Supplementary materials

Appendix 1 : PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: Recommended items to address in a systematic review protocol

Section and topic	Item	Checklist item
ADMINISTRATIVE INFORMATION		
Title :		
Identification	1a	Identify the report as a protocol of a systematic review **See title**
Update	1b	If the protocol is for an update of a previous systematic review, identify as such **Not applicable**
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number **See Methods**
Authors :		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author **See footnotes**
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review **See footnotes**
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments **Not applicable**
Support :		
Sources	5a	Indicate sources of financial or other support for the review **See footnotes (none)**
Sponsor	5b	Provide name for the review funder and/or sponsor **See footnotes (none)**
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol **See footnotes (none)**
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known **See introduction**

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) **See introduction**
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review **See methods**
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage **See methods**
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated **See methods and additional file 2**
STUDY RECORDS		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review **See methods**
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) **See methods**
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators **See methods**
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications. **See methods**
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale **See methods**
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis **See methods**
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised **See methods**

	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ) **See methods**
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) **See methods**
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned **See methods**
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) **Not applicable**
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) **See methods**

Appendix 2 : Search strategies

Step 1. Identifying systematic reviews

Ovid - Medline

1. exp Vitamin D/
2. ((d? adj1 vitamin*) or cholecalciferol* or calciol or calcifediol or hydroxycholecalciferol* or dihydroxycholecalciferol* or calciferol* or hydroxyvitamin d or hydroxyvitamin d? or dihydroxyvitamin d or dihydroxyvitamin d? or dihydrotachysterol*).tw.
3. calcium.hw.
4. calcium.tw.
5. exp Fractures, Bone/
6. (fractur* or microfractur*).tw.
7. Accidental Falls/
8. (falls or faller$1).tw.
9. 1 or 2 or 3 or 4
10. 5 or 6 or 7 or 8
11. 9 and 10
12. (systematic review or meta-analysis).pt.
13. meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/
14. ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.
15. ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.
16. ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.

17. (data synthes* or data extraction* or data abstraction*).ti,ab,kf.
18. (handsearch* or hand search*).ti,ab,kf.
19. (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.
20. (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.
21. (meta regression* or metaregression*).ti,ab,kf.
22. (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
23. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
24. (cochrane or (health adj2 technology assessment) or evidence report).jw.
25. (comparative adj3 (efficacy or effectiveness)).ti,ab,kf.
26. (outcomes research or relative effectiveness).ti,ab,kf.
27. ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.
28. (meta-analysis or systematic review).md.
29. (multi* adj3 treatment adj3 comparison*).ti,ab,kf.
30. (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.
31. umbrella review*.ti,ab,kf.
32. (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
33. (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.
34. (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
35. or/12-34
36. 11 and 35
37. limit 36 to yr="2014 -Current"

Ovid - Embase

1. exp Vitamin D/
2. ((d? adj1 vitamin*) or cholecalciferol* or calciol or calcifediol or hydroxycholecalciferol* or dihydroxycholecalciferol* or calciferol* or hydroxyvitamin d or hydroxyvitamin d? or dihydroxyvitamin d or dihydroxyvitamin d? or dihydrotachysterol*).tw.
3. Calcium/ or calcium intake/ or calcium carbonate/ or Calcium Gluconate/
4. calcium.tw.
5. 1 or 2 or 3 or 4
6. exp bone injury/
7. (fractur* or microfractur*).tw.
8. Falling/
9. (falls or fallers).tw.
10. 6 or 7 or 8 or 9
11. 5 and 10
12. (systematic review or meta-analysis).pt.
13. meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/
14. ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.
15. ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.

16. ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.
17. (data synthes* or data extraction* or data abstraction*).ti,ab,kf.
18. (handsearch* or hand search*).ti,ab,kf.
19. (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.
20. (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.
21. (meta regression* or metaregression*).ti,ab,kf.
22. (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
23. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
24. (cochrane or (health adj2 technology assessment) or evidence report).jw.
25. (comparative adj3 (efficacy or effectiveness)).ti,ab,kf.
26. (outcomes research or relative effectiveness).ti,ab,kf.
27. ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.
28. (meta-analysis or systematic review).md.
29. (multi* adj3 treatment adj3 comparison*).ti,ab,kf.
30. (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.
31. umbrella review*.ti,ab,kf.
32. (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
33. (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.
34. (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
35. or/12-34
36. 11 and 35
37. limit 36 to yr="2014 -Current"

Step 2. Identifying RCTs

Ovid - Medline

1. exp Vitamin D/
2. ((d? adj1 vitamin*) or cholecalciferol* or calciol or calcifediol or hydroxycholecalciferol* or dihydroxycholecalciferol* or calciferol* or hydroxyvitamin d or hydroxyvitamin d? or dihydroxyvitamin d or dihydroxyvitamin d? or dihydrotachysterol*).tw.
3. calcium.hw.
4. calcium.tw.
5. exp Fractures, Bone/
6. (fractur* or microfractur*).tw.
7. Accidental Falls/
8. (falls or faller$1).tw.
9. 1 or 2 or 3 or 4
10. 5 or 6 or 7 or 8
11. 9 and 10
12. (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt.
13. (Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial Protocol).pt.
14. Multicenter Study.pt.

15. Clinical Studies as Topic/
16. exp Clinical Trial/ or exp Clinical Trials as Topic/ or Clinical Trial Protocol/ or Clinical Trial Protocols as Topic/ or exp "Clinical Trial (topic)"/
17. Multicenter Study/ or Multicenter Studies as Topic/ or "Multicenter Study (topic)"/
18. Randomization/
19. Random Allocation/
20. Double-Blind Method/
21. Double Blind Procedure/
22. Double-Blind Studies/
23. Single-Blind Method/
24. Single Blind Procedure/
25. Single-Blind Studies/
26. Placebos/
27. Placebo/
28. Control Groups/
29. Control Group/
30. Cross-Over Studies/ or Crossover Procedure/
31. (random* or sham or placebo*).ti,ab,hw,kf.
32. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
33. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
34. (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf.
35. (clinical adj3 (study or studies or trial*)).ti,ab,hw,kf.
36. (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
37. (phase adj3 (study or studies or trial*)).ti,ab,hw,kf.
38. ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf.
39. ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf.
40. allocated.ti,ab,hw.
41. ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
42. ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
43. (pragmatic study or pragmatic studies).ti,ab,hw,kf.
44. ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
45. ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
46. trial.ti,kf.
47. or/12-46
48. 11 and 47
49. limit 48 to yr="2017 -Current"

Ovid - Embase (*8836 hits*)

1. exp Vitamin D/
2. ((d? adj1 vitamin*) or cholecalciferol* or calciol or calcifediol or hydroxycholecalciferol* or dihydroxycholecalciferol* or calciferol* or hydroxyvitamin d or hydroxyvitamin d? or dihydroxyvitamin d or dihydroxyvitamin d? or dihydrotachysterol*).tw.
3. Calcium/ or calcium intake/ or calcium carbonate/ or Calcium Gluconate/
4. calcium.tw.
5. 1 or 2 or 3 or 4
6. exp bone injury/

7. (fractur* or microfractur*).tw.
8. Falling/
9. (falls or fallers).tw.
10. 6 or 7 or 8 or 9
11. 5 and 10
12. (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt.
13. (Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV or Clinical Trial Protocol).pt.
14. Multicenter Study.pt.
15. Clinical Studies as Topic/
16. exp Clinical Trial/ or exp Clinical Trials as Topic/ or Clinical Trial Protocol/ or Clinical Trial Protocols as Topic/ or exp "Clinical Trial (topic)"/
17. Multicenter Study/ or Multicenter Studies as Topic/ or "Multicenter Study (topic)"/
18. Randomization/
19. Random Allocation/
20. Double-Blind Method/
21. Double Blind Procedure/
22. Double-Blind Studies/
23. Single-Blind Method/
24. Single Blind Procedure/
25. Single-Blind Studies/
26. Placebos/
27. Placebo/
28. Control Groups/
29. Control Group/
30. Cross-Over Studies/ or Crossover Procedure/
31. (random* or sham or placebo*).ti,ab,hw,kf.
32. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
33. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
34. (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf.
35. (clinical adj3 (study or studies or trial*)).ti,ab,hw,kf.
36. (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
37. (phase adj3 (study or studies or trial*)).ti,ab,hw,kf.
38. ((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf.
39. ((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf.
40. allocated.ti,ab,hw.
41. ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
42. ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
43. (pragmatic study or pragmatic studies).ti,ab,hw,kf.
44. ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
45. ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
46. trial.ti,kf.
47. or/12-46
48. 11 and 47
49. limit 48 to yr="2017 -Current"

Ovid - Cochrane Central Register of Controlled Trials

1. exp Vitamin D/
2. ((d? adj1 vitamin*) or cholecalciferol* or calciol or calcifediol or hydroxycholecalciferol* or dihydroxycholecalciferol* or calciferol* or hydroxyvitamin d or hydroxyvitamin d? or dihydroxyvitamin d or dihydroxyvitamin d? or dihydrotachysterol*).ti,ab.
3. calcium.hw.
4. calcium.ti,ab.
5. exp Fractures, Bone/
6. (fractur* or microfractur*).ti,ab.
7. Accidental Falls/
8. (falls or faller*).ti,ab.
9. or/1-4
10. or/5-8
11. 9 and 10
12. limit 11 to yr="2017 -Current"

Appendix 3 : Extraction form

1. General information : Covidence ID, first author, year of publication, study citation, lead author contact details, language of publication, type of publication, conflict of interests, funding source, country.

2. Trial characteristics: study design, cluster details (for cluster-RCTs), start date, end date, treatment, control and co-intervention(s) description, nontrial use of calcium supplements, nontrial use of vitamin D supplements, brief description of the population, inclusion and exclusion criteria, method of recruitment of participants, duration of intervention, duration of follow up, overall no of patient-years, other relevant information.

3. Patient characteristics: age, gender, ethnicity, type of residence, fracture history, fall history, osteoporosis diagnosis, baseline vitamin D concentration, no of participants with a baseline 25OHD < 25 nmolL, no of participants with a baseline 25OHD < 50 nmolL, achieved vitamin D concentration, no of participants with a drawn vitamin D concentration, antiosteoporotic drugs use, active vitamin D analogs use, chronic corticosteroids use, hormone therapy use, dietary calcium intake.

4. Outcomes : how outcomes were measured, timing of outcome measurements, number of events for each outcome and sample size in each group, rate ratio of falls.

Appendix 4 : Subgroup analysis plan

<u>Subgroup analysis plan for vitamin D alone</u>

- High risk population vs low-risk population
- ≥ 65 years vs < 65 years
- ≥ 80 years vs < 80 years
- Women-only vs both sex or men trials
- Institutionalised vs community dwelling
- Previous vs no previous fracture

- Previous vs no previous fall
- With vs without an osteoporosis diagnosis
- Vit-25OHD level < 25 vs ≥ 25 nmol/L
- Vit-25OHD level < 50 vs ≥ 50 nmol/L
- Baseline dietary calcium intake : < 800 mg vs ≥ 800mg
- Type of vitD : D2 vs D3
- Frequency of administration of vitD : daily to monthly vs intermittent bolus
- Mean daily dose of vitD excluding intermittent bolus : < 1000 vs 1000-2000 vs > 2000 units/day
- Trial size : < 1000 vs ≥ 1000 participants
- Mean follow-up : ≤ 1 vs > 1 year

Subgroup analysis plan for calcium alone

- High risk population vs low-risk population
- ≥ 65 years vs < 65 years
- ≥ 80 years vs < 80 years
- Women-only vs both sex or men trials
- Institutionalised vs community dwelling
- Previous vs no previous fracture
- Previous vs no previous fall
- With vs without an osteoporosis diagnosis
- Vit-25OHD level < 25 vs ≥ 25 nmol/L
- Vit-25OHD level < 50 vs ≥ 50 nmol/L
- Baseline dietary calcium intake : < 800 mg vs ≥ 800mg
- Trial size : < 1000 vs ≥ 1000 participants
- Mean follow-up : ≤ 1 vs > 1 year

Subgroup analysis plan for vitamin D combined with calcium

- High risk population vs low-risk population
- ≥ 65 years vs < 65 years
- ≥ 80 years vs < 80 years
- Women-only vs both sex or men trials
- Institutionalised vs community dwelling
- Previous vs no previous fracture
- Previous vs no previous fall
- With vs without an osteoporosis diagnosis
- Vit-25OHD level < 25 vs ≥ 25 nmol/L
- Vit-25OHD level < 50 vs ≥ 50 nmol/L
- Baseline dietary calcium intake : < 800 mg vs ≥ 800mg
- Type of vitD : D2 vs D3
- Frequency of administration of vitD : daily to monthly vs intermittent bolus
- Mean daily dose of vitD excluding intermittent bolus : < 1000 vs 1000-2000 vs > 2000 units/day
- Trial size : < 1000 vs ≥ 1000 participants
- Mean follow-up : ≤ 1 vs > 1 year