

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Protocol for a systematic review and meta-analysis assessing the effectiveness of deprescribing in falls prevention in older people

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-047190
Article Type:	Protocol
Date Submitted by the Author:	24-Nov-2020
Complete List of Authors:	<p>Seppala, Lotta; Amsterdam UMC Location AMC, Department of Internal Medicine, Section of Geriatric Medicine, Amsterdam Public Health Research Institute</p> <p>Kamkar, Nellie; Lawson Research Health Institute, Parkwood Hospital, Gait and Brain Laboratory; University of Western Ontario, Department of Epidemiology and Biostatistics</p> <p>Ryg, Jesper; Odense University Hospital, Department of Geriatric Medicine; University of Southern Denmark, Geriatric Research Unit, Department of Clinical Research</p> <p>Masud, Tahir ; Nottingham University Hospitals NHS Trust</p> <p>Daams, Joost; Amsterdam UMC, University of Amsterdam, Research Support, Medical Library</p> <p>Montero-Odasso, Manuel; Lawson Research Health Institute, Parkwood Hospital, Gait and Brain Lab; University of Western Ontario, Departments of Medicine (Geriatrics) and of Epidemiology and Biostatistics</p> <p>Hartikainen, Sirpa; University of Eastern Finland School of Pharmacy</p> <p>Petrovic, Mirko; Ghent University, Department of Internal Medicine and Paediatrics (section of Geriatrics)</p> <p>van der Velde, Nathalie; Amsterdam UMC Location AMC, Department of Internal Medicine, Section of Geriatric Medicine, Amsterdam Public Health Research Institute</p>
Keywords:	GERIATRIC MEDICINE, PUBLIC HEALTH, Adverse events < THERAPEUTICS

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1

1
2
3 1 **Protocol for a systematic review and meta-analysis assessing the effectiveness of deprescribing in**
4 2 **falls prevention in older people**

5
6 3 **Authors:** L.J. Seppala,¹ N. Kamkar², J. Ryg³, T. Masud⁴, J.G. Daams⁵, M. Montero-Odasso⁶, S.
7 4 Hartikainen⁷, M. Petrovic⁸, N. van der Velde¹, The World Falls Guidelines Task Force

8
9
10 5 **Contact:**

11
12 6 ¹ l.j.seppala@amsterdamumc.nl, Department of Internal Medicine, Section of Geriatric Medicine,
13 7 Amsterdam Public Health Research Institute, Amsterdam UMC, University of Amsterdam,
14 8 Meibergdreef 9, 1105AZ Amsterdam, The Netherlands

15
16
17 9 ² nellie.kamkar@sjhc.london.on.ca, Gait and Brain Laboratory, Lawson Research Health Institute,
18 10 Parkwood Hospital, London Ontario, Canada; Department of Epidemiology and Biostatistics,
19 11 University of Western Ontario, London Ontario, Canada.

20
21 12 ³ Jesper.Ryg@rsyd.dk, Department of Geriatric Medicine, Odense University Hospital, Odense,
22 13 Denmark; Geriatric Research Unit, Department of Clinical Research, University of Southern Denmark,
23 14 Odense, Denmark; ODIN (Odense Deprescribing INitiative), Denmark

24
25 15
26 16 ⁴ Tahir.Masud@nuh.nhs.uk, Nottingham University Hospitals NHS Trust, Nottingham, UK

27
28 17 ⁵ j.g.daams@amsterdamumc.nl, Research Support, Medical Library, Amsterdam UMC, University
29 18 of Amsterdam, Meibergdreef 9, 1105AZ Amsterdam, The Netherlands

30
31 19 ⁶ mmontero@uwo.ca, Gait and Brain Laboratory, Lawson Research Health Institute, Parkwood
32 20 Hospital, London Ontario, Canada; Schulich School of Medicine and Dentistry, London Ontario,
33 21 Canada; Departments of Medicine (Geriatrics) and of Epidemiology and Biostatistics, University of
34 22 Western Ontario, London Ontario, Canada.

35
36 23 ⁷ s.hartikainen@uef.fi, School of Pharmacy, University of Eastern Finland, Kuopio, Finland

37
38 24 ⁸ mirko.petrovic@ugent.be, Department of Internal Medicine and Paediatrics (section of Geriatrics),
39 25 Ghent University, Ghent, Belgium

40
41 26 ¹ n.vandervelde@amsterdamumc.nl, Department of Internal Medicine, Section of Geriatric Medicine,
42 27 Amsterdam Public Health Research Institute, Amsterdam UMC, University of Amsterdam,
43 28 Meibergdreef 9, 1105AZ Amsterdam, The Netherlands

44
45
46
47 29 **Corresponding author:**

48
49 30 Nathalie van der Velde

50
51 31 Department of Internal Medicine, Section of Geriatric Medicine, Amsterdam Public Health Research
52 32 Institute, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105AZ Amsterdam,
53 33 The Netherlands

54
55 34

56
57
58
59
60

1

2

Abstract**Introduction**

One of the known risk factors for fall incidents is the use of specific medications, fall-risk-increasing drugs (FRIDs). However, to date, there is uncertainty related to the effectiveness of deprescribing (reducing or stopping) FRIDs as a single intervention in falls prevention. Thus, a comprehensive update of the literature focusing on all geriatric settings and all deprescribing interventions is warranted to enhance the current knowledge.

Methods and analysis

This systematic review protocol was conducted following the PRISMA guidelines. A systematic search was performed in Cochrane Central Register of Controlled Trials, MEDLINE, Embase, and PsycINFO. We will also search in trial registers. We will include Randomized Controlled Trials, in which any deprescribing intervention is compared to usual care in falls prevention. Both title and abstract screening and full-text screening will be done by two reviewers. The Cochrane Collaboration revised tool of Risk of Bias will be applied to perform risk of bias assessment. We will categorize the results separately for every setting. If a group of sufficiently comparable studies will be identified, we will perform a meta-analysis applying random effects model. We will investigate heterogeneity using a combination of visual inspection of the forest plot along with consideration of the Chi² test and the I² statistic results. We have pre-specified several subgroup and sensitivity analyses.

Ethics and dissemination

Ethics approval is not applicable for this study since no original data will be collected. The results will be disseminated through peer-reviewed publication and conference presentations. Furthermore, this systematic review will inform the recommendations of working group of polypharmacy and fall-risk-increasing drugs of the anticipated World's Falls Guidelines.

2

3

1
2
3 58 **Registration:** CRD42020218231
4
5

6 59 **Key words:** Medication withdrawal, deprescribing, older adults, accidental falls, falls prevention
7
8

9 60 **Article summary**
10

11 61
12 62 **Strengths and limitations of this study**
13

- 14 63
- 15 • we aim to create the most comprehensive systematic review of the effectiveness of
16
17 64 deprescribing as a single intervention in falls prevention to date by focusing on all geriatric
18
19 65 settings and all deprescribing interventions
20
21 66 • we will use rigorous methodology in accordance with the Cochrane handbook and the results
22
23 67 will be reported as stated by PRISMA statement
24
25 68 • the search algorithm was developed by an experienced librarian and customized to four large
26
27 69 databases
28
29 70 • no language restriction will be applied in the selection of the studies
30
31 71 • the certainty of the evidence of this systematic review may be limited by the limited number
32
33 72 of studies available and the possible low quality of the individual studies
34
35
36
37
38
39
40

41 74 **Background**
42
43

44 75 Fall incidents are a growing major public health concern leading to associated morbidity, mortality
45
46 76 and substantial healthcare costs (1). Of the community-dwelling older adults aged 65 years and
47
48 77 older, approximately a third will sustain a fall each year (1). In long term care, residents are even at
49
50 78 higher risk of falls; more than half of the residents will fall each year (2). One of the well-established
51
52 79 risk factors for fall incidents is the use of specific medications, so-called fall-risk-increasing drugs
53
54 80 (FRIDs) (3-5). The prevalence of FRID use in older person with a fall-related injury is high, ranging
55
56 81 from 65%-93% (6). However, to date, there is uncertainty related to the effectiveness of
57
58 82 deprescribing (reducing or stopping) FRIDs as a single intervention in falls prevention.
59
60

3

4

1
2
3 83 Few systematic reviews and meta-analyses have aimed to summarize the evidence-related to FRIDs
4
5 84 deprescribing as a single intervention (6-8). A comparison of the conclusions of these systematic
6
7 85 reviews is difficult due to the variation in included trials in the reviews and the heterogeneous results
8
9
10 86 of the individual studies. The trials performed in long-term care settings or hospitals were
11
12 87 summarized by Cameron et al. in 2018 (8). They concluded that general medication review may make
13
14 88 little or no difference to the rate of falls or risk of falling in long term care facilities. However, there
15
16 89 was very high heterogeneity between the studies ($I^2=93\%$), and three of the six pooled studies
17
18 90 reported an effect. In addition, they identified only one deprescribing intervention study that was
19
20 91 performed in a hospital. Furthermore, the Cochrane review by Gillespie et al. in 2012 assessing fall
22
23 92 prevention approaches in community-dwelling older adults identified a total of five studies
24
25 93 investigating medication withdrawal as a single intervention (9). Two of the five included studies
26
27 94 found an effect of the intervention. Furthermore, Hart et al. concluded in 2020 that reducing FRIDs
28
29 95 use as a stand-alone intervention may not be effective (6). However, only studies performed in older
30
31 96 adults presenting with a fall-related injury or a history of falls were included in the review.
32
33
34 97 Eventually, only four intervention studies were identified and the two studies, which had shown an
35
36 98 effect and identified by Gillespie et al. were not included.
37
38
39
40 99 Thus, a comprehensive update of the literature focusing on all geriatric settings and all deprescribing
41
42 100 interventions is warranted to enhance the current knowledge. Therefore, our aim is to perform a
43
44 101 systematic review concerning the effectiveness of deprescribing (e.g., including general medication
45
46 102 reviews or FRIDs deprescribing) as a single intervention in falls prevention performed in any geriatric
47
48 103 setting among older persons. Furthermore, we aim to perform a meta-analysis if sufficiently
49
50 104 comparable studies will be identified.
51
52
53

105 **Methods**

56
57 106 This systematic review will be conducted and reported following the Preferred Reporting Items for
58
59 107 Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
60

4

5

108 Eligibility criteria**109 Type of studies**

110 Only Randomized Controlled Trials (RCTs), including quasi-randomized trials (for example, allocation
111 by alternation), cluster-randomized trials and trials in which treatment allocations are inadequately
112 concealed, will be included. We will include studies without language restriction.

113 Types of Participants

114 Trials will be considered for inclusion if they included participants aged ≥ 60 years or if the majority of
115 participants are aged >65 years or the mean age is >65 years. We will include trials from all settings
116 e.g., community, hospital ward, long term care facilities.

117 Type of interventions

118 The intervention can be any deprescribing intervention. "Deprescribing" has been described as "the
119 process of withdrawal of an inappropriate medication, supervised by a health care professional with
120 the goal of managing polypharmacy and improving outcomes" (10). The interventions can be, for
121 example, pharmacist-led medication reviews, physician-led interventions, prescriber education
122 programs, multidisciplinary interventions or clinical decision support systems. The intervention can
123 target specific drug classes (e.g., psychotropics) or general medication regimen (i.e. comprehensive
124 medication review). If deprescribing intervention is a part of a multi-modal intervention (e.g., including
125 an exercise component in addition to deprescribing), the study will be excluded.

126 Type of Control

127 The comparison intervention will be usual care (i.e. no deprescribing or no change in usual activities of
128 care).

129 Type of outcomes

5

6

1
2
3 130 We will include trials that report raw data or statistics related to falls outcomes. We will include any
4
5 131 type of falls outcome: number of falls, number of fallers/non-fallers/frequent fallers, fall rate per
6
7 132 person-year, and time to first fall. Our secondary outcome is injurious falls (for example fall-related
8
9 133 fractures, fall-related hospital admissions or fall-related healthcare use).

13 134 **Information sources**

16 135 A systematic search was be performed in Cochrane Central Register of Controlled Trials, MEDLINE,
17
18 136 Embase, and PsycINFO to search for literature published from onset until 2nd of November. A
19
20 137 customized search strategy was conducted for each database. We will also search in trial registers. In
21
22 138 the case that a relevant conference abstract is identified, we will contact the authors to obtain full text
23
24 139 article. Reference lists of included studies, reviews (e.g., Cochrane reviews) and falls prevention
25
26 140 guidelines will be reviewed to identify additional studies.

30 141 **Search strategy**

33 142 The search contained the following key search concepts: 1) “deprescribing” AND “falls/health care
34
35 143 assessment” AND “geriatric” OR 2) “prescribing tools” (e.g. Screening tool of inappropriate
36
37 144 prescriptions of older persons [STOPP]). The strategies 1-2 were combined with “RCT filter”. A search
38
39 145 for Medline is provided as an example and provided in Appendix I.

146

44 147 **Data records and management**

47 148 First, title and abstract screening will be done independently by two reviewers using Rayyan, a web-
48
49 149 based systematic review program. In case of disagreement, a third reviewer will be consulted.
50
51 150 Following the title and abstract screening, a full-text screening will be done using Rayyan by two
52
53 151 independent reviewers. A third reviewer will be consulted in case of disagreement. Reasons for
54
55 152 exclusion of studies will be collected during the full-text screening phase.

6

7

1
2
3 153 Two authors will independently extract data from each article using a structured data collection form.
4
5 154 In case of disagreement, a third reviewer will be consulted. The following information will be collected:
6
7 155 study design, country, setting, inclusion criteria, total number of participants and age (mean and
8
9 156 standard deviation), intervention type, control type, all fall-related outcomes, and how collected,
10
11 157 adjustment of outcomes if applicable, follow-up duration, compliance to the intervention and if the
12
13 158 trials have reported possible adverse effects related to the intervention or economic outcomes. If data
14
15 159 to be extracted are missing, incomplete or unclear, inquiries will be sent to the authors.
16
17
18
19
20

21 161 **Effect measures**

22
23 162
24
25 163 We will report the treatment effects between the intervention and control group as a Rate Ratio (RaR),
26
27 164 a Risk Ratio (RR) and/or a Hazard Ratio (HR) and accompanying 95% confidence intervals (95% CI).
28
29
30
31

32 166 For rate of falls, we will use RaR as a treatment effect measure and the rate is the total number of falls
33
34 167 per unit of person time that falls were monitored. We will use the unadjusted RaR, unless the
35
36 168 adjustment is performed due to clustering. Furthermore, if needed due to missing reporting, we will
37
38 169 calculate RaR from appropriate the raw data if possible. For dichotomous outcomes e.g., fallers or
39
40 170 frequent fallers, we will use RR as a treatment effect measure. We will use the unadjusted RR, unless
41
42 171 the adjustment is performed due to clustering. Furthermore, if needed due to missing reporting or if
43
44 172 Odds Ratio is reported, we will calculate RR from the raw data if possible. For survival time-to-event
45
46 173 data, we will use HR as a treatment effect measure. We will use the unadjusted HR, unless the
47
48 174 adjustment is performed due to clustering.
49
50
51

52
53 175 Furthermore, we will adjust for clustering, if not already done in the published report using intra-
54
55 176 cluster coefficient estimates and average cluster size.
56
57

58 177 **Risk of bias**

7

8

1
2
3 178
4
5 179 Two reviewers will assess the risk of bias independently by applying the Cochrane Collaboration revised
6
7 180 tool of Risk of Bias (RoB 2.0) to all the included studies. In case of disagreement, a third reviewer will
8
9
10 181 be consulted. The tool covers five domains: bias arising from randomization process, bias due to
11
12 182 deviations from intended interventions, bias due to missing outcome data, bias in measurement of
13
14 183 outcome, bias in selection of the reported result. In addition, an additional domain is available for
15
16 184 cluster randomized trials; bias arising from identification or recruitment of individual participants
17
18 185 within clusters. Each domain has signalling questions aiming to elicit relevant information. Responses
19
20 186 to these questions are fed into algorithms to score each domain either low risk of bias, some concerns
21
22
23 187 or high risk of bias. The scores of each domain are further mapped into overall risk-of-bias-judgement
24
25 188 including categories of low risk of bias, some concerns and high risk of bias.
26
27
28 189

190 **Data synthesis**

31
32 191
33
34 192 We will categorize the results separately for every setting (e.g., community, hospital, or long term care
35
36 193 facilities) due to different participant and environment characteristics.
37
38
39 194 First, a narrative synthesis will be provided in the text and tables to summarize the study characteristics
40
41 195 and results.
42
43 196
44
45 197 If a group of studies with a sufficiently comparable intervention and outcome and performed in a same
46
47 198 setting will be identified, we will perform a meta-analysis applying the intention-to-treat principle.
48
49
50 199 The results will be pooled using a random-effects model considering the expected heterogeneity
51
52 200 between the studies. We will try to minimize the heterogeneity by grouping the trials per setting and
53
54 201 similar intervention. We will investigate remaining heterogeneity within a pooled group of trials using
55
56 202 a combination of visual inspection of the forest plot along with consideration of the Chi^2 test (with
57
58 203 statistical significance set at $P < 0.10$), and the I^2 statistic results according to the recommendations
59
60

8

9

1
2
3 204 from the Cochrane Handbook. We will explore heterogeneity by conducting a subgroup analysis based
4
5 205 on 1) age, 2) whether the trial is targeted to known fallers (or recurrent fallers if applicable) or also
6
7 206 non-fallers are included, 3) different possible healthcare professionals conducting the medication
8
9 207 review e.g., by physician or pharmacist, 4) whether the medication review is done with the help of a
10
11 208 prescribing tool e.g., STOPP/START or the Beers criteria and which tool is used and 5) population e.g.
12
13 209 if the trial is conducted only in dementia patients in comparison to general nursing home population.
14
15 210 We will perform a sensitivity analysis according to overall study quality; low risk of bias, some concerns
16
17 211 and high risk of bias, by comparing random and fixed-effect model and by excluding possible outlying
18
19 212 studies, if the visual inspection of the forest plot shows poorly overlapping confidence intervals.
20
21
22

23 213
24
25 214 We will explore the possibility of publication bias by constructing funnel plots and by conducting Eggers
26
27 215 test for analyses that contain more than ten studies.
28
29
30

31 216
32 217 The software Review Manager (RevMan) will be used for all statistical tests (Review Manager (RevMan)
33
34 218 [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane
35
36 219 Collaboration, 2014).
37
38
39

220

221 **Confidence in cumulative evidence**

222
223 The confidence in effect estimates for each reported outcome will be assessed using the Grading of
224
225 Recommendations, Assessment, Development and Evaluation (GRADE) approach by two reviewers
226
227 and possible disagreement will be assessed by third reviewer.
228

226

227 **Ethics and dissemination**

228 Ethics approval is not applicable for this study since no original data will be collected. The results will
229
be disseminated through peer-reviewed publication and conference presentations. Furthermore, this

9

10

230 systematic review will inform the recommendations of working group of polypharmacy and fall-risk-
231 increasing drugs of the anticipated World's Falls Guidelines.

232

233 Discussion

234 Although FRIDs use is an important risk factor for falls, there is uncertainty regarding the
235 effectiveness of deprescribing interventions as a single intervention in falls prevention in older
236 people. Identifying effective falls prevention interventions is of importance, considering the burden-
237 related to fall injuries to both individuals and society.

238 This systematic review will help update the knowledge on the effectiveness of deprescribing, since
239 we aim to create the most comprehensive systematic review to date by focusing on all geriatric
240 settings and all deprescribing interventions. In addition, we will use rigorous methodology in
241 accordance with the Cochrane handbook and the results will be reported as stated by PRISMA
242 statement. Therefore, we will provide relevant knowledge that will be implemented into anticipated
243 World's Falls Guidelines and may influence future clinical practice. However, the certainty of the
244 evidence of this systematic review may be limited by the limited number of studies available and the
245 possible low quality of the individual studies.

246

247 References

- 248 1. Berry SD, Miller RR. Falls: epidemiology, pathophysiology, and relationship to fracture. *Curr*
249 *Osteoporos Rep.* 2008;6(4):149-54.
- 250 2. Kennedy CC, Ioannidis G, Thabane L, Adachi JD, Marr S, Giangregorio LM, et al. Successful
251 knowledge translation intervention in long-term care: final results from the vitamin D and
252 osteoporosis study (ViDOS) pilot cluster randomized controlled trial. *Trials.* 2015;16(1):214.
- 253 3. de Vries M, Seppala LJ, Daams JG, van de Glind EMM, Masud T, van der Velde N. Fall-Risk-
254 Increasing Drugs: A Systematic Review and Meta-Analysis: I. Cardiovascular Drugs. *Journal of the*
255 *American Medical Directors Association.* 2018;19(4):371.e1-.e9.
- 256 4. Seppala LJ, van de Glind EMM, Daams JG, Ploegmakers KJ, de Vries M, Wermelink A, et al.
257 Fall-Risk-Increasing Drugs: A Systematic Review and Meta-analysis: III. Others. *Journal of the*
258 *American Medical Directors Association.* 2018;19(4):372.e1-.e8.

10

11

- 1
2
3 259 5. Seppala LJ, Wermelink A, de Vries M, Ploegmakers KJ, van de Glind EMM, Daams JG, et al.
4 260 Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: II. Psychotropics. Journal of the
5 261 American Medical Directors Association. 2018;19(4):371.e11-.e17.
6 262 6. Hart LA, Phelan EA, Yi JY, Marcum ZA, Gray SL. Use of Fall Risk-Increasing Drugs Around a
7 263 Fall-Related Injury in Older Adults: A Systematic Review. Journal of the American Geriatrics Society.
8 264 2020;68(6):1334-43.
9 265 7. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al.
10 266 Interventions for preventing falls in older people living in the community. Cochrane Database Syst
11 267 Rev. 2012(9):Cd007146.
12 268 8. Cameron ID, Dyer SM, Panagoda CE, Murray GR, Hill KD, Cumming RG, et al. Interventions for
13 269 preventing falls in older people in care facilities and hospitals. Cochrane Database of Systematic
14 270 Reviews. 2018(9).
15 271 9. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM. Interventions
16 272 for preventing falls in older people living in the community. Cochrane Database Syst Rev. 2012;9.
17 273 10. Reeve E, Gnjjidic D, Long J, Hilmer S. A systematic review of the emerging definition of
18 274 'deprescribing' with network analysis: implications for future research and clinical practice. British
19 275 journal of clinical pharmacology. 2015;80(6):1254-68.
20
21
22
23 276

25 277 **Authors' contributions**

26
27
28 278 L.S. and N.V. designed the protocol. L.S. and N.V. wrote the first draft of the protocol. All the authors
29 279 contributed and approved the final version of the protocol.
30
31

33 280 **Funding**

34
35
36 281 This work was supported by funding from the Canadian Institute of Health Research (CIHR; MOP
37 282 211220; PTJ 153100) and the Clementine Brigitta Maria Dalderup fund (grant number 7303), which is
38 283 an Amsterdam University fund. The sponsors played no part in the design and writing of the protocol.
39
40
41

42 284 **Competing interests**

43
44
45 285 The authors declare that they have no competing interests.
46
47

48 286 **Word Count**

49 287 Abstract: 265

50 288 Text: 1991
51
52
53
54
55 289
56
57 290
58
59 291
60

11

12

1
2
3 292
4
5 293
6
7 294
8
9 295
10
11 296
12
13 297
14
15 298
16
17 299
18
19 300
20
21 301
22
23 302
24
25 303
26
27 304
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

12

Appendix 1. Search strategy for Medline

1. inappropriate prescribing/ or exp medication errors/ or deprescriptions/ or exp drug prescriptions/ or exp drug utilization/
2. (deprescri* or ((antidepress* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*) adj2 withdrawal) or ((dose or dosage) adj3 reduc*) or ((discontinu* or problem* or alternative?) adj3 (antidepress* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*)) or (chang* adj5 (antidepress* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*)) or ((polypharmac* or medication) adj2 (risk? or review)) or ((polypharmac* or medication) adj2 management) or prescribing problem? or overprescri* or underprescri* or under prescri* or over prescri* or (frid? and adverse) or medication errors or inappropriate prescri* or (appropriat* adj2 (prescri* or medicine or medication)) or harmful medic* or medication reconciliation).ab,kf,ti
3. or/1-2 [deprescription]
4. accidental falls/
5. (fall? or fell or falling or fallen or faller or stumble? or stumbling or stumbles or slip or slips or slipping or slipped or trip or tripped or physical self maintenance or ambulation or ambulatory).ab,kf,. ti.
6. "Outcome Assessment, Health Care"/
7. (assess* and health care).mp.
8. or/4-7 [Falls | health care assessment]
9. Geriatric assessment/ or frail elderly/ or exp aged/ or middle aged/ or exp nursing homes/ or "homes for the aged"/ or exp aging/
10. (older person? or older patient? or seniors or senior citiz* or elder or elders or elderly or geriatric* or frailty or postmenopausal women or community-dwelling or nursing home? or resident* or old* people or old* person? or old* patient? or old* client? or old* adult? or older m?n or older wom?n).ab,kf,ti.
11. (geriatr* or age or aging or elderl*).in,jw.
12. or/9-11 [Geriatric]
13. and/3,8,12
14. (Beers criteria or Stuck criteria or Beers-Fick criteria or McLeod criteria or Zhan criteria or Rancourt criteria or Lindblad criteria or HEDIS or "Healthcare Effectiveness Data and Information Set" or Japanese Beers or French criteria or Thailand criteria or STOPP or "Screening Tool of Older Person's Prescriptions" or NORGEP or "Norwegian General Practice criteria" or Italian Criteria or Priscus or Korean criteria or Taiwan criteria or Austrian Criteria or Australian Prescribing Indicators Tool or APIT or New Mexico criteria or Czech National criteria or Clyne criteria or Castillo-Paramo criteria or FORTA or "Fit FOR The Aged list" or Galan-Retamal criteria or "EU 7 PIM list" or "European list of potentially inappropriate medications for older people" or Kim criteria or GheOP3S or "Ghent Older People's Prescriptions community Pharmacy Screening" or Chilean criteria or Mazhar criteria or Khodyakov criteria or "Systematic Tool to Reduce Inappropriate Prescribing" or (STRIP adj2 criteria) or Medication Appropriateness Index or MAI or (Assessment of Underutilization adj2 index) or WWADR Profile or West Wales ADR or "lawton and brody").mp [specific tools | outcomes]
15. 13 or 14
16. (randomized or randomly or double blind* or controlled trial? or controlled clinical trial?).ab,kf,ti.
17. (randomized controlled trial or controlled clinical trial).pt.
18. trial.ti.
19. or/16-18 [RCT's sensitive]
20. 15 and 19

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 1, line 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3, line 58
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 1, lines 3-33
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 11, line 277
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	<input type="checkbox"/>	<input type="checkbox"/>	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 11, lines 280-283
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 10, lines 280-283
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 10, lines 280-283
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3, line 75 to Page 4, line 98

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 4, lines 99-104
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 5, line 109 to Page 6, line 133
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 6, lines 135-140
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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 6, lines 142-145 and Appendix 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 6, lines 148-152
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 6, lines 148-152
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 7, lines 153-154, Page 7 lines 158-159
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 7, lines 154-158
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 6, lines 130-133, Page 7, lines 163-176
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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 8, lines 179-188, Page 9 lines 210-211

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 8, lines 197-198
	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 (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 8, lines 197-203
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 9, lines 204-212
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 8, lines 192-195
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 9, lines 214-215
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 9, lines 223-225

BMJ Open

Protocol for a systematic review and meta-analysis assessing the effectiveness of deprescribing in falls prevention in older people

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-047190.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Apr-2021
Complete List of Authors:	<p>Seppala, Lotta; Amsterdam UMC Location AMC, Department of Internal Medicine, Section of Geriatric Medicine, Amsterdam Public Health Research Institute</p> <p>Kamkar, Nellie; Lawson Research Health Institute, Parkwood Hospital, Gait and Brain Laboratory; University of Western Ontario, Department of Epidemiology and Biostatistics</p> <p>Ryg, Jesper; Odense University Hospital, Department of Geriatric Medicine; University of Southern Denmark, Geriatric Research Unit, Department of Clinical Research</p> <p>Masud, Tahir ; Nottingham University Hospitals NHS Trust</p> <p>Daams, Joost; Amsterdam UMC, University of Amsterdam, Research Support, Medical Library</p> <p>Montero-Odasso, Manuel; Lawson Research Health Institute, Parkwood Hospital, Gait and Brain Lab; University of Western Ontario, Departments of Medicine (Geriatrics) and of Epidemiology and Biostatistics</p> <p>Hartikainen, Sirpa; University of Eastern Finland School of Pharmacy</p> <p>Petrovic, Mirko; Ghent University, Department of Internal Medicine and Paediatrics (section of Geriatrics)</p> <p>van der Velde, Nathalie; Amsterdam UMC Location AMC, Department of Internal Medicine, Section of Geriatric Medicine, Amsterdam Public Health Research Institute</p>
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Pharmacology and therapeutics, Public health
Keywords:	GERIATRIC MEDICINE, PUBLIC HEALTH, Adverse events < THERAPEUTICS

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1

1
2
3 1 **Protocol for a systematic review and meta-analysis assessing the effectiveness of deprescribing in**
4 2 **falls prevention in older people**

6 3 **Authors:** L.J. Seppala,¹ N. Kamkar², J. Ryg³, T. Masud⁴, J.G. Daams⁵, M. Montero-Odasso⁶, S.
7 4 Hartikainen⁷, M. Petrovic⁸, N. van der Velde¹, The World Falls Guidelines Task Force

9
10 5 **Contact:**

11
12 6 ¹ l.j.seppala@amsterdamumc.nl, Department of Internal Medicine, Section of Geriatric Medicine,
13 7 Amsterdam Public Health Research Institute, Amsterdam UMC, University of Amsterdam,
14 8 Meibergdreef 9, 1105AZ Amsterdam, The Netherlands

15
16 9 ² nellie.kamkar@sjhc.london.on.ca, Gait and Brain Laboratory, Lawson Research Health Institute,
17 10 Parkwood Hospital, London Ontario, Canada; Department of Epidemiology and Biostatistics,
18 11 University of Western Ontario, London Ontario, Canada.

19
20 12 ³ Jesper.Ryg@rsyd.dk, Department of Geriatric Medicine, Odense University Hospital, Odense,
21 13 Denmark; Geriatric Research Unit, Department of Clinical Research, University of Southern Denmark,
22 14 Odense, Denmark; ODIN (Odense Deprescribing INitiative), Denmark

23 15
24 16 ⁴ Tahir.Masud@nuh.nhs.uk, Nottingham University Hospitals NHS Trust, Nottingham, UK

25
26 17 ⁵ j.g.daams@amsterdamumc.nl, Research Support, Medical Library, Amsterdam UMC, University
27 18 of Amsterdam, Meibergdreef 9, 1105AZ Amsterdam, The Netherlands

28
29 19 ⁶ mmontero@uwo.ca, Gait and Brain Laboratory, Lawson Research Health Institute, Parkwood
30 20 Hospital, London Ontario, Canada; Schulich School of Medicine and Dentistry, London Ontario,
31 21 Canada; Departments of Medicine (Geriatrics) and of Epidemiology and Biostatistics, University of
32 22 Western Ontario, London Ontario, Canada.

33
34 23 ⁷ s.hartikainen@uef.fi, School of Pharmacy, University of Eastern Finland, Kuopio, Finland

35
36 24 ⁸ mirko.petrovic@ugent.be, Department of Internal Medicine and Paediatrics (section of Geriatrics),
37 25 Ghent University, Ghent, Belgium

38
39 26 ¹ n.vandervelde@amsterdamumc.nl, Department of Internal Medicine, Section of Geriatric Medicine,
40 27 Amsterdam Public Health Research Institute, Amsterdam UMC, University of Amsterdam,
41 28 Meibergdreef 9, 1105AZ Amsterdam, The Netherlands

42
43 29 **Corresponding author:**

44
45 30 Nathalie van der Velde

46
47 31 Department of Internal Medicine, Section of Geriatric Medicine, Amsterdam Public Health Research
48 32 Institute, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105AZ Amsterdam,
49 33 The Netherlands

1

2

Abstract**Introduction**

One of the known risk factors for fall incidents is the use of specific medications, fall-risk-increasing drugs. However, to date, there is uncertainty related to the effectiveness of deprescribing as a single intervention in falls prevention. Thus, a comprehensive update of the literature focusing on all geriatric settings and all deprescribing interventions is warranted to enhance the current knowledge.

Methods and analysis

This systematic review protocol follows the PRISMA guidelines. A systematic search was performed in Cochrane Central Register of Controlled Trials, MEDLINE, Embase, and PsycINFO (2nd of November 2020). We will also search in trial registers. We will include Randomized Controlled Trials, in which any deprescribing intervention is compared to usual care and reports falls as an outcome. Both title and abstract screening and full-text screening will be done by two reviewers. The Cochrane Collaboration revised tool of Risk of Bias will be applied to perform risk of bias assessment. We will categorize the results separately for every setting. If a group of sufficiently comparable studies will be identified, we will perform a meta-analysis applying random effects model. We will investigate heterogeneity using a combination of visual inspection of the forest plot along with consideration of the Chi² test and the I² statistic results. We have pre-specified several subgroup and sensitivity analyses.

Ethics and dissemination

Ethics approval is not applicable for this study since no original data will be collected. The results will be disseminated through peer-reviewed publication and conference presentations. Furthermore, this systematic review will inform the recommendations of working group of polypharmacy and fall-risk-increasing drugs of the anticipated World's Falls Guidelines.

Registration: Registered in PROSPERO. Registration number: CRD42020218231

2

3

1
2
3 58 **Key words:** Medication withdrawal, deprescribing, older adults, accidental falls, falls prevention
4
5

6 59 **Article summary**
7 60

8 61 **Strengths and limitations of this study**
9

- 10
11 62 • we aim to create the most comprehensive systematic review of the effectiveness of
12
13 63 deprescribing as a single intervention in falls prevention to date by focusing on all geriatric
14
15 64 settings and all deprescribing interventions
16
17 65 • we will use rigorous methodology in accordance with the Cochrane handbook and the results
18
19 66 will be reported as stated by PRISMA statement
20
21 67 • the search algorithm was developed by an experienced librarian and customized to four large
22
23 68 databases
24
25 69 • no language restriction will be applied in the selection of the studies
26
27 70 • the certainty of the evidence of this systematic review may be limited by the limited number
28
29 71 of studies available and the possible low quality of the individual studies
30
31
32
33
34
35
36
37

38 73 **Background**
39
40

41 74 Fall incidents are a growing major public health concern leading to associated morbidity, mortality
42
43 75 and substantial healthcare costs (1). Of the community-dwelling older adults aged 65 years and
44
45 76 older, approximately a third will sustain a fall each year (1). In long term care, residents are even at
46
47 77 higher risk of falls; more than half of the residents will fall each year (2). One of the well-established
48
49 78 risk factors for falls is the use of specific medications, so-called fall-risk-increasing drugs (FRIDs) (3-5).
50
51 79 The prevalence of FRID use in older people with a fall-related injury is high, ranging from 65%-93%
52
53 80 (6). Medication review is a common component of the multifactorial falls prevention intervention
54
55 81 and the Cochrane review by Hopewell et al. 2018 concluded that multifactorial interventions may
56
57
58
59
60

3

4

1
2
3 82 reduce the rate of falls compared with usual care or attention control (7). However, to date, there is
4
5 83 uncertainty related to the effectiveness of deprescribing as a single intervention in falls prevention.
6
7
8 84 Few systematic reviews and meta-analyses have aimed to summarize the evidence-related to
9
10 85 deprescribing as a single intervention (6, 8-11). A comparison of the conclusions of these systematic
11
12 86 reviews is difficult due to the variation in included trials in the different reviews. The trials performed
13
14 87 in long-term care settings or hospitals were summarized by Cameron et al. in 2018 (9). They
15
16 88 concluded that general medication review may make little or no difference to the rate of falls or risk
17
18 89 of falling in long term care facilities. In addition, they identified only one deprescribing intervention
19
20 90 study that was performed in a hospital. Furthermore, the Cochrane review by Gillespie et al. in 2012
21
22 91 assessing fall prevention approaches in community-dwelling older adults identified a total of five
23
24 92 studies investigating medication withdrawal as a single intervention (8). Two of the five included
25
26 93 studies found an effect of the intervention. Page et al. found in 2016 in their meta-analysis that
27
28 94 deprescribing led to fewer falls overall but did not significantly improve the risk of experiencing at
29
30 95 least one fall (11). However, very heterogeneous trials were pooled together from placebo-
31
32 96 controlled psychotropics withdrawal in primary care to education program regarding appropriate
33
34 97 medication use for physicians in nursing homes. Furthermore, Hart et al. concluded in 2020 that
35
36 98 reducing FRIDs use as a stand-alone intervention may not be effective (6). However, only studies
37
38 99 performed in older adults presenting with a fall-related injury or a history of falls were included in
39
40 100 the review. The most recent meta-analysis on this topic by Lee et al. found no effect of FRIDs
41
42 101 deprescribing on fall outcomes (10). However, all studies assessing medication reviews and
43
44 102 management with a broader focus on reducing polypharmacy and potentially inappropriate
45
46 103 prescribing were excluded.
47
48
49
50
51
52
53
54 104 Thus, a comprehensive update of the literature focusing all deprescribing interventions including
55
56 105 medication reviews with broader focus is warranted to enhance current knowledge as important
57
58 106 deprescribing trials have been published in recent years. Therefore, our aim is to perform a
59
60

4

5

1
2
3 107 systematic review concerning the effectiveness of deprescribing (e.g., including general medication
4
5 108 reviews or FRIDs deprescribing) as a single intervention in falls prevention performed in any geriatric
6
7 109 setting among older persons. Furthermore, we aim to report the results separately for each geriatric
8
9 110 setting and perform a meta-analysis if sufficiently comparable studies will be identified.
10
11
12

111 **Methods**

13
14
15
16 112 This systematic review will be conducted and reported following the Preferred Reporting Items for
17
18 113 Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
19
20

21 114 **Eligibility criteria**

22 23 24 115 Type of studies

25
26
27 116 Only Randomized Controlled Trials (RCTs), including quasi-randomized trials (for example, allocation
28
29 117 by alternation), cluster-randomized trials and trials in which treatment allocations are inadequately
30
31 118 concealed, will be included. We will include studies without language restriction.
32
33

34 35 119 Types of Participants

36
37
38 120 Trials will be considered for inclusion if they included participants aged ≥ 60 years or if the majority of
39
40 121 participants are aged >65 years or the mean age is >65 years. We will include trials from all settings
41
42 122 e.g., community, hospital ward, long term care facilities.
43
44

45 123 Type of interventions

46
47
48 124 The intervention can be any deprescribing intervention. "Deprescribing" has been described as "the
49
50 125 process of withdrawal of an inappropriate medication, supervised by a health care professional with
51
52 126 the goal of managing polypharmacy and improving outcomes" (12). The interventions can be, for
53
54 127 example, pharmacist-led medication reviews, physician-led interventions, prescriber education
55
56 128 programs, multidisciplinary interventions or clinical decision support systems. The intervention can
57
58 129 target specific drug classes (e.g., psychotropics) or general medication regimen (i.e. comprehensive
59
60

5

6

1
2
3 130 medication review). The intervention might target multiple medication issues in case of
4
5 131 comprehensive medication review in addition to withdrawal such as polypharmacy, non-adherence,
6
7 132 education, and starting medications. If deprescribing intervention is a part of a multi-modal
8
9 133 intervention (e.g., including an exercise component in addition to deprescribing), the study will be
10
11
12 134 excluded.

15 135 Type of Control

17
18 136 The comparison intervention will be usual care (i.e. no deprescribing or no change in usual activities of
19
20 137 care).

23 138 Type of outcomes

25
26 139 We will include trials that report raw data or statistics related to falls outcomes. We will include any
27
28 140 type of falls outcome: number of falls, number of fallers/non-fallers/frequent fallers, fall rate per
29
30 141 person-year, and time to first fall. Our secondary outcome is injurious falls (for example fall-related
31
32 142 fractures, fall-related hospital admissions or fall-related healthcare use).

36 143 Information sources

38
39 144 A systematic search was performed in Cochrane Central Register of Controlled Trials, MEDLINE,
40
41 145 Embase, and PsycINFO to search for literature published from onset until 2nd of November 2020. A
42
43 146 customized search strategy was conducted for each database. We will also search in trial registers. In
44
45 147 the case that a relevant conference abstract is identified, we will contact the authors to obtain full text
46
47 148 article. Reference lists of included studies, reviews (e.g., Cochrane reviews) and falls prevention
48
49 149 guidelines will be reviewed to identify additional studies.

53 150 Search strategy

57 151

58
59 152 A search for Medline is provided as an example and is available in Appendix I.

60
6

7

1
2
3 153 The search terms used were:
4

5 154 1. Deprescription: inappropriate prescribing, medication errors, deprescriptions, drug prescriptions,
6
7 155 drug utilization, dose in combination with reduction, polypharmacy or medication in combination
8
9 156 with risk, management or review, harmful medication, medication reconciliation, appropriate in
10
11 157 combination with prescribing or medicine or medication, prescribing problem, overprescribing, under
12
13 158 prescribing, withdrawal or discontinuation or problem or alternative or change in combination with
14
15 159 medicine, medication or drug or frid or polypharmacy, antidepressant or antipsychotic.

16
17
18 160 2. Falls or health care assessment: accidental falls, fall, fell, stumble, slip, trip,
19
20
21 161 physical self-maintenance, ambulatory, health care outcome assessment

22
23 162 3. Geriatric: geriatric assessment, frail, elderly, aged, middle aged, nursing homes, homes for the
24
25 163 aged, aging, older person, older patient, senior, elder, geriatric, frailty, postmenopausal women,
26
27 164 community-dwelling, resident, old people, old client, old adult, older man, older woman

28
29
30 165 4. 1 AND 2 AND 3

31
32 166 5. Prescribing tools: e.g. STOPP, "Screening Tool of Older Person's Prescriptions"

33
34 167 6. 4 OR 5

35
36 168 7. RCT: randomized, randomly, double blind, controlled trial, controlled clinical trial

37
38
39 169 8. 6 AND 7

40
41 170

42
43 171 The search was built by an experienced clinical librarian. We used 30 potentially relevant test articles
44
45 172 to test and build the search. These articles were a priori identified using the function similar articles in
46
47 173 PubMed and by reading references of the selected articles. These test articles included also articles
48
49 174 that were identified from systematic reviews on deprescribing and included falls as a secondary
50
51 175 outcome and not as a main interest.

52
53 176

54
55
56 177 **Data records and management**

7

8

1
2
3 178 First, title and abstract screening will be done independently by two reviewers using Rayyan, a web-
4
5 179 based systematic review program. In case of disagreement, a third reviewer will be consulted.
6
7 180 Following the title and abstract screening, a full-text screening will be done using Rayyan by two
8
9 181 independent reviewers. A third reviewer will be consulted in case of disagreement. Reasons for
10
11 182 exclusion of studies will be collected during the full-text screening phase.
12
13
14

15 183 Two authors will independently extract data from each article using a structured data collection form.
16
17 184 In case of disagreement, a third reviewer will be consulted. The following information will be collected:
18
19 185 study design, country, setting, inclusion criteria, total number of participants and age (mean and
20
21 186 standard deviation), intervention type, control type, all fall-related outcomes, and how collected,
22
23 187 adjustment of outcomes if applicable, follow-up duration, compliance to the intervention and if the
24
25 188 trials have reported possible adverse effects related to the intervention or economic outcomes. If data
26
27 189 to be extracted are missing, incomplete or unclear, inquiries will be sent to the authors.
28
29
30

190

191 **Effect measures**

192

33
34
35
36
37 193 We will report the treatment effects between the intervention and control group as a Rate Ratio (RaR),
38
39 194 a Risk Ratio (RR) and/or a Hazard Ratio (HR) and accompanying 95% confidence intervals (95% CI).
40
41

195

42
43
44 196 For rate of falls, we will use RaR as a treatment effect measure and the rate is the total number of falls
45
46 197 per unit of person time that falls were monitored. We will use the unadjusted RaR, unless the
47
48 198 adjustment is performed due to clustering. Furthermore, if needed due to missing reporting, we will
49
50 199 calculate RaR from appropriate raw data if possible. For dichotomous outcomes e.g., fallers or frequent
51
52 200 fallers, we will use RR as a treatment effect measure. We will use the unadjusted RR, unless the
53
54 201 adjustment is performed due to clustering. Furthermore, if needed due to missing reporting or if Odds
55
56 202 Ratio is reported, we will calculate RR from the raw data if possible. For survival time-to-event data,
57
58
59
60

8

9

203 we will use HR as a treatment effect measure. We will use the unadjusted HR, unless the adjustment
204 is performed due to clustering.

205 Furthermore, we will adjust for clustering, if not already done in the published report using intra-
206 cluster coefficient estimates and average cluster size.

207 **Risk of bias**

208

209 Two reviewers will assess the risk of bias independently by applying the Cochrane Collaboration revised
210 tool of Risk of Bias (RoB 2.0) to all the included studies. In case of disagreement, a third reviewer will
211 be consulted. The tool covers five domains: bias arising from randomization process, bias due to
212 deviations from intended interventions, bias due to missing outcome data, bias in measurement of
213 outcome, bias in selection of the reported result. In addition, an additional domain is available for
214 cluster randomized trials; bias arising from identification or recruitment of individual participants
215 within clusters. Each domain has signalling questions aiming to elicit relevant information. Responses
216 to these questions are fed into algorithms to score each domain either low risk of bias, some concerns
217 or high risk of bias. The scores of each domain are further mapped into overall risk-of-bias-judgement
218 including categories of low risk of bias, some concerns and high risk of bias.

219

220 **Data synthesis**

221

222 We will categorize the results separately for every setting (e.g., community, hospital, or long term care
223 facilities) due to different participant and environment characteristics.

224 First, a narrative synthesis will be provided in the text and tables to summarize the study characteristics
225 and results.

226

9

10

1
2
3 227 If a group of studies with a sufficiently comparable intervention and outcome and performed in a same
4
5 228 setting is identified, we will perform a meta-analysis applying the intention-to-treat principle.
6
7 229 The results will be pooled using a random-effects model considering the expected heterogeneity
8
9 230 between the studies. We will try to minimize the heterogeneity by grouping the trials per setting and
10
11 231 similar intervention. We will investigate remaining heterogeneity within a pooled group of trials using
12
13 232 a combination of visual inspection of the forest plot along with consideration of the Chi² test (with
14
15 233 statistical significance set at P < 0.10), and the I² statistic results according to the recommendations
16
17 234 from the Cochrane Handbook. We will explore heterogeneity by conducting a subgroup analysis based
18
19 235 on 1) age, 2) whether the trial is targeted to known fallers (or recurrent fallers if applicable) or also
20
21 236 non-fallers are included, 3) different possible healthcare professionals conducting the medication
22
23 237 review e.g., by physician or pharmacist, 4) whether the medication review is done with the help of a
24
25 238 prescribing tool e.g., STOPP/START or the Beers criteria and which tool is used and 5) population e.g.
26
27 239 if the trial is conducted only in dementia patients in comparison to general nursing home population.
28
29 240 We will perform a sensitivity analysis according to overall study quality; low risk of bias, some concerns
30
31 241 and high risk of bias, by comparing random and fixed-effect model and by excluding possible outlying
32
33 242 studies, if the visual inspection of the forest plot shows poorly overlapping confidence intervals.
34
35 243
36
37 244 We will explore the possibility of publication bias by constructing funnel plots and by conducting Eggers
38
39 245 test for analyses that contain more than ten studies.
40
41 246
42
43 247 The software Review Manager (RevMan) will be used for all statistical tests (Review Manager (RevMan)
44
45 248 [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane
46
47 249 Collaboration, 2014).
48
49 250
50
51
52
53
54
55
56
57 251 **Confidence in cumulative evidence**
58
59 252
60

10

11

1
2
3 253 The confidence in effect estimates for each reported outcome will be assessed using the Grading of
4
5 254 Recommendations, Assessment, Development and Evaluation (GRADE) approach by two reviewers
6
7 255 and possible disagreement will be assessed by third reviewer.
8
9

256

257 **Ethics and dissemination**

15 258 Ethics approval is not applicable for this study since no original data will be collected. The results will
16
17 259 be disseminated through peer-reviewed publication and conference presentations. Furthermore, this
18
19 260 systematic review will inform the recommendations of working group of polypharmacy and fall-risk-
20
21 261 increasing drugs of the anticipated World's Falls Guidelines.
22
23
24

262

263 **Patient and Public involvement**

31 264 Patients or the public were not involved in the design, or conduct, or reporting, or dissemination
32
33 265 plans of our research.
34
35

266

267 **Discussion**

42 268 Although FRIDs use is an important risk factor for falls, there is uncertainty regarding the
43
44 269 effectiveness of deprescribing interventions as a single intervention in falls prevention in older
45
46 270 people. Identifying effective falls prevention interventions is of importance, considering the burden-
47
48 271 related to fall injuries to both individuals and society.
49
50

52 272 This systematic review will help update the knowledge on the effectiveness of deprescribing, since
53
54 273 we aim to create the most comprehensive systematic review to date by focusing on all geriatric
55
56 274 settings and all deprescribing interventions. In addition, we will use rigorous methodology in
57
58 275 accordance with the Cochrane handbook and the results will be reported as stated by PRISMA
59
60

11

12

1
2
3 276 statement. Therefore, we will provide relevant knowledge that will be implemented into anticipated
4
5 277 World's Falls Guidelines and may influence future clinical practice. However, the certainty of the
6
7 278 evidence of this systematic review may be limited by the limited number of studies available and the
8
9
10 279 possible low quality of the individual studies.

280

281 **References**

- 18 282 1. Berry SD, Miller RR. Falls: epidemiology, pathophysiology, and relationship to fracture. *Curr*
19 283 *Osteoporos Rep.* 2008;6(4):149-54.
- 20 284 2. Kennedy CC, Ioannidis G, Thabane L, Adachi JD, Marr S, Giangregorio LM, et al. Successful
21 285 knowledge translation intervention in long-term care: final results from the vitamin D and
22 286 osteoporosis study (ViDOS) pilot cluster randomized controlled trial. *Trials.* 2015;16(1):214.
- 23 287 3. de Vries M, Seppala LJ, Daams JG, van de Glind EMM, Masud T, van der Velde N. Fall-Risk-
24 288 Increasing Drugs: A Systematic Review and Meta-Analysis: I. Cardiovascular Drugs. *Journal of the*
25 289 *American Medical Directors Association.* 2018;19(4):371.e1-.e9.
- 26 290 4. Seppala LJ, van de Glind EMM, Daams JG, Ploegmakers KJ, de Vries M, Wermelink A, et al.
27 291 Fall-Risk-Increasing Drugs: A Systematic Review and Meta-analysis: III. Others. *Journal of the*
28 292 *American Medical Directors Association.* 2018;19(4):372.e1-.e8.
- 29 293 5. Seppala LJ, Wermelink A, de Vries M, Ploegmakers KJ, van de Glind EMM, Daams JG, et al.
30 294 Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: II. Psychotropics. *Journal of the*
31 295 *American Medical Directors Association.* 2018;19(4):371.e11-.e17.
- 32 296 6. Hart LA, Phelan EA, Yi JY, Marcum ZA, Gray SL. Use of Fall Risk-Increasing Drugs Around a
33 297 Fall-Related Injury in Older Adults: A Systematic Review. *Journal of the American Geriatrics Society.*
34 298 2020;68(6):1334-43.
- 35 299 7. Hopewell S, Adedire O, Copsey BJ, Boniface GJ, Sherrington C, Clemson L, et al. Multifactorial
36 300 and multiple component interventions for preventing falls in older people living in the community.
37 301 *Cochrane Database of Systematic Reviews.* 2018(7).
- 38 302 8. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al.
39 303 Interventions for preventing falls in older people living in the community. *Cochrane Database Syst*
40 304 *Rev.* 2012(9):Cd007146.
- 41 305 9. Cameron ID, Dyer SM, Panagoda CE, Murray GR, Hill KD, Cumming RG, et al. Interventions for
42 306 preventing falls in older people in care facilities and hospitals. *Cochrane Database of Systematic*
43 307 *Reviews.* 2018(9).
- 44 308 10. Lee J, Negm A, Peters R, Wong EKC, Holbrook A. Deprescribing fall-risk increasing drugs
45 309 (FRIDs) for the prevention of falls and fall-related complications: a systematic review and meta-
46 310 analysis. *BMJ Open.* 2021;11(2):e035978.
- 47 311 11. Page AT, Clifford RM, Potter K, Schwartz D, Etherton-Ber CD. The feasibility and effect of
48 312 deprescribing in older adults on mortality and health: a systematic review and meta-analysis. *British*
49 313 *journal of clinical pharmacology.* 2016;82(3):583-623.
- 50 314 12. Reeve E, Gnjjidic D, Long J, Hilmer S. A systematic review of the emerging definition of
51 315 'deprescribing' with network analysis: implications for future research and clinical practice. *British*
52 316 *journal of clinical pharmacology.* 2015;80(6):1254-68.

317

318 **Authors' contributions**

12

13

1
2
3 319 L.S. and N.V. designed the protocol. L.S. and N.V. wrote the first draft of the protocol. N.K., J.R., T.M.,
4
5 320 J.G.D., M. M-O., S.H. and M.P. provided critical appraisal regarding the design of the systematic
6
7 321 review and revised the manuscript. J.G.D. designed and performed the search. All the authors
8
9 322 approved the final version of the protocol.
10
11
12

13 323 **Funding**

16 324 This work was supported by funding from the Canadian Institute of Health Research (CIHR; MOP
17 325 211220; PTJ 153100) and the Clementine Brigitta Maria Dalderup fund (grant number 7303), which is
18 326 an Amsterdam University fund. The sponsors played no part in the design and writing of the protocol.
19
20
21

22 327 **Competing interests**

25 328 The authors declare that they have no competing interests.
26
27

28 329 **Word Count**

30 330 Abstract: 265

32 331 Text: 2336
33
34 332
35
36 333
37
38 334
39
40 335
41
42 336
43
44 337
45
46 338
47
48 339
49
50 340
51
52 341
53
54 342
55
56 343
57
58 344
59
60

13

14

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

345
346
347

For peer review only

14

Appendix 1. Search strategy for Medline

1. inappropriate prescribing/ or exp medication errors/ or deprescriptions/ or exp drug prescriptions/ or exp drug utilization/
2. (deprescri* or ((antidepress* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*) adj2 withdrawal) or ((dose or dosage) adj3 reduc*) or ((discontinu* or problem* or alternative?) adj3 (antidepress* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*)) or (chang* adj5 (antidepress* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*)) or ((polypharmac* or medication) adj2 (risk? or review)) or ((polypharmac* or medication) adj2 management) or prescribing problem? or overprescri* or underprescri* or under prescri* or over prescri* or (frid? and adverse) or medication errors or inappropriate prescri* or (appropriat* adj2 (prescri* or medicine or medication)) or harmful medic* or medication reconciliation).ab,kf,ti
3. or/1-2 [deprescription]
4. accidental falls/
5. (fall? or fell or falling or fallen or faller or stumble? or stumbling or stumbles or slip or slips or slipping or slipped or trip or tripped or physical self maintenance or ambulation or ambulatory).ab,kf,. ti.
6. "Outcome Assessment, Health Care"/
7. (assess* and health care).mp.
8. or/4-7 [Falls | health care assessment]
9. Geriatric assessment/ or frail elderly/ or exp aged/ or middle aged/ or exp nursing homes/ or "homes for the aged"/ or exp aging/
10. (older person? or older patient? or seniors or senior citiz* or elder or elders or elderly or geriatric* or frailty or postmenopausal women or community-dwelling or nursing home? or resident* or old* people or old* person? or old* patient? or old* client? or old* adult? or older m?n or older wom?n).ab,kf,ti.
11. (geriatr* or age or aging or elderl*).in,jw.
12. or/9-11 [Geriatric]
13. and/3,8,12
14. (Beers criteria or Stuck criteria or Beers-Fick criteria or McLeod criteria or Zhan criteria or Rancourt criteria or Lindblad criteria or HEDIS or "Healthcare Effectiveness Data and Information Set" or Japanese Beers or French criteria or Thailand criteria or STOPP or "Screening Tool of Older Person's Prescriptions" or NORGEP or "Norwegian General Practice criteria" or Italian Criteria or Priscus or Korean criteria or Taiwan criteria or Austrian Criteria or Australian Prescribing Indicators Tool or APIT or New Mexico criteria or Czech National criteria or Clyne criteria or Castillo-Paramo criteria or FORTA or "Fit FOR The Aged list" or Galan-Retamal criteria or "EU 7 PIM list" or "European list of potentially inappropriate medications for older people" or Kim criteria or GheOP3S or "Ghent Older People's Prescriptions community Pharmacy Screening" or Chilean criteria or Mazhar criteria or Khodyakov criteria or "Systematic Tool to Reduce Inappropriate Prescribing" or (STRIP adj2 criteria) or Medication Appropriateness Index or MAI or (Assessment of Underutilization adj2 index) or WWADR Profile or West Wales ADR or "lawton and brody").mp [specific tools | outcomes]
15. 13 or 14
16. (randomized or randomly or double blind* or controlled trial? or controlled clinical trial?).ab,kf,ti.
17. (randomized controlled trial or controlled clinical trial).pt.
18. trial.ti.
19. or/16-18 [RCT's sensitive]
20. 15 and 19

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 1, line 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 2, line 57
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 1, lines 3-33
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 12, line 317
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	<input type="checkbox"/>	<input type="checkbox"/>	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 13, line 322
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 13, lines 322
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 13, lines 322
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3, line 73 to Page 4, line 103

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 4, lines 104-110
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 5, line 114 to Page 6, line 142
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 6, lines 144-149
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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 6 -7, lines 152-169 and Appendix 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 8, lines 178-182
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 8, lines 178-182
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 8, lines 183-189
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 8, lines 185-188
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 6, lines 139-142 lines 193-206
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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 9, lines 209-218 Page 10 lines 240-214

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 10, lines 227-228
	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 (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 10, lines 229-234
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 10, lines 234--242
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 9, lines 222-225
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 10, lines 244-254
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 11, lines 253-255

BMJ Open

Protocol for a systematic review and meta-analysis assessing the effectiveness of deprescribing in falls prevention in older people

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-047190.R2
Article Type:	Protocol
Date Submitted by the Author:	02-Sep-2021
Complete List of Authors:	<p>Seppala, Lotta; Amsterdam UMC Location AMC, Department of Internal Medicine, Section of Geriatric Medicine, Amsterdam Public Health Research Institute</p> <p>Kamkar, Nellie; Lawson Research Health Institute, Parkwood Hospital, Gait and Brain Laboratory; University of Western Ontario, Department of Epidemiology and Biostatistics</p> <p>Ryg, Jesper; Odense University Hospital, Department of Geriatric Medicine; University of Southern Denmark, Geriatric Research Unit, Department of Clinical Research</p> <p>Masud, Tahir ; Nottingham University Hospitals NHS Trust</p> <p>Daams, Joost; Amsterdam UMC, University of Amsterdam, Research Support, Medical Library</p> <p>Montero-Odasso, Manuel; Lawson Research Health Institute, Parkwood Hospital, Gait and Brain Lab; University of Western Ontario, Departments of Medicine (Geriatrics) and of Epidemiology and Biostatistics</p> <p>Hartikainen, Sirpa; University of Eastern Finland School of Pharmacy</p> <p>Petrovic, Mirko; Ghent University, Department of Internal Medicine and Paediatrics (section of Geriatrics)</p> <p>van der Velde, Nathalie; Amsterdam UMC Location AMC, Department of Internal Medicine, Section of Geriatric Medicine, Amsterdam Public Health Research Institute</p>
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Pharmacology and therapeutics, Public health
Keywords:	GERIATRIC MEDICINE, PUBLIC HEALTH, Adverse events < THERAPEUTICS

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1

1
2
3 1 **Protocol for a systematic review and meta-analysis assessing the effectiveness of deprescribing in**
4 2 **falls prevention in older people**

5
6 3 **Authors:** L.J. Seppala,¹ N. Kamkar², J. Ryg³, T. Masud⁴, J.G. Daams⁵, M. Montero-Odasso⁶, S.
7 4 Hartikainen⁷, M. Petrovic⁸, N. van der Velde¹, The World Falls Guidelines Task Force

8
9
10 5 **Contact:**

11
12 6 ¹ l.j.seppala@amsterdamumc.nl, Department of Internal Medicine, Section of Geriatric Medicine,
13 7 Amsterdam Public Health Research Institute, Amsterdam UMC, University of Amsterdam,
14 8 Meibergdreef 9, 1105AZ Amsterdam, The Netherlands

15
16
17 9 ² nellie.kamkar@sjhc.london.on.ca, Gait and Brain Laboratory, Lawson Research Health Institute,
18 10 Parkwood Hospital, London Ontario, Canada; Department of Epidemiology and Biostatistics,
19 11 University of Western Ontario, London Ontario, Canada.

20
21 12 ³ Jesper.Ryg@rsyd.dk, Department of Geriatric Medicine, Odense University Hospital, Odense,
22 13 Denmark; Geriatric Research Unit, Department of Clinical Research, University of Southern Denmark,
23 14 Odense, Denmark; ODIN (Odense Deprescribing INitiative), Denmark

24
25 15
26 16 ⁴ Tahir.Masud@nuh.nhs.uk, Nottingham University Hospitals NHS Trust, Nottingham, UK

27
28 17 ⁵ j.g.daams@amsterdamumc.nl, Research Support, Medical Library, Amsterdam UMC, University
29 18 of Amsterdam, Meibergdreef 9, 1105AZ Amsterdam, The Netherlands

30
31 19 ⁶ mmontero@uwo.ca, Gait and Brain Laboratory, Lawson Research Health Institute, Parkwood
32 20 Hospital, London Ontario, Canada; Schulich School of Medicine and Dentistry, London Ontario,
33 21 Canada; Departments of Medicine (Geriatrics) and of Epidemiology and Biostatistics, University of
34 22 Western Ontario, London Ontario, Canada.

35
36 23 ⁷ s.hartikainen@uef.fi, School of Pharmacy, University of Eastern Finland, Kuopio, Finland

37
38 24 ⁸ mirko.petrovic@ugent.be, Department of Internal Medicine and Paediatrics (section of Geriatrics),
39 25 Ghent University, Ghent, Belgium

40
41 26 ¹ n.vandervelde@amsterdamumc.nl, Department of Internal Medicine, Section of Geriatric Medicine,
42 27 Amsterdam Public Health Research Institute, Amsterdam UMC, University of Amsterdam,
43 28 Meibergdreef 9, 1105AZ Amsterdam, The Netherlands

44
45
46
47 29 **Corresponding author:**

48
49 30 Nathalie van der Velde

50
51 31 Department of Internal Medicine, Section of Geriatric Medicine, Amsterdam Public Health Research
52 32 Institute, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105AZ Amsterdam,
53 33 The Netherlands

54
55
56 34

57

58

59

60

1

2

Abstract**Introduction**

One of the known risk factors for fall incidents is the use of specific medications, fall-risk-increasing drugs. However, to date, there is uncertainty related to the effectiveness of deprescribing as a single intervention in falls prevention. Thus, a comprehensive update of the literature focusing on all settings in which older people receive health care and all deprescribing interventions is warranted to enhance the current knowledge.

Methods and analysis

This systematic review protocol follows the PRISMA guidelines. A systematic search was performed in Cochrane Central Register of Controlled Trials, MEDLINE, Embase, and PsycINFO (2nd of November 2020). We will also search in trial registers. We will include Randomized Controlled Trials, in which any deprescribing intervention is compared to usual care and reports falls as an outcome. Both title and abstract screening and full-text screening will be done by two reviewers. The Cochrane Collaboration revised tool of Risk of Bias will be applied to perform risk of bias assessment. We will categorize the results separately for every setting. If a group of sufficiently comparable studies will be identified, we will perform a meta-analysis applying random effects model. We will investigate heterogeneity using a combination of visual inspection of the forest plot along with consideration of the Chi² test and the I² statistic results. We have pre-specified several subgroup and sensitivity analyses.

Ethics and dissemination

Ethics approval is not applicable for this study since no original data will be collected. The results will be disseminated through peer-reviewed publication and conference presentations. Furthermore, this systematic review will inform the recommendations of working group of polypharmacy and fall-risk-increasing drugs of the anticipated World's Falls Guidelines.

2

3

58 **Registration: Registered in PROSPERO. Registration number:** CRD42020218231

59 **Key words:** Medication withdrawal, deprescribing, older adults, accidental falls, falls prevention

60 **Article summary**

61

62 **Strengths and limitations of this study**

- 63 • we aim to create the most comprehensive systematic review of the effectiveness of
- 64 deprescribing as a single intervention in falls prevention to date by focusing on all settings in
- 65 which older people receive health care and all deprescribing interventions
- 66 • we will use rigorous methodology in accordance with the Cochrane handbook and the results
- 67 will be reported as stated by PRISMA statement
- 68 • the search algorithm was developed by an experienced librarian and customized to four large
- 69 databases
- 70 • no language restriction will be applied in the selection of the studies
- 71 • the certainty of the evidence of this systematic review may be limited by the limited number
- 72 of studies available and the possible low quality of the individual studies

73

74 **Background**

75 Fall incidents are a growing major public health concern leading to associated morbidity, mortality
76 and substantial health care costs (1). Of the community-dwelling older adults aged 65 years and
77 older, approximately a third will sustain a fall each year (1). In long term care, residents are even at
78 higher risk of falls; more than half of the residents will fall each year (2). One of the well-established
79 risk factors for falls is the use of specific medications, so-called fall-risk-increasing drugs (FRIDs) (3-5).
80 The prevalence of FRID use in older people with a fall-related injury is high, ranging from 65%-93%
81 (6). Medication review is a common component of the multifactorial falls prevention intervention
82 and the Cochrane review by Hopewell et al. 2018 concluded that multifactorial interventions may

3

4

1
2
3 83 reduce the rate of falls compared with usual care or attention control (7). However, to date, there is
4
5 84 uncertainty related to the effectiveness of deprescribing as a single intervention in falls prevention.
6
7
8 85 Few systematic reviews and meta-analyses have aimed to summarize the evidence-related to
9
10 86 deprescribing as a single intervention (6, 8-11). A comparison of the conclusions of these systematic
11
12 87 reviews is difficult due to the variation in included trials in the different reviews. The trials performed
13
14 88 in long-term care settings or hospitals were summarized by Cameron et al. in 2018 (9). They
15
16 89 concluded that general medication review may make little or no difference to the rate of falls or risk
17
18 90 of falling in long term care facilities. In addition, they identified only one deprescribing intervention
19
20 91 study that was performed in a hospital. Furthermore, the Cochrane review by Gillespie et al. in 2012
21
22 92 assessing fall prevention approaches in community-dwelling older adults identified a total of five
23
24 93 studies investigating medication withdrawal as a single intervention (8). Two of the five included
25
26 94 studies found an effect of the intervention. Page et al. found in 2016 in their meta-analysis that
27
28 95 deprescribing led to fewer falls overall but did not significantly improve the risk of experiencing at
29
30 96 least one fall (11). However, very heterogeneous trials were pooled together from placebo-
31
32 97 controlled psychotropics withdrawal in primary care to education program regarding appropriate
33
34 98 medication use for physicians in nursing homes. Furthermore, Hart et al. concluded in 2020 that
35
36 99 reducing FRIDs use as a stand-alone intervention may not be effective (6). However, only studies
37
38 100 performed in older adults presenting with a fall-related injury or a history of falls were included in
39
40 101 the review. The most recent meta-analysis on this topic by Lee et al. found no effect of FRIDs
41
42 102 deprescribing on fall outcomes (10). However, all studies assessing medication reviews and
43
44 103 management with a broader focus on reducing polypharmacy and potentially inappropriate
45
46 104 prescribing were excluded.
47
48
49
50
51
52
53
54 105 Thus, a comprehensive update of the literature focusing all deprescribing interventions including
55
56 106 medication reviews with broader focus is warranted to enhance current knowledge as important
57
58 107 deprescribing trials have been published in recent years. Therefore, our aim is to perform a
59
60

4

5

108 systematic review concerning the effectiveness of deprescribing (e.g., including general medication
109 reviews or FRIDs deprescribing) as a single intervention in falls prevention performed in any setting in
110 which older people receive health care. Furthermore, we aim to report the results separately for
111 each setting and perform a meta-analysis if sufficiently comparable studies will be identified.

112 **Methods**

113 This systematic review will be conducted and reported following the Preferred Reporting Items for
114 Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

115 **Eligibility criteria**

116 Type of studies

117 Only Randomized Controlled Trials (RCTs), including quasi-randomized trials (for example, allocation
118 by alternation), cluster-randomized trials and trials in which treatment allocations are inadequately
119 concealed, will be included. We will include studies without language restriction.

120 Types of Participants

121 Trials will be considered for inclusion if they included participants aged ≥ 60 years or if the majority of
122 participants are aged >65 years or the mean age is >65 years. We will include trials from all settings
123 e.g., community, hospital ward, long term care facilities.

124 Type of interventions

125 The intervention can be any deprescribing intervention. "Deprescribing" has been described as "the
126 process of withdrawal of an (inappropriate) medication, supervised by a health care professional with
127 the goal of managing polypharmacy and improving outcomes" (12). The interventions can be, for
128 example, pharmacist-led medication reviews, physician-led interventions, prescriber education
129 programs, multidisciplinary interventions or clinical decision support systems. The intervention can
130 target specific drug classes (e.g., psychotropics) or general medication regimen (i.e. comprehensive

5

6

1
2
3 131 medication review). The intervention might target multiple medication issues in case of
4
5 132 comprehensive medication review in addition to withdrawal such as polypharmacy, non-adherence,
6
7 133 education, and starting medications. If deprescribing intervention is a part of a multi-modal
8
9 134 intervention (e.g., including an exercise component in addition to deprescribing), the study will be
10
11
12 135 excluded.

15 136 Type of Control

17
18 137 The comparison intervention will be usual care (i.e. no deprescribing or no change in usual activities of
19
20 138 care).

23 139 Type of outcomes

25
26 140 We will include trials that report raw data or statistics related to falls outcomes. We will include any
27
28 141 type of falls outcome: number of falls, number of fallers/non-fallers/frequent fallers, fall rate per
29
30 142 person-year, and time to first fall. Our secondary outcome is injurious falls (for example fall-related
31
32 143 fractures, fall-related hospital admissions or fall-related health care use).

36 144 Information sources

38
39 145 A systematic search was performed in Cochrane Central Register of Controlled Trials, MEDLINE,
40
41 146 Embase, and PsycINFO to search for literature published from onset until 2nd of November 2020 which
42
43 147 will be updated to prior manuscript submission. A customized search strategy was conducted for each
44
45 148 database. We will also search in trial registers. In the case that a relevant conference abstract is
46
47 149 identified, we will contact the authors to obtain full text article. Reference lists of included studies,
48
49 150 reviews (e.g., Cochrane reviews) and falls prevention guidelines will be reviewed to identify additional
50
51 151 studies.

56 152 Search strategy

59 153

6

7

154 A search for Medline is provided as an example and is available in Appendix I.

155 The search terms used were:

- 156 1. Deprescription: inappropriate prescribing, medication errors, deprescriptions, drug prescriptions,
157 drug utilization, dose in combination with reduction, polypharmacy or medication in combination
158 with risk, management or review, harmful medication, medication reconciliation, appropriate in
159 combination with prescribing or medicine or medication, prescribing problem, overprescribing, under
160 prescribing, withdrawal or discontinuation or problem or alternative or change in combination with
161 medicine, medication or drug or frid or polypharmacy, antidepressant or antipsychotic.
- 162 2. Falls or health care assessment: accidental falls, fall, fell, stumble, slip, trip,
163 physical self-maintenance, ambulatory, health care outcome assessment
- 164 3. Geriatric: geriatric assessment, frail, elderly, aged, middle aged, nursing homes, homes for the
165 aged, aging, older person, older patient, senior, elder, geriatric, frailty, postmenopausal women,
166 community-dwelling, resident, old people, old client, old adult, older man, older woman
- 167 4. 1 AND 2 AND 3
- 168 5. Prescribing tools: e.g. STOPP, "Screening Tool of Older Person's Prescriptions"
- 169 6. 4 OR 5
- 170 7. RCT: randomized, randomly, double blind, controlled trial, controlled clinical trial
- 171 8. 6 AND 7

172

173 The search was built by an experienced clinical librarian. We used 30 potentially relevant test articles
174 to test and build the search. These articles were a priori identified using the function similar articles in
175 PubMed and by reading references of the selected articles. These test articles included also articles
176 that were identified from systematic reviews on deprescribing and included falls as a secondary
177 outcome and not as a main interest.

178

179 **Data records and management**

7

8

1
2
3 180 First, title and abstract screening will be done independently by two reviewers using Rayyan, a web-
4
5 181 based systematic review program. In case of disagreement, a third reviewer will be consulted.
6
7 182 Following the title and abstract screening, a full-text screening will be done using Rayyan by two
8
9
10 183 independent reviewers. A third reviewer will be consulted in case of disagreement. Reasons for
11
12 184 exclusion of studies will be collected during the full-text screening phase.

13
14
15 185 Two authors will independently extract data from each article using a structured data collection form.
16
17 186 In case of disagreement, a third reviewer will be consulted. The following information will be collected:
18
19 187 study design, country, setting, inclusion criteria, total number of participants and age (mean and
20
21 188 standard deviation), intervention type, control type, all fall-related outcomes, and how collected,
22
23 189 adjustment of outcomes if applicable, follow-up duration, compliance to the intervention and if the
24
25 190 trials have reported possible adverse effects related to the intervention or economic outcomes. If data
26
27 191 to be extracted are missing, incomplete or unclear, inquiries will be sent to the authors.
28
29

30 192

31 193 **Effect measures**

32 194

33 195 We will report the treatment effects between the intervention and control group as a Rate Ratio (RaR),
34
35 196 a Risk Ratio (RR) and/or a Hazard Ratio (HR) and accompanying 95% confidence intervals (95% CI).
36
37

38 197

39 198 For rate of falls, we will use RaR as a treatment effect measure and the rate is the total number of falls
40
41 199 per unit of person time that falls were monitored. We will use the unadjusted RaR, unless the
42
43 200 adjustment is performed due to clustering. Furthermore, if needed due to missing reporting, we will
44
45 201 calculate RaR from appropriate raw data if possible. For dichotomous outcomes e.g., fallers or frequent
46
47 202 fallers, we will use RR as a treatment effect measure. We will use the unadjusted RR, unless the
48
49 203 adjustment is performed due to clustering. Furthermore, if needed due to missing reporting or if Odds
50
51 204 Ratio is reported, we will calculate RR from the raw data if possible. For survival time-to-event data,
52
53
54
55
56
57
58
59
60

8

9

205 we will use HR as a treatment effect measure. We will use the unadjusted HR, unless the adjustment
206 is performed due to clustering.

207 Furthermore, we will adjust for clustering, if not already done in the published report using intra-
208 cluster coefficient estimates and average cluster size.

209 **Risk of bias**

210

211 Two reviewers will assess the risk of bias independently by applying the Cochrane Collaboration revised
212 tool of Risk of Bias (RoB 2.0) to all the included studies. In case of disagreement, a third reviewer will
213 be consulted. The tool covers five domains: bias arising from randomization process, bias due to
214 deviations from intended interventions, bias due to missing outcome data, bias in measurement of
215 outcome, bias in selection of the reported result. In addition, an additional domain is available for
216 cluster randomized trials; bias arising from identification or recruitment of individual participants
217 within clusters. Each domain has signalling questions aiming to elicit relevant information. Responses
218 to these questions are fed into algorithms to score each domain either low risk of bias, some concerns
219 or high risk of bias. The scores of each domain are further mapped into overall risk-of-bias-judgement
220 including categories of low risk of bias, some concerns and high risk of bias.

221

222 **Data synthesis**

223

224 We will categorize the results separately for every setting (e.g., community, hospital, or long term care
225 facilities) due to different participant and environment characteristics.

226 First, a narrative synthesis will be provided in the text and tables to summarize the study characteristics
227 and results.

228

9

10

1
2
3 229 If a group of studies with a sufficiently comparable intervention and outcome and performed in a same
4
5 230 setting is identified, we will perform a meta-analysis applying the intention-to-treat principle. For
6
7 231 example a study purely investigating antihypertensive withdrawal will not be pooled with a study
8
9 232 purely investigating antidepressant withdrawal.

11 233 The results will be pooled using a random-effects model considering the expected heterogeneity
12
13 234 between the studies. We will try to minimize the heterogeneity by grouping the trials by setting and
14
15 235 similar intervention. We will investigate remaining heterogeneity within a pooled group of trials using
16
17 236 a combination of visual inspection of the forest plot along with consideration of the Chi^2 test (with
18
19 237 statistical significance set at $P < 0.10$), and the I^2 statistic results according to the recommendations
20
21 238 from the Cochrane Handbook. We will explore heterogeneity by conducting a subgroup analysis based
22
23 239 on the following: 1) age, 2) whether the trial is targeted to known fallers (or recurrent fallers if
24
25 240 applicable) or also to non-fallers, 3) health care professionals conducting the medication review e.g.,
26
27 241 by physician or pharmacist, 4) whether the medication review is done with the help of a prescribing
28
29 242 tool e.g., STOPP/START or the Beers criteria and which tool is used and 5) population e.g. if the trial is
30
31 243 conducted only in dementia patients in comparison to general nursing home population. We will
32
33 244 perform a sensitivity analysis according to overall study quality; low risk of bias, some concerns and
34
35 245 high risk of bias, by comparing random and fixed-effect model and by excluding possible outlying
36
37 246 studies, if the visual inspection of the forest plot shows poorly overlapping confidence intervals.
38
39
40
41
42
43
44

45 247
46 248 We will explore the possibility of publication bias by constructing funnel plots and by conducting Eggers
47
48 249 test for analyses that contain more than ten studies.

49
50 250
51
52 251 The software Review Manager (RevMan) will be used for all statistical tests (Review Manager (RevMan)
53
54 252 [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane
55
56 253 Collaboration, 2014).

57
58
59 254
60

10

11

255 Confidence in cumulative evidence

256

257 The confidence in effect estimates for each reported outcome will be assessed using the Grading of
258 Recommendations, Assessment, Development and Evaluation (GRADE) approach by two reviewers
259 and possible disagreement will be assessed by third reviewer.

260

261 Ethics and dissemination

262 Ethics approval is not applicable for this study since no original data will be collected. The results will
263 be disseminated through peer-reviewed publication and conference presentations. Furthermore, this
264 systematic review will inform the recommendations of working group of polypharmacy and fall-risk-
265 increasing drugs of the anticipated World's Falls Guidelines.

266

267 Patient and Public involvement

268 Patients or the public were not involved in the design, or conduct, or reporting, or dissemination
269 plans of our research.

270

271 Discussion

272 Although FRIDs use is an important risk factor for falls, there is uncertainty regarding the
273 effectiveness of deprescribing interventions as a single intervention in falls prevention in older
274 people. Identifying effective falls prevention interventions is of importance, considering the burden-
275 related to fall injuries to both individuals and society.

276 This systematic review will help update the knowledge on the effectiveness of deprescribing, since
277 we aim to create the most comprehensive systematic review to date by exploring all settings in

11

12

1
2
3 278 which older people receive health care and all deprescribing interventions. In addition, we will use
4
5 279 rigorous methodology in accordance with the Cochrane handbook and the results will be reported as
6
7 280 stated by PRISMA statement. Therefore, we will provide relevant knowledge that will be
8
9
10 281 implemented into anticipated World's Falls Guidelines and may influence future clinical practice.
11
12 282 However, the certainty of the evidence of this systematic review may be limited by the limited
13
14 283 number of studies available and the possible low quality of the individual studies.
15
16
17 284

20 285 **References**

- 23 286 1. Berry SD, Miller RR. Falls: epidemiology, pathophysiology, and relationship to fracture. *Curr*
24 287 *Osteoporos Rep.* 2008;6(4):149-54.
- 25 288 2. Kennedy CC, Ioannidis G, Thabane L, Adachi JD, Marr S, Giangregorio LM, et al. Successful
26 289 knowledge translation intervention in long-term care: final results from the vitamin D and
27 290 osteoporosis study (ViDOS) pilot cluster randomized controlled trial. *Trials.* 2015;16(1):214.
- 28 291 3. de Vries M, Seppala LJ, Daams JG, van de Glind EMM, Masud T, van der Velde N. Fall-Risk-
29 292 Increasing Drugs: A Systematic Review and Meta-Analysis: I. Cardiovascular Drugs. *Journal of the*
30 293 *American Medical Directors Association.* 2018;19(4):371.e1-.e9.
- 31 294 4. Seppala LJ, van de Glind EMM, Daams JG, Ploegmakers KJ, de Vries M, Wermelink A, et al.
32 295 Fall-Risk-Increasing Drugs: A Systematic Review and Meta-analysis: III. Others. *Journal of the*
33 296 *American Medical Directors Association.* 2018;19(4):372.e1-.e8.
- 34 297 5. Seppala LJ, Wermelink A, de Vries M, Ploegmakers KJ, van de Glind EMM, Daams JG, et al.
35 298 Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: II. Psychotropics. *Journal of the*
36 299 *American Medical Directors Association.* 2018;19(4):371.e11-.e17.
- 37 300 6. Hart LA, Phelan EA, Yi JY, Marcum ZA, Gray SL. Use of Fall Risk-Increasing Drugs Around a
38 301 Fall-Related Injury in Older Adults: A Systematic Review. *Journal of the American Geriatrics Society.*
39 302 2020;68(6):1334-43.
- 40 303 7. Hopewell S, Adedire O, Copsey BJ, Boniface GJ, Sherrington C, Clemson L, et al. Multifactorial
41 304 and multiple component interventions for preventing falls in older people living in the community.
42 305 *Cochrane Database of Systematic Reviews.* 2018(7).
- 43 306 8. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al.
44 307 Interventions for preventing falls in older people living in the community. *Cochrane Database Syst*
45 308 *Rev.* 2012(9):Cd007146.
- 46 309 9. Cameron ID, Dyer SM, Panagoda CE, Murray GR, Hill KD, Cumming RG, et al. Interventions for
47 310 preventing falls in older people in care facilities and hospitals. *Cochrane Database of Systematic*
48 311 *Reviews.* 2018(9).
- 49 312 10. Lee J, Negm A, Peters R, Wong EKC, Holbrook A. Deprescribing fall-risk increasing drugs
50 313 (FRIDs) for the prevention of falls and fall-related complications: a systematic review and meta-
51 314 analysis. *BMJ Open.* 2021;11(2):e035978.
- 52 315 11. Page AT, Clifford RM, Potter K, Schwartz D, Etherton-Beer CD. The feasibility and effect of
53 316 deprescribing in older adults on mortality and health: a systematic review and meta-analysis. *British*
54 317 *journal of clinical pharmacology.* 2016;82(3):583-623.

12

13

1
2
3 318 12. Reeve E, Gnjjidic D, Long J, Hilmer S. A systematic review of the emerging definition of
4 319 'deprescribing' with network analysis: implications for future research and clinical practice. British
5 320 journal of clinical pharmacology. 2015;80(6):1254-68.

321

322 **Authors' contributions**

323 L.S. and N.V. designed the protocol. L.S. and N.V. wrote the first draft of the protocol. N.K., J.R., T.M.,
324 J.G.D., M. M-O., S.H. and M.P. provided critical appraisal regarding the design of the systematic
325 review and revised the manuscript. J.G.D. designed and performed the search. All the authors
326 approved the final version of the protocol.

327 **Funding**

328 This work was supported by funding from the Canadian Institute of Health Research (CIHR; MOP
329 211220; PTJ 153100) and the Clementine Brigitta Maria Dalderup fund (grant number 7303), which is
330 an Amsterdam University fund. The sponsors played no part in the design and writing of the protocol.

331 **Competing interests**

332 The authors declare that they have no competing interests.

333 **Word Count**

334 Abstract: 265

335 Text: 2336

336

337

338

339

340

341

342

343

13

14

- 1
- 2
- 3 344
- 4
- 5 345
- 6
- 7 346
- 8
- 9 347
- 10
- 11 348
- 12
- 13 349
- 14
- 15 350
- 16
- 17 351
- 18
- 19
- 20
- 21
- 22
- 23
- 24
- 25
- 26
- 27
- 28
- 29
- 30
- 31
- 32
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

For peer review only

14

Appendix 1. Search strategy for Medline

1. inappropriate prescribing/ or exp medication errors/ or deprescriptions/ or exp drug prescriptions/ or exp drug utilization/
2. (deprescri* or ((antidepress* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*) adj2 withdrawal) or ((dose or dosage) adj3 reduc*) or ((discontinu* or problem* or alternative?) adj3 (antidepress* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*)) or (chang* adj5 (antidepress* anti depress* or antipsychotic* or anti psychotic* or medicine or medication or drug? or frid? or polypharmac*)) or ((polypharmac* or medication) adj2 (risk? or review)) or ((polypharmac* or medication) adj2 management) or prescribing problem? or overprescri* or underprescri* or under prescri* or over prescri* or (frid? and adverse) or medication errors or inappropriate prescri* or (appropriat* adj2 (prescri* or medicine or medication)) or harmful medic* or medication reconciliation).ab,kf,ti
3. or/1-2 [deprescription]
4. accidental falls/
5. (fall? or fell or falling or fallen or faller or stumble? or stumbling or stumbles or slip or slips or slipping or slipped or trip or tripped or physical self maintenance or ambulation or ambulatory).ab,kf,. ti.
6. "Outcome Assessment, Health Care"/
7. (assess* and health care).mp.
8. or/4-7 [Falls | health care assessment]
9. Geriatric assessment/ or frail elderly/ or exp aged/ or middle aged/ or exp nursing homes/ or "homes for the aged"/ or exp aging/
10. (older person? or older patient? or seniors or senior citiz* or elder or elders or elderly or geriatric* or frailty or postmenopausal women or community-dwelling or nursing home? or resident* or old* people or old* person? or old* patient? or old* client? or old* adult? or older m?n or older wom?n).ab,kf,ti.
11. (geriatr* or age or aging or elderl*).in,jw.
12. or/9-11 [Geriatric]
13. and/3,8,12
14. (Beers criteria or Stuck criteria or Beers-Fick criteria or McLeod criteria or Zhan criteria or Rancourt criteria or Lindblad criteria or HEDIS or "Healthcare Effectiveness Data and Information Set" or Japanese Beers or French criteria or Thailand criteria or STOPP or "Screening Tool of Older Person's Prescriptions" or NORGEP or "Norwegian General Practice criteria" or Italian Criteria or Priscus or Korean criteria or Taiwan criteria or Austrian Criteria or Australian Prescribing Indicators Tool or APIT or New Mexico criteria or Czech National criteria or Clyne criteria or Castillo-Paramo criteria or FORTA or "Fit FOR The Aged list" or Galan-Retamal criteria or "EU 7 PIM list" or "European list of potentially inappropriate medications for older people" or Kim criteria or GheOP3S or "Ghent Older People's Prescriptions community Pharmacy Screening" or Chilean criteria or Mazhar criteria or Khodyakov criteria or "Systematic Tool to Reduce Inappropriate Prescribing" or (STRIP adj2 criteria) or Medication Appropriateness Index or MAI or (Assessment of Underutilization adj2 index) or WWADR Profile or West Wales ADR or "lawton and brody").mp [specific tools | outcomes]
15. 13 or 14
16. (randomized or randomly or double blind* or controlled trial? or controlled clinical trial?).ab,kf,ti.
17. (randomized controlled trial or controlled clinical trial).pt.
18. trial.ti.
19. or/16-18 [RCT's sensitive]
20. 15 and 19

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 1, line 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 2, line 57
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 1, lines 3-33
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 12, line 317
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	<input type="checkbox"/>	<input type="checkbox"/>	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 13, line 322
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 13, lines 322
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 13, lines 322
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 3, line 73 to Page 4, line 103

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 4, lines 104-110
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 5, line 114 to Page 6, line 142
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 6, lines 144-149
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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 6 -7, lines 152-169 and Appendix 1
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 8, lines 178-182
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 8, lines 178-182
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 8, lines 183-189
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 8, lines 185-188
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 6, lines 139-142 lines 193-206
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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 9, lines 209-218 Page 10 lines 240-214

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 10, lines 227-228
	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 (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 10, lines 229-234
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 10, lines 234--242
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 9, lines 222-225
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 10, lines 244-254
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Page 11, lines 253-255