012-6.
41. Imazio M, Bobbio M, Cecchi E, et al. Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (COlchicine for REcurrent pericarditis) trial. Arch Intern Med 2005;165:1987-91.
42. Imazio M, Brucato A, Cemin R, et al. Colchicine for recurrent pericarditis (CORP): a randomized trial. Ann Intern Med 2011;155:409-14.
43. Lilly LS. Treatment of acute and recurrent idiopathic pericarditis. Circulation 2013;127:1723-6.
44. Maisch B, Seferovic PM, Ristic AD, et al. Guidelines on the diagnosis and management of pericardial diseases executive summary; The Task force on the diagnosis and management of pericardial diseases of the European society of cardiology. European heart journal 2004;25:587-610.
45. Van Wagoner DR. Colchicine for the prevention of postoperative atrial fibrillation: a new indication for a very old drug? Circulation 2011;124:2281-2.
46. Deftereos S, Giannopoulos G, Kossyvakis C, et al. Colchicine for prevention of early atrial fibrillation recurrence after pulmonary vein isolation: a randomized controlled study. Journal of the American College of Cardiology 2012;60:1790-6.
47. Nidorf M, Thompson PL. Effect of colchicine (0.5 mg twice daily) on high-sensitivity C-reactive protein independent of aspirin and atorvastatin in patients with stable coronary artery disease. The American journal of cardiology 2007;99:805-7.
48. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. The New England journal of medicine 2000;342:836-43.
49. Biasucci LM, Liuzzo G, Colizzi C, Rizzello V. Clinical use of C-reactive protein for the prognostic stratification of patients with ischemic heart disease. Ital Heart J 2001;2:164-71.
50. Morrow DA, Rifai N, Antman EM, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in Myocardial Infarction. Journal of the American College of Cardiology 1998;31:1460-5.
51. Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. Journal of the American College of Cardiology 2013;61:404-10.
52. Raju NC, Yi Q, Nidorf M, Fagel ND, Hiralal R, Eikelboom JW. Effect of colchicine compared with placebo on high sensitivity C-reactive protein in patients with acute coronary syndrome or acute stroke: a pilot randomized controlled trial. J Thromb Thrombolysis 2012;33:88-94.
53. Huang C, Cen C, Wang C, Zhan H, Ding X. Synergistic effects of colchicine combined with atorvastatin in rats with hyperlipidemia. Lipids Health Dis 2014;13:67.

54. Langevitz P, Livneh A, Neumann L, et al. Prevalence of ischemic heart disease in patients with familial Mediterranean fever. Isr Med Assoc J 2001;3:9-12.
55. Crittenden DB, Lehmann RA, Schneck L, et al. Colchicine use is associated with decreased prevalence of myocardial infarction in patients with gout. J Rheumatol 2012;39:1458-64.
56. Deftereos S, Giannopoulos G, Raisakis K, et al. Colchicine treatment for the prevention of bare-metal stent restenosis in diabetic patients. Journal of the American College of Cardiology 2013;61:1679-85.
57. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology 2014;63:2889-934.
58. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). European heart journal 2011;32:2999-3054.
59. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European heart journal 2012;33:2569-619.
60. Both T, van Laar JA, Bonte-Mineur F, van Hagen PM, van Daele PL. [Colchicine has no negative effect on fertility and pregnancy]. Nederlands tijdschrift voor geneeskunde 2012;156:A4196.
61. National Cancer Institute NIoH, U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2009.
62. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.
63. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized Trial of Complete Versus Lesion-Only Revascularization in Patients Undergoing Primary Percutaneous Coronary Intervention for STEMI and Multivessel Disease: The CvLPRIT Trial. Journal of the American College of Cardiology 2015;65:963-72.
64. Rosner GF, Kirtane AJ, Genereux P, et al. Impact of the presence and extent of incomplete angiographic revascularization after percutaneous coronary intervention in acute coronary syndromes: the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. Circulation 2012;125:2613-20.
65. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. The New England journal of medicine 2011;364:226-35.
66. Chew DP, Amerena JV, Coverdale SG, et al. Invasive management and late clinical outcomes in contemporary Australian management of acute coronary syndromes: observations from the ACACIA registry. Med J Aust 2008;188:691-7.

Appendix 1 Definitions of outcome/clinical events

Acute coronary syndrome (ACS)	ACS is defined by presence of ischaemic symptoms AND one of the following: • Elevated cardiac troponin • ECG changes
Acute myocardial infarction (AMI)	Detection of a rise and/or fall of cardiac troponin with at least one value above the 99th percentile upper reference limit and with at least one of the following: • Symptoms of ischaemia • New or presumed new ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB) • Development of pathological Q waves in the ECG • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality • Identification of an intracoronary thrombus by angiography or autopsy
Unstable angina	Recent acceleration of ischaemic symptoms without a rise in serum troponin
Ischaemic-driven revascularization	Repeat revascularization is defined as: 1. Target lesion re-interventions (TLR) inside the implanted stent or within 5 mm proximally or distally or repeated interventions in the same vessel (TVR) by percutaneous coronary interventions (PCI) or by coronary artery bypass graft surgery. 2. PCI to lesions not identified previously 3. Coronary artery bypass graft surgery … as a result of recurrent ACS OR positive functional testing (exercise/dobutamine stress echo or nuclear stress testing) following recurrent ischaemic symptoms.
Non-cardioembolic ischaemic stroke	Computed tomography (CT)- or magnetic resonance imaging (MRI)-proven ischaemic stroke judged by the treating neurologist as not being due to atrial fibrillation or intracranial haemorrhage
Death due to cardiovascular disease	Death resulting from myocardial infarction, sudden cardiac death, death due to heart failure, and death due to stroke

Appendix 2 CYP3A4 and P-glycoprotein inhibitors

CYP3A4/5 inhibitors
aprepitant (moderate), atazanavir (moderate)
boceprevir (strong)
cimetidine, clarithromycin (strong), cobicistat (strong), crizotinib
darunavir, diltiazem (moderate)
erythromycin (moderate)
fluconazole (moderate), fluvoxamine, fosamprenavir (moderate)
grapefruit juice (moderate)
imatinib (moderate), indinavir (strong), itraconazole (strong)
ketoconazole (strong)
lopinavir
posaconazole (strong)
ritonavir (strong)
saquinavir (strong)
telaprevir (strong), ticagrelor, tipranavir
verapamil (moderate), voriconazole (strong)

P-glycoprotein inhibitors
amiodarone, azithromycin
carvedilol, clarithromycin, cobicistat, cyclosporin
erythromycin, everolimus
itraconazole
ketoconazole
lapatinib
ritonavir
telaprevir, ticagrelor (weak), tolvaptan
vandetanib (weak), verapamil

Information obtained from Australian Medicine Handbook (AMH)

Appendix 3 Data Collection Form

Baseline Data

Participant Study ID		
Enrolment Date		
Hospital UR		
Surname		
First name		
Date of birth		
Address		
Contact number	(T) (M)	
Alternative contact	Name: Contact no.:	
General Practitioner	Name:	
	Address:	
	Contact no.: (T) (F)	
Date of first hospital presentation		
Admission diagnosis	☐STEMI ☐NSTEMI ☐Unstable Angina	
Demographics		
Age		
Gender	☐Male ☐Female	
Medical history	Diabetes	☐Yes ☐No
	Hypertension	☐Yes ☐No
	Hypercholesterolaemia	☐Yes ☐No
	Smoking	☐Current ☐Ex-smoker ☐Non-smoker
	Family history of CAD	☐Yes ☐No
	Obesity (BMI>30)	☐Yes ☐No
	Previous stroke	☐Yes ☐No
	Previous MI	☐Yes ☐No
	Previous PCI	☐Yes ☐No
	Previous CABG	☐Yes ☐No
	Peripheral vascular disease	☐Yes ☐No
Pathology		

Full blood count	Haemoglobin	
	White cell count	
	Platelet count	
Renal function	Creatinine	
	eGFR (mL/min/1.73m^2)	
Liver function	ALT/AST	☐Normal ☐<2xULN ☐≥2xULN
	GGT/ALP	☐Normal ☐<2xULN ☐≥2xULN
	Bilirubin	☐Normal ☐<2xULN ☐≥2xULN
Coagulation	INR	☐<1.5 ☐≥1.5
	Is patient taking anticoagulant?	☐Yes ☐No
Fasting lipids	Total cholesterol	
	LDL	
	HDL	
	Triglyceride	
Glucose	Fasting glucose	
Cardiac enzymes	Max troponin elevation	
	Max CK elevation	
Angiographic characteristics		
Date of angiogram		
Infarct-related artery	Artery/branch: Segment: Proximal/Mid/Distal Severity of stenosis (%):	
Non-infarct related artery (≥2.5mm luminal diameter) with stenosis ≥30%	Artery/branch: Segment: Proximal/Mid/Distal Severity of stenosis (%):	
	Artery/branch: Segment: Proximal/Mid/Distal Severity of stenosis (%):	
	Artery/branch: Segment: Proximal/Mid/Distal Severity of stenosis (%):	
	Artery/branch: Segment: Proximal/Mid/Distal Severity of stenosis (%):	
EF (%)		

Procedural details	
Artery/branch stented	
Number of stents, *n*	
Type of stent	☐Bare metal stent ☐Drug eluting stent
Discharge medications	
Aspirin	☐Yes ☐No
Dual antiplatelet	☐Clopidogrel ☐Prasugrel ☐Ticagrelor ☐No
Statin	☐Yes ☐No
ACEI/ARB	☐Yes ☐No
Beta-blocker or CCB	☐Yes ☐No
Oral hypoglycaemic	☐Yes ☐No
Insulin	☐Yes ☐No
Adverse reaction to study drug	☐Yes, please specify: ☐No
Additional information if applicable	
Others	
For patient who is screened but not enrolled in the study, please do not include personally identifiable information on this form. This information (number of patient screened) is collected to assist the Trial Steering Committee in reviewing the progress of the project. Please provide reason for not enrolling this patient in the study: ☐Does not meet the eligibility criteria ☐Patient declines to participate ☐Others:	

Data collection at 1, 6 and 12 months

Patient study ID	
Primary Outcome	
Acute coronary syndrome	Date of event:
	Diagnosis: ☐STEMI ☐NSTEMI ☐Unstable angina
Revascularization ☐PCI ☐CABG	Date of procedure: Artery being revascularized: Lesion severity on previous angio (%):
	Date of procedure: Artery being revascularized: Lesion severity on previous angio (%):
	Date of procedure: Artery being revascularized: Lesion severity on previous angio (%):
Death	Date of event:
Non-cardioembolic Ischaemic stroke	Date of event:
Study withdrawal	
Withdrawal from study	☐Yes, Date of withdrawal: Reason: ☐No
Adverse reactions to the study drug	
Gastrointestinal	
Skin	
Alopecia	
Peripheral neuropathy	
Myalgia, myositis	
Myelosupression	
Medication compliance	
Aspirin	☐Yes ☐No
Dual antiplatelet therapy	☐Clopidogrel ☐Prasugrel ☐Ticagrelor
Statin	☐Yes ☐No

ACEI/ARB	☐Yes ☐No
Beta-blocker or CCB	☐Yes ☐No
Compliance to cardiac medications	☐Missed >1 dose/week ☐Missed ≤1 dose/week
Compliance to study drug	Number of pills left in the medication bottle:
Cessation of study drug	☐Yes, Date of cessation: Reason: ☐No
Additional information if applicable	

Appendix 4 Letter to General Practitioner

Dear Doctor,

Re: Name of Participant

Enrolment in 'Colchicine in Patients with Acute Coronary Syndromes – the COPS Trial'

This is to inform you that this patient is enrolled in the COPS trial – a study to investigate the long-term outcomes of colchicine in patients who present with acute coronary syndromes. The patient is randomised to receive *either* (a) placebo or (b) colchicine (0.5mg twice daily for the first month followed by 0.5mg daily for another 11 months), in addition to standard medical therapy. The patient will be followed up for 12 months by the research team.

Your patient and the hospital treating team do not know whether he/she is receiving placebo or colchicine tablets. The patient is given three months' supply of the study drug prior to discharge from the hospital and will be receiving subsequent medications from the study team via registered post.

Routine blood tests are not required for your patient. However, the patient should be monitored for serious (rare) side effects such as bone marrow suppression (bleeding, mouth ulcers or severe infection), peripheral neuropathy, myopathy and rhabdomyolysis.

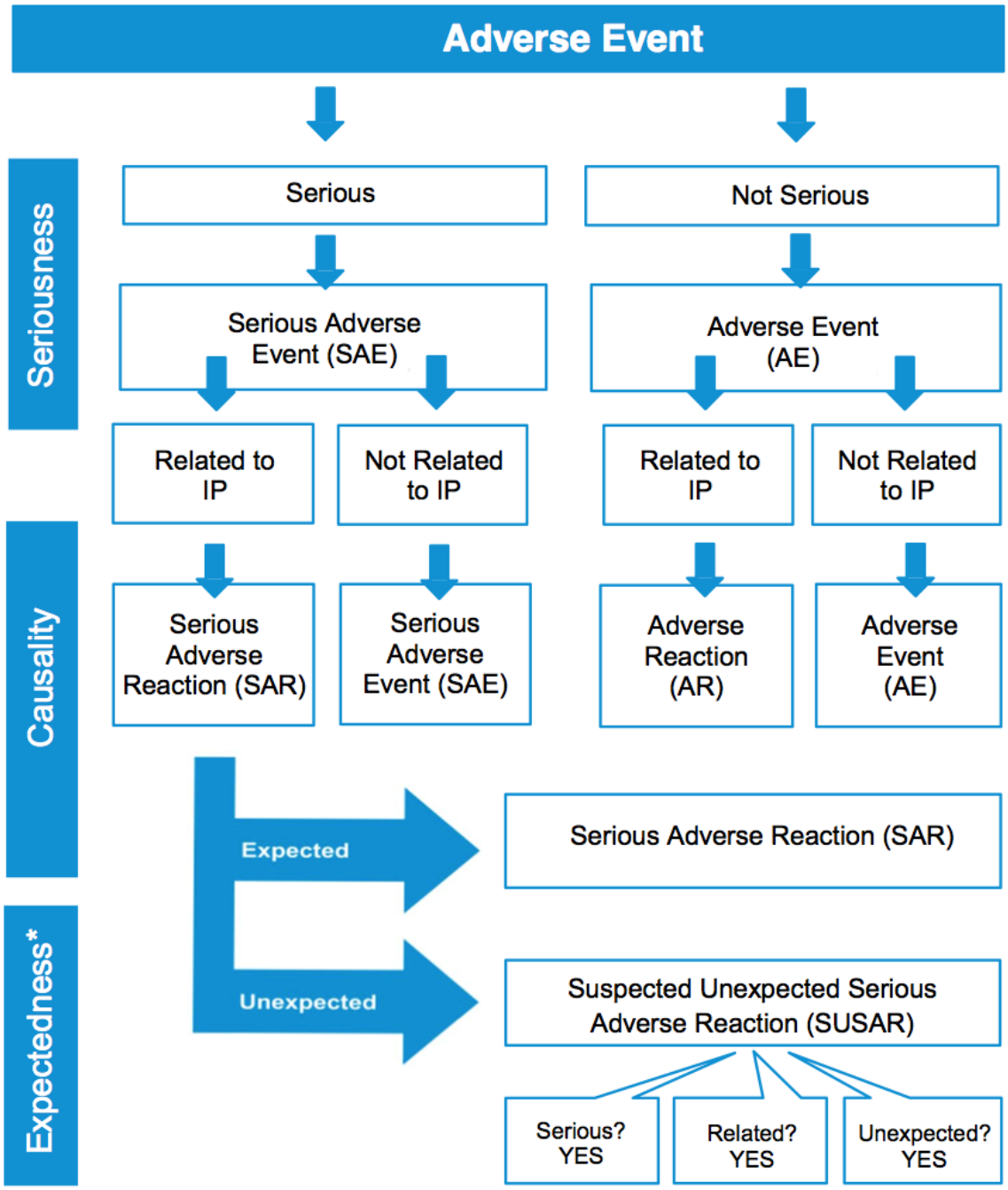
We recommend all doctors to exercise precaution in prescribing new medications that may interfere with colchicine metabolism. Medications that should be **avoided** include: cyclosporine, erythromycin, clarithromycin, antiretroviral and oral antifungal drugs. Further information is available online via the MIMS and Australian Medicine Handbook websites.

If you require further information regarding this project or if you have any concerns related to the patient's involvement in the project, please do not hesitate to contact the principal investigators at any time. Their contact details are:

Name: Dr David Tong	or	Dr Jamie Layland
Phone: (03) 9231 2211		(03) 9784 7777
Email: DavidCK.Tong@svhm.org.au		JLayland@phcn.vic.gov.au

Kind regards,
The COPS Study Team

Appendix 5 Safety Reporting Assessment Flowchart


Adverse Event
Seriousness
Serious
Not Serious
Serious Adverse Event (SAE)
Adverse Event (AE)
Causality
Related to IP
Not Related to IP
Related to IP
Not Related to IP
Serious Adverse Reaction (SAR)
Serious Adverse Event (SAE)
Adverse Reaction (AR)
Adverse Event (AE)
Expectedness*
Expected
Unexpected
Serious Adverse Reaction (SAR)
Suspected Unexpected Serious Adverse Reaction (SUSAR)
Serious? YES
Related? YES
Unexpected? YES

Glossary	
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product would qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship.
Investigational Medicinal Product (IMP)	A pharmaceutical form of an active substance or placebo being tested or used, as a reference in a Clinical Trial – refers to Colchicine in this study.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any adverse event or adverse reaction that results in death, is life-threatening*, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious. *Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
Suspected Unexpected Serious Adverse Reactions (SUSAR)	An adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the definition of a Serious Adverse Reaction

Adapted from T Symons Associates Ltd Clinical Research Consultancy's 'Safety reporting assessment flowchart' flyer. *http://www.ct-toolkit.ac.uk/__data/assets/pdf_file/0011/35021/safety-reporting-assessment-flowchart.pdf*

Appendix 6 Telephone Interview Structured Questions

1. Have you represented to emergency department or been admitted to hospital due to heart-related problem since you were last contacted by a research team member?
    a. What was the medical problem?
    b. What were you told of the diagnosis?
    c. Did you have another coronary angiogram or stent?
    d. Did you have a stroke?

2. Have you experienced any chest pain or discomfort similar to your heart attack pain?

3. Have you seen your GP?

4. How many study pills left in the medication bottle?

5. Have you experienced any side effects? Such as …
    a. Nausea, diarrhoea, abdominal bloating
    b. Skin rash or itch
    c. Excessive hair loss
    d. Muscle aches or weakness
    e. Tingling or numbness in the fingers or toes
    f. Gum bleeding, mouth ulcers, bruises, severe infection associated with low blood count

6. Are there any recent changes to your medications? What are they?

7. Are you taking any blood thinners such as ticagrelor (Brilinta), clopidogrel (Plavix) or prasugrel (Effient)? On average, do you miss more than one dose of the medication every week?

8. Are you taking cholesterol-lowering tablet? On average, do you miss more than one dose of the medication every week?

9. Have you ever missed any of the other heart tablets that were prescribed by your doctors? On average, do you miss more than one dose of your medications every week?

10. What is your current smoking status?

Appendix 7 EQ-5D-5L Questionnaire

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking around	❑	PLEASE TICK
I have some problems in walking around	❑	ONE BOX
I am confined to bed	❑	

Personal Care

I have no problems with personal care	❑	PLEASE TICK
I have some problems washing or dressing myself	❑	ONE BOX
I am unable to wash or dress myself	❑	

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑	PLEASE TICK
I have some problems with performing my usual activities	❑	ONE BOX
I am unable to perform my usual activities	❑	

Pain/Discomfort

I have no pain or discomfort	❑	PLEASE TICK
I have moderate pain or discomfort	❑	ONE BOX
I have extreme pain or discomfort	❑	

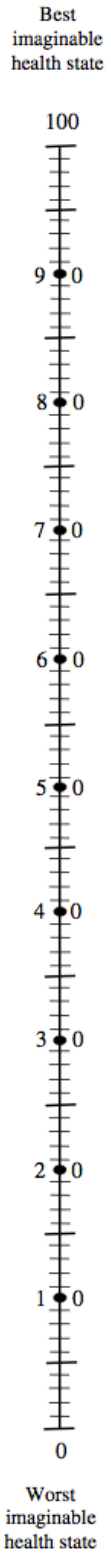
Anxiety/Depression

I am not anxious or depressed	❑	PLEASE TICK
I am moderately anxious or depressed	❑	ONE BOX
I am extremely anxious or depressed	❑	

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 8 Seattle Angina Questionnaire

The Seattle Angina Questionnaire

1. The following is a list of activities that people often do during a normal week. Although for some people with several medical problems it is difficult to determine what it is that limits them, please go over the activities listed below and indicate how much limitation you have had **due to chest pain, chest tightness, or anginal attacks over the past 4 weeks:**

Place an x in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not Limited at all	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Walking indoors on level ground	☐	☐	☐	☐	☐	☐
Showering	☐	☐	☐	☐	☐	☐
Climbing a hill or a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Gardening, vacuuming, or carrying groceries	☐	☐	☐	☐	☐	☐
Walking more than 100 m at a brisk pace	☐	☐	☐	☐	☐	☐
Running or jogging	☐	☐	☐	☐	☐	☐
Lifting or moving heavy objects like furniture or lifting children	☐	☐	☐	☐	☐	☐
Participating in strenuous sports (e.g. tennis, dancing)	☐	☐	☐	☐	☐	☐

2. Compared with 4 weeks ago, how often do you have **chest pain**, **chest tightness**, or **anginal attacks** when doing your **most strenuous** activities?

   I have **chest pain**, **chest tightness**, or **anginal attacks**...

Much more often	**Slightly more** often	About **the same**	**Slightly less** often	**Much less** often	I have had **no chest pain** over the last 4 weeks
☐	☐	☐	☐	☐	☐

3. Over the past 4 weeks, on average, how many times have you had **chest pain**, **chest tightness**, or **anginal attacks**?

   I have had **chest pain**, **chest tightness**, or **anginal attacks**...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

4. Over the past 4 weeks, on average, how many times have you had to use nitrolingual spray, or put an anginine, or isordil tablet under the tongue, to relieve **chest pain**, **chest tightness**, or **anginal attacks**?

   I have used them...

4 or more times per day	1-3 times per day	3 or more times per week but not every day	1-2 times per week	Less than once a week	None over the past 4 weeks
☐	☐	☐	☐	☐	☐

5. How bothersome is it for you to take your pills for **chest pain**, **chest tightness** or **anginal attacks** as prescribed?

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not** bothersome at all	My doctor has **not prescribed** pills
☐	☐	☐	☐	☐	☐

6. How satisfied are you that everything possible is being done to treat your **chest pain**, **chest tightness**, or **anginal attacks**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

7. How satisfied are you with the explanations your doctor has given you about your **chest pain**, **chest tightness**, or **anginal attacks**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

8. Overall, how satisfied are you with the current treatment of your **chest pain**, **chest tightness**, or **anginal attacks**?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

9. Over the <u>past 4 weeks</u>, how much has your **chest pain**, **chest tightness**, or **anginal attacks** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not** limited my enjoyment of life at all
☐	☐	☐	☐	☐

10. If you had to spend the rest of your life with your **chest pain**, **chest tightness**, or **anginal attacks** the way it is at the moment, how would you feel about this?

Not satisfied at all	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

11. How often do you think or worry that you may have a heart attack or die suddenly?

I think or worry about it **all the time**	I **often** think or worry about it	I **occasionally** think or worry about it	I **rarely** think or worry about it	I **never** think or worry about it
☐	☐	☐	☐	☐

Appendix 9 Colchicine Consumer Medicine Information (CMI)

Colgout®
Colchicine

Consumer Medicine Information

What is in this leaflet

This leaflet answers some common questions about Colgout. It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risks of you taking Colgout against the benefits they expect it will have for you.

If you have any concerns about taking this medicine, ask your doctor or pharmacist.

Keep this leaflet with the medicine.
You may need to read it again.

What Colgout is used for

Colgout contains colchicine as the active ingredient. Colgout is used for the relief of pain in acute attacks of gout. It is not an analgesic and does not provide relief from other types of pain.

Colgout has a preventative effect that helps to reduce the incidence of acute attacks. It will not reduce the amount of uric acid in the body.

Colgout belongs to a group of medicines called antigout drugs.

Ask your doctor if you have any questions about why Colgout has been prescribed for you.
Your doctor may have prescribed it for another reason.

This medicine is only available with a doctor's prescription.

There is no evidence that it is addictive.

Before you take it

When you must not take it

Do not take Colgout if you have an allergy to:

- any medicine containing colchicine
- any of the ingredients listed at the end of this leaflet.

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips or tongue; skin rash, itching or hives.

Do not give this medicine to children.
This medication may be dangerous to children. It is important that it is kept out of reach of children at all times.

Do not take Colgout if you have:

- combined kidney and liver disease
- serious kidney or liver disease
- serious heart disease
- severe stomach disorder
- a blood disorder.

Do not take this medicine after the expiry date (EXP) printed on the pack.
If you take this medicine after the expiry date has passed, it may not work as well.

Do not take this medicine if the bottle shows signs of having been tampered with.

If you are not sure whether you should start taking this medicine, talk to your doctor.

Before you start to take it

Tell your doctor if you are allergic to any other medicines or any foods, preservatives or dyes.

Tell your doctor if you have or have had any of the following medical conditions:

- stomach problems
- kidney or liver disease
- heart disease
- alcoholism.

Tell your doctor if you are pregnant or plan to become pregnant.
Colgout may affect your developing baby if you take it during pregnancy.

Tell your doctor if you are breast-feeding or plan to breastfeed.
Your doctor will discuss the risks and benefits of you taking Colgout when breast-feeding.

If you have not told your doctor about any of the above, tell them before you start taking Colgout.

Taking other medicines

Tell your doctor or pharmacist if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with Colgout. These include:

- cyclosporin - a medicine used to suppress the immune system
- erythromycin, clarithromycin and telithromycin - antibiotics used to treat bacterial infection
- protease inhibitors, including atazanavir, indinavir, nelfinavir, ritonavir and saquinavir, used to treat HIV and other viral infections
- ketoconazole and itraconazole, used to treat certain fungal infections
- nefazodone, used to treat depression
- acidifying and alkalinising agents, such as ammonium chloride, ascorbic acid (vitamin C), sodium bicarbonate
- medicines to help you sleep
- alcohol
- NSAIDs or aspirin - anti-inflammatory drugs used to treat pain
- medicines used to treat cancer including radiation therapy
- vitamin B12
- anticoagulants such as coumarin, heparin
- antithyroid medicines.

These medicines may be affected by Colgout or may affect how well it works. You may need to take different amounts of your medicines or you may need to take different medicines. Your doctor or pharmacist has a more complete list of medicines to be careful with or avoid while taking Colgout.

Use in elderly or debilitated patients

Elderly or debilitated patients may be more sensitive to the effects or side effects of this medicine.

How to take it

Follow all directions given to you by your doctor carefully.
They may differ from the information contained in this leaflet.

If you do not understand the instructions on the bottle, ask your doctor or pharmacist for help.

How much to take

Your doctor will tell you how much Colgout to take.

Do not take more than your doctor tells you to.

Do not take more than 12 tablets in total over 4 days.

How to take it

Swallow the tablet whole with a full glass of water.

When to take it

Colgout may be taken before or after food.

How long to take it

Continue taking your medicine for as long as your doctor tells you.
This will depend on your condition and your response to the treatment.

Colgout helps to control your condition but does not cure it.

Immediately stop taking Colgout at the first sign of stomach pain, nausea, vomiting or diarrhoea. Do this even if your symptoms have not been relieved.

If you forget to take it

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose that you missed.
This may increase the chance of you getting an unwanted side effect.

If you are not sure what to do, ask your doctor or pharmacist.

If you have trouble remembering to take your medicine, ask your pharmacist for some hints.

If you take too much (overdose)

Immediately telephone your doctor or the Poisons Information Centre (telephone 13 11 26) for advice, or go to Accident and Emergency at the nearest hospital if you think that you or anyone else may have taken too much Colgout. Do this even if there are no signs of discomfort or poisoning.

You may need urgent medical attention.

Symptoms of an overdose may include:

- severe nausea, vomiting, stomach pain and diarrhoea
- burning feeling or rawness in the mouth and throat
- difficulty in breathing or swallowing
- fever
- muscle weakness
- mental confusion, delirium, convulsions.

While you are taking it

Things you must do

Immediately stop taking Colgout at the first sign of stomach pain, nausea, vomiting or diarrhoea. Do this even if your symptoms have not been relieved.

Remember to take note of the number of tablets you took before the onset of these symptoms so that you can take fewer tablets during subsequent attacks.

Tell any other doctors, dentists, and pharmacists who are treating you that you are taking this medicine, especially if you are being started on any new medicines.

Tell your doctor, surgeon or anaesthetist that you are taking Colgout if you are about to undergo surgery or an operation.

Tell your doctor immediately if you become pregnant while taking Colgout.

If you are about to have any blood tests, remind your doctor that you are taking Colgout.
It may interfere with the results of some tests.

Keep all of your doctor's appointments so that your progress can be checked.
Your doctor may do some tests from time to time to make sure the medicine is working and to prevent unwanted side effects.

Things you must not do

Do not take Colgout to treat any other complaints unless your doctor tells you to.

Do not give your medicine to anyone else, even if they have the same condition as you.

Things to be careful of

Be careful driving or operating machinery until you know how Colgout affects you.

Check with your doctor or pharmacist before drinking alcohol while you are taking Colgout.
If you drink alcohol while taking this medicine, you may develop stomach problems.

This medication may be dangerous to children. It is important that it is kept out of reach of children at all times.

Side effects

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking Colgout.
This medicine helps most people with gout, but it may have unwanted side effects in a few people. All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

If you are elderly you may have an increased chance of getting side effects.

Ask your doctor or pharmacist to answer any questions you may have.

Immediately stop taking Colgout at the first sign of stomach pain, nausea, vomiting or diarrhoea. Do this even if your symptoms have not been relieved.

The above list includes the more common side effects of your medicine.

Tell your doctor as soon as possible if you notice any of the following:

- loss of appetite
- loss of hair.

The above list includes more serious side effects which may require medical attention.

Tell your doctor immediately, or go to Accident and Emergency at your nearest hospital if you notice any of the following symptoms:

- burning feeling in the stomach or throat
- severe stomach pain, nausea, vomiting
- severe diarrhoea with bloody or black tarry stools
- itchy skin, skin rash, hives, unusual bleeding or bruising under the skin
- difficulty in passing urine or blood in urine
- confusion, convulsions
- fever
- muscle weakness
- numbness or weakness in the fingers and toes.

These are all very serious side effects. You may need urgent medical attention or hospitalisation.

Tell your doctor or pharmacist if you notice anything else that is making you feel unwell.
Some people may get other side effects while taking Colgout.

Some of these side effects (e.g. changes in thyroid function or in the blood) can only be found when your doctor does tests from time to time to check your progress.

Do not be alarmed by this list of possible side effects.
You may not experience any of them.

After taking it

Storage

Keep your tablets in the bottle until it is time to take them.
If you take the tablets out of the bottle they may not keep well.

Keep your tablets in a cool dry place where the temperature stays below 30°C.

Do not store Colgout or any other medicine in the bathroom or near a sink. Do not leave it on a window sill or in the car.
Heat and dampness can destroy some medicines.

Keep it where children cannot reach it.
A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop taking Colgout or the expiry date has passed, ask your pharmacist what to do with any medicine that is left over.

Product description

What it looks like

Colgout tablets are round, white tablets and are available in bottles of 30.

Ingredients

Active ingredient:
Each tablet contains 0.5 mg of colchicine.

Inactive ingredients:

- magnesium stearate
- lactose
- starch-maize
- povidone.

Sponsor

Aspen Pharmacare Australia Pty Limited
34-36 Chandos Street
St Leonards NSW 2065
Australia

Australian Registration Number:
AUST R 27909

This leaflet was prepared in December 2011.

Appendix 10 Checklist for Site Principal Investigators

1	Written consent is obtained	
2	For female participants of childbearing age, confirm a negative serum or urine pregnancy test prior to first dose of study drug	
3	Perform web-based randomisation	
4	Signed copy of PICF/consent given to participant	
5	Quality of life questionnaires given to participant tot complete	
6	Colchicine consumer medicine information (CMI) given to participant	
7	Ensure participant's contact details are correct	
8	Ensure participant's GP details are correct	
9	Ensure participant receives 3 months' supply of study drug prior to discharge	
10	Complete data collection form. Attach quality of life questionnaires. Attach angiogram (and echocardiogram if available) reports. Attach consent form. Scan and email OR fax to chief principal investigators.	