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# Colchicine for the secondary prevention of cardiovascular events (Protocol)

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[Intervention Protocol]

# Colchicine for the secondary prevention of cardiovascular events

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## ABSTRACT

### Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To evaluate the benefits and harms of low-dose colchicine in the prevention of cardiovascular events in adults with a history of stable CVD or following myocardial infarction or stroke.

# BACKGROUND

## Description of the condition

Cardiovascular disease (CVD) is the leading cause of death and disease burden worldwide (WHO 2016), and despite improvements in primary prevention (to prevent the onset of the disease) and secondary prevention (to reduce the risk of occurrence of a CVD event in individuals with existing CVD), its burden continues to increase globally (Roth 2020; WHO CVDs 2021). The main contributing factor to the progression of CVD is atherosclerosis, that is, the deposition of cholesterol deposits known as 'plaques' inside blood vessels, that build up and impede blood flow (Libby 2013; Shah 2003; Shah 2009). The standard of care for decreasing the occurrence of cardiovascular events includes intensive modification of risk factors, such as blood pressure and cholesterol levels. However, recently, the general understanding about how atherosclerosis progresses has shifted towards the inflammatory hypothesis (Blankenberg 2006; Boland 2021; DeWeerdt 2021; Moriya 2019). It has been shown that chronic low-grade inflammation is the key contributing factor in both the initiation and the progression of atherosclerotic lesions (Hansson 2005; Libby 2009). Research shows that high levels of inflammatory cytokines occur in atherosclerotic plaques (Whayne 2020), inflammatory cells concentrate at ruptured plaques (Carr 1997; Libby 2013), and high levels of inflammatory markers (C-reactive protein, CRP) in the blood are associated with a higher risk of coronary events (The Emerging Risk Factors Collaboration 2010). As a consequence, several anti-inflammatory drugs have been proposed to target inflammation in CVD.

## Description of the intervention

Colchicine is an ancient drug with strong anti-inflammatory effects (Niel 2006). For centuries, acute gout was treated with extracts from autumn crocus (*Colchicum autumnale*) (Cocco 2010; Slobodnick 2015), until the active pharmaceutical ingredient (the lipophilic alkaloid, colchicine) was identified in the 18th century (Slobodnick 2015; Slobodnick 2018). Colchicine blocks cell division, specifically mitosis, by binding to tubulin and preventing the elongation of microtubules. At lower concentrations it leads to microtubule arrest, and at higher concentrations it leads to microtubule depolymerization (Dalbeth 2014). Although the exact mechanisms by which colchicine acts on the immune system are not fully understood, it appears to exert anti-inflammatory effects through multiple modes of action, which, together, result in altered leukocyte adhesion and migration, as well as cytokine production and secretion (Leung 2015; Slobodnick 2018). In addition to gout, colchicine is used to treat numerous systemic inflammatory diseases, including familial Mediterranean fever, Behçet's disease, primary biliary cirrhosis, and pericarditis (Cocco 2010; Imazio 2020; Slobodnick 2018). In clinical practice it is important to note that the therapeutic window of colchicine is relatively narrow and inter-individual pharmacokinetic variability is high (D'Amario 2021; Leung 2015; Niel 2006). At low doses the most commonly reported adverse effects are usually mild and transient gastrointestinal symptoms, such as abdominal pain, diarrhoea or nausea.

Chronic low-grade inflammations with elevated inflammatory biomarkers such as high-sensitivity C-reactive protein (hs-CRP) have been shown to be predictive of future major adverse cardiovascular events (MACE). Colchicine has been shown to reduce systemic and intracoronary concentrations of several pro-inflammatory mediators significantly (Kurup 2021; Masding 2009; Tardif 2021; Whayne 2020). A number of trials in the field of cardiovascular prevention and treatment have used low-dose colchicine given over six months in doses of 0.5 mg/day (Hemkens 2016), and 1 mg/day (Imazio 2020), in people with established cardiovascular disease, i.e. coronary artery disease or recent myocardial infarction.

## How the intervention might work

Treatment with colchicine is associated with lower intracoronary levels of several pro-inflammatory mediators in the context of both acute and chronic coronary syndromes (Nidorf 2007; Pello 2021; Tucker 2019). It inhibits the major inflammatory pathways that lead to the development or destabilization of atherosclerotic plaques. The anti-inflammatory effects of colchicine are expected to reduce the incidence of plaque ruptures and would thus reduce rates of cardiovascular events in people at high cardiovascular risk (Samuel 2020).

In animals, colchicine seems to prevent adverse cardiac remodelling after myocardial infarction, and reduces the infarct size and area of post-infarct fibrosis (Akodad 2017; Fujisue 2017). In vitro studies have shown an association with reduced platelet aggregation, which would be highly beneficial in the context of CVD (Cimmino 2018). During an acute coronary syndrome event, there is an exacerbation of inflammatory processes, which is why an effective reduction of inflammation might provide benefits - especially in the aftermath of an acute myocardial infarction. In recent years, several studies have attempted to confirm whether low-dose colchicine reduces rates of adverse cardiovascular events in people with stable coronary artery disease or recent myocardial infarction (Pello 2021; Samuel 2021). Colchicine has several advantages over the anti-inflammatory drugs that have been tested to date, in that it is inexpensive and widely used for several medical conditions, and shows protective effects against cardiovascular diseases in patients with gout (Ma 2021).

## Why it is important to do this review

In 2016, the first Cochrane Review on this topic summarized the available evidence for both primary and secondary CVD prevention. It showed that colchicine may provide substantial benefit and reduce the risk of myocardial infarction in secondary CVD prevention, as indicated by a statistically significant dose effect of colchicine on all-cause mortality in favour of lower-dose treatment (i.e. 0.5 mg to 1 mg; P = 0.03) (Hemkens 2016). The review also concluded that more evidence from large-scale randomized trials was needed. Since then, several other large randomized trials have provided new evidence, and the US Food and Drug Administration (FDA) recently approved low-dose colchicine (0.5 mg per day) as the first anti-inflammatory treatment for secondary prevention of CVD to reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, and cardiovascular death in adult patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease (FDA Approval 2023).

Recent non-Cochrane meta-analyses have attempted to pool the data and to provide a thorough overview of the effects of colchicine (Kassab 2021; Xia 2021; Xiang 2021), but its role in the treatment of CVD is still not established, and current guidelines state that low-dose colchicine should only be considered in secondary prevention

of CVD in patients with inadequately controlled risk factors or recurrent CVD events, despite optimal therapy (Visseren 2021).

It is now time to update the original Cochrane Review (Hemkens 2016). A decision has been made to split it into two separate reviews; this one addressing secondary prevention, and another that is still in development addressing primary prevention (Martí-Carvajal 2022). This review will focus on the secondary prevention of CVD and follows the methodology of the original review (Hemkens 2016), and its protocol (Hemkens 2014), closely.

## OBJECTIVES

To evaluate the benefits and harms of low-dose colchicine in the prevention of cardiovascular events in adults with a history of stable CVD or following myocardial infarction or stroke.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include individually randomized controlled trials (RCTs). We will include studies reported as full-text, those published as abstracts only, and unpublished data. We will exclude cluster-randomized trials, cross-over randomized trials, 'N-of-1' trials (multiple cross-over trials, usually randomized and often blinded, conducted in a single patient) (Shamseer 2015), trials described as 'pseudo-randomized' or 'quasi-randomized' (sequence of numbers that appears to be statistically random, despite having been produced by a deterministic process), and non-randomized (observational) research.

#### Types of participants

We will include trials in people of any age with any condition or disease but with a history of stable CVD, or following myocardial infarction or stroke. We will only consider studies where at least 90% of participants had a history of stable CVD, or had experienced myocardial infarction or stroke, or studies that reported subgroups that included 90% of participants with these characteristics.

#### Types of interventions

We will include trials that compare treatment with colchicine for any condition or any disease on a continuous basis (treatment over at least six months at any dose and with any type of application) with non-active treatment (e.g. placebo), or with no treatment. Trials with active comparators will be excluded. We will accept any co-interventions, provided they are identical in the study groups compared and not part of the treatment that is randomized.

#### Types of outcome measures

Colchicine is typically intended to be used as lifelong treatment for a chronic condition. Thus, we require a sufficiently long treatment duration to allow valid assessment of its long-term benefits and harms. Therefore, we will only use data obtained a minimum of six months after randomization, and the longest available follow-up for any of the outcomes.

If a published report does not appear to report one of our outcomes of interest, we will access the trial protocol and contact the trial authors to ascertain whether the outcomes were measured, but not reported. This will only be done if the trial fulfils criteria for follow-up and other inclusion criteria. Studies where no relevant outcomes are reported and where we receive no information from the trialists will be placed in the awaiting classification section. We will not request data from trialists for subgroup analyses we intend to perform, or for data from subgroups they may have included in eligible studies.

For all outcomes, we will use the number of participants with at least one event (except for quality of life). If the number of participants with at least one event is not reported, we will describe this issue, but we will not use the data for analyses.

##### *Primary outcomes*

1. All-cause mortality
2. Myocardial infarction
3. Serious adverse events

Following the US Food and Drug Administration (FDA) definition, we will consider an adverse event or suspected adverse reaction to be serious if it results in any of the following outcomes:

1. death;
2. a life-threatening adverse event;
3. inpatient hospitalization or prolongation of existing hospitalization;
4. a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
5. a congenital anomaly or birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgement, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include:

1. allergic bronchospasm requiring intensive treatment in an emergency room or at home;
2. blood dyscrasias;
3. convulsions that do not result in inpatient hospitalization; or
4. the development of drug dependency or drug abuse (FDA 2019).

If adverse events are reported as 'serious' but the definition is unclear, and if this cannot be clarified with the authors, or the definition does not agree with the FDA version (FDA 2019), we will consider these outcomes 'serious' for the main analysis, but will exclude such studies in a sensitivity analysis.

We will not consider composites of the three primary outcomes listed above.

##### *Secondary outcomes*

1. Cardiovascular mortality
2. Stroke
3. All-cause hospitalizations
4. Coronary revascularization (percutaneous coronary intervention (PCI)/angioplasty or coronary artery bypass graft (CABG))
5. Quality of life

6. Gastrointestinal adverse events (i.e. diarrhoea, nausea, abdominal pain, or vomiting)

We will not consider composites of the six secondary outcomes listed above.

For quality of life we will use only data reported using validated scales (such as SF-36) (Ware 1992). Should data for quality of life be reported from non-validated scales, or if cost data are available in any eligible study, we will comment on these in a narrative form. We will prefer a global quality-of-life scale (e.g. SF-36) over disease-specific scales.

We will consider gastrointestinal adverse events that are specifically reported as 'diarrhoea', 'nausea', 'abdominal pain', or 'vomiting' (Hemkens 2016).

## Search methods for identification of studies

### Electronic searches

We will identify trials through systematic searches of the following bibliographic databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (latest issue);
2. MEDLINE (Ovid) (1 January 2015 onwards);
3. Embase (Elsevier) (1 January 2015 onwards).

We will use the search strategies that were developed in the original review (Hemkens 2016). The Embase strategy was originally run on the Ovid platform, but will be adapted for the Elsevier platform, since our institutional licences have been changed (Appendix 1: Appendix 2; Appendix 3). As the searches in Hemkens 2016 were conducted on 22 January and 30 January 2015, we will search all databases from 1 January 2015 to the present, and we will impose no restrictions on language of publication or publication status.

For ongoing or unpublished trials, we will not conduct a separate search in ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch), since the registry entries are collected for inclusion in CENTRAL on a daily or weekly basis (Cochrane Library 2023).

### Searching other resources

We will check reference lists of all included studies, and any relevant systematic reviews that are identified, for additional references to trials. We will also examine any relevant retraction statements and errata for included studies.

We will investigate published FDA approval documents for colchicine in cardiovascular disease in the drugs@FDA database, considering the framework by Ladanie 2018.

We will not perform a separate search for adverse effects of interventions used for the prevention of cardiovascular events. Thus, we will only consider the adverse effects described in the included studies.

## Data collection and analysis

### Selection of studies

Two review authors (two from FE, JH, CS, PJ, MB) will independently screen titles and abstracts for inclusion of all the potential studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible or unclear) or 'do not retrieve'. If there are any disagreements, a third author will be asked to arbitrate (LGH or MB). We will retrieve full-text publications of all we mark as 'retrieve', and two review authors (two from FE, JH, CS, PJ, MB) will independently screen the full-texts and identify studies for inclusion, and record reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult with a third person (LGH or MB). In case of any uncertainties regarding the eligibility of a study, we will contact the authors to confirm eligibility.

We will identify and exclude duplicates and collate multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Page 2021).

### Data extraction and management

We will use a data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. One review author (from FE, JH, CS, PJ, MB) will extract study characteristics from included studies and a second author will verify the extractions. We will extract the following study characteristics.

1. **Methods:** study design, total duration of study, number of study centres and location, study setting, and date of study
2. **Participants:** number randomized, number lost to follow-up/withdrawn, number analyzed (per outcome for outcomes relevant to this review), mean or median age, age range, sex or gender (as reported), condition and severity of cardiovascular disease and diagnostic criteria (at baseline or time point of randomization; as reported), inclusion criteria, and exclusion criteria
3. **Interventions:** colchicine dose, comparison, concomitant medications and therapy, and prohibited medications and therapy
4. **Outcomes:** primary and secondary outcomes and time points reported
5. **Notes:** funding for trial, and notable conflicts of interest of trial authors

Two review authors (from FE, JH, CS, PJ, MB, LGH) will independently extract outcome data from the included studies. We will resolve disagreements by consensus or by involving a third person (LGH or MB). One review author (FE) will transfer data into Review Manager Web (RevMan Web 2023). We will double-check that data have been entered correctly by comparing the data presented in the review with the data extraction forms. A second review author (LGH) will spot-check study characteristics for accuracy against trial reports.

### Assessment of risk of bias in included studies

Two review authors (from FE, JH, CS, PJ, MB, LGH) will independently assess risk of bias on an intention-to-treat effect

basis (this resembles the clinical question of whether treatment with colchicine should be started with the goal of adhering to it). The risk of bias assessment relates to the outcomes as analysed (i.e. regarding the time point of assessment). We will use the new version of the Cochrane risk of bias tool (RoB 2) (Higgins 2023a), as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2023b). We will resolve any disagreements by discussion or by involving another author (from FE, JH, CS, PJ, MB, or LGH). We will assess the risk of bias of a specific outcome of a trial according to the following domains:

1. bias arising from the randomization process;
2. bias due to deviations from intended interventions;
3. bias due to missing outcome data;
4. bias in measurement of the outcome; and
5. bias in selection of the reported result.

We will assess the risk of bias for the outcomes that will be included in our summary of findings table.

We will use the signalling questions in the RoB 2 tool and rate each domain as having 'low risk of bias', 'some concerns' or 'high risk of bias'. We will summarize the risk of bias judgements across different studies for each of the domains listed for each outcome. The overall risk of bias for the result will be the least favourable assessment across the domains of bias.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Risk of bias assessment will be managed using the RoB 2 Excel tool (Higgins 2019). Detailed RoB 2 data will be provided as supplementary data.

### Measures of treatment effect

We will analyze dichotomous data as risk ratios and absolute risk differences with 95% confidence intervals. For dichotomous data, we will present relative risks and absolute risk differences with 95% confidence intervals. We will analyze continuous data as mean differences or standardized mean differences depending on whether outcomes are assessed by means of the same measurement scales, or not. In our interpretation, we will consider effects which are larger than 0.2 (Hedges g) as clinically relevant (IQWiG 2020), unless we identify established frameworks for minimal clinical important differences (MCID) with a different MCID.

We will undertake meta-analyses only where this is meaningful, that is, if the treatments, participants and the underlying clinical questions are similar enough for pooling to make sense.

### Unit of analysis issues

We will include RCTs with parallel group design (unit of randomization will typically be the individual participant) and we do not anticipate any major unit of analysis issues. If a study includes multiple intervention groups, we will not include the same intervention group more than once in the meta-analyses. We will split groups with shared individuals into two groups to ensure having pair-wise independent comparisons (Higgins 2023b).

### Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and to obtain missing numerical outcome data where needed (e.g. when a study is identified as abstract only). Where this is not possible, and the missing data are thought to introduce serious risk of bias (e.g. because of a very high percentage of missing data, substantial differences in missing data; considering the framework described by Guyatt 2017), we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

### Assessment of heterogeneity

We will inspect forest plots visually to consider the direction and magnitude of effects and the degree of overlap between confidence intervals. We will use the $I^2$ statistic to measure heterogeneity among the trials in each analysis, but acknowledge that there is substantial uncertainty in the value of $I^2$ when only a small number of studies is pooled. We will also consider the P value from the $Chi^2$ test.

Given the wide perspective of the review, with broad inclusion criteria and highly diverse fields of application of the intervention in various settings, we do not expect the true effects of the intervention to be homogeneous.

### Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study biases for the primary outcomes.

### Data synthesis

We will undertake meta-analyses only where this is meaningful, that is, if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. We will not exclude trials from meta-analysis on the basis of the risk of bias assessments.

We will use a random-effects model to synthesize the identified treatment effects, because we anticipate that the true effects of colchicine treatment will be very variable across included studies, especially given our broad inclusion criteria.

If we are unable to conduct a meta-analysis on an outcome, we will consider the Synthesis Without Meta-analysis (SWiM) guidelines (Campbell 2020).

### Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analyses that focus on people with previous myocardial infarction versus people without previous myocardial infarction but with established CVD.

We also plan to carry out additional subgroup analyses according to the following parameters:

1. colchicine dose (≤ 1 mg/day versus > 1 mg/day);
2. type of condition for which colchicine was given.

We will assess the following outcomes in the additional subgroup analyses:

1. all-cause mortality;

2. myocardial infarction;
3. serious adverse events;
4. stroke.

Subgroup analyses will only be conducted if there are at least three studies per subgroup category. We will use the formal test for subgroup differences in RevMan Web ($Chi^2$ test, P value) and base our interpretation on this.

### Sensitivity analysis

We plan to carry out the following sensitivity analyses, to test whether key methodological factors or decisions have affected the main results:

1. including only studies with an overall low risk of bias (all outcomes);
2. including only studies with a definition of serious adverse events that clearly agrees with the FDA definition (FDA 2019) (for serious adverse events only).

When missing data are thought to have introduced serious bias, we will explore the impact of including such studies in the overall assessment of results by an additional sensitivity analysis.

### Summary of findings and assessment of the certainty of the evidence

We will create a summary of findings table for colchicine versus no colchicine interventions as this is the only comparison we expect. We will use the following outcomes:

1. all-cause mortality;
2. myocardial infarction;
3. serious adverse events;
4. cardiovascular mortality;
5. stroke;
6. all-cause hospitalizations;
7. coronary revascularization.

We will use the five GRADE considerations (study limitations (risk of bias), consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. The overall RoB 2 judgement will be used to feed into the GRADE assessment. We will use methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2023), and use GRADEpro software (GRADEpro GDT 2022). We will justify all decisions to downgrade the certainty of the evidence using footnotes, and we will make comments to aid the reader's understanding of the review.

Judgements about certainty of the evidence (very low, low, moderate, and high certainty) will be made by two review authors (two of FE, JH, PJ, MB or LGH) working independently, with disagreements resolved by discussion or involving a third author (MB or LGH). Judgements will be justified, documented and incorporated into the reporting of results for each outcome.

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This protocol is based on a previous Cochrane Review Hemkens 2016 and the corresponding protocol.

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# APPENDICES

## Appendix 1. MEDLINE (Ovid) search strategy

1. exp Colchicine/
2. colcemid*.tw.
3. demecolcine.tw.
4. colchamine.tw.
5. lumicolchicine*.tw.
6. gamma-lumicolchicine*.tw.
7. beta-lumicolchicine.tw.
8. colchicin*.tw.
9. colchichine.tw.
10. aqua colchin.tw.
11. colchicum.tw.
12. colchily.tw.

13. colchimedio.tw.
14. colchiquim.tw.
15. colchisol.tw.
16. colchysat.tw.
17. colcine.tw.
18. colcrys.tw.
19. colgout.tw.
20. goutichine.tw.
21. goutnil.tw.
22. kolkicin.tw.
23. nsc 757.tw.
24. tolchicine.tw.
25. or/1-24
26. randomized controlled trial.pt.
27. controlled clinical trial.pt.
28. randomized.ab.
29. placebo.ab.
30. clinical trials as topic.sh.
31. randomly.ab.
32. trial.ti.
33. 26 or 27 or 28 or 29 or 30 or 31 or 32
34. exp animals/ not humans.sh.
35. 33 not 34
36. 25 and 35
37. (trial* or random*).tw.
38. 33 or 37
39. 38 not 34
40. 25 and 39

## Appendix 2. CENTRAL (Cochrane Library) search strategy

#1 MeSH descriptor: [Colchicine] explode all trees
#2 colcemid*
#3 demecolcine
#4 colchamine
#5 lumicolchicine*
#6 gamma-lumicolchicine*
#7 beta-lumicolchicine
#8 colchicin*
#9 colchichine
#10 aqua next colchin
#11 colchicum
#12 colchily
#13 colchimedio
#14 colchiquim
#15 colchisol
#16 colchysat
#17 colcine
#18 colcrys
#19 colgout
#20 goutichine
#21 goutnil
#22 kolkicin
#23 nsc next 757
#24 tolchicine
#25 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
Limit to CENTRAL/Trials

## Appendix 3. Embase (Elsevier) search strategy

1. colchicine/exp
2. colcemid*:ti,ab,kw

3. demecolcine:ti,ab,kw
4. colchamine:ti,ab,kw
5. lumicolchicine*:ti,ab,kw
6. gamma-lumicolchicine*:ti,ab,kw
7. beta-lumicolchicine:ti,ab,kw
8. colchicin*:ti,ab,kw
9. colchichine:ti,ab,kw
10. aqua colchin:ti,ab,kw
11. colchicum:ti,ab,kw
12. colchily:ti,ab,kw
13. colchimedio:ti,ab,kw
14. colchiquim:ti,ab,kw
15. colchisol:ti,ab,kw
16. colchysat:ti,ab,kw
17. colcine:ti,ab,kw
18. colcrys:ti,ab,kw
19. colgout:ti,ab,kw
20. goutichine:ti,ab,kw
21. goutnil:ti,ab,kw
22. kolkicin:ti,ab,kw
23. nsc 757:ti,ab,kw
24. tolchicine:ti,ab,kw
25. or/1-24
26. random*:ti,ab,kw
27. factorial*:ti,ab,kw
28. crossover*:ti,ab,kw
29. cross over*:ti,ab,kw
30. cross-over*:ti,ab,kw
31. placebo*:ti,ab,kw
32. (doubl* NEAR/3 blind*):ti,ab,kw
33. (singl* NEAR/3 blind*):ti,ab,kw
34. assign*:ti,ab,kw
35. allocat*:ti,ab,kw
36. volunteer*:ti,ab,kw
37. crossover procedure/exp
38. double blind procedure/exp
39. randomized controlled trial/exp
40. single blind procedure/exp
41. or/26-40
42. (animal/exp or nonhuman/exp) NOT human/exp
43. #41 NOT #42
44. 25 AND 43
45. limit 44 to embase: #44 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

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Concept and design: Ebrahimi, Hemkens.

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CS declares having no conflicts of interest.

HE declares having no conflicts of interest.

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PJ declares having no conflicts of interest.

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