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BMJ Open

Computerized decision to reduce inappropriate medication in the elderly: A systematic review with a meta-analysis protocol

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Keywords:	Medical Informatics Applications, Deprescriptions, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, GENERAL MEDICINE (see Internal Medicine), PRIMARY CARE

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Manuscripts

Title

Computerized decision to reduce inappropriate medication in the elderly: A systematic review with a meta-analysis protocol

Registration: PROSPERO, nr. CRD42017067021.

Authors:

Luis Monteiro, luismonteiro.net@gmail.com

Faculdade de Ciências da Saúde, Universidade da Beira Interior, Covilhã, Portugal
USF Esgueira +, Aveiro, Portugal

Tiago Maricoto, tiago.maricoto@gmail.com

Faculdade de Ciências da Saúde, Universidade da Beira Interior, Covilhã, Portugal
USF Aveiro Aradas, Aveiro, Portugal

Isabel Solha, isabel.solha@gmail.com

USF Terras de Souza, Paredes, Portugal

Matilde Monteiro-Soares, matsoares@med.up.pt

MEDCIDS – *Department of Community Medicine, Information and Health Decision Sciences,*
Oporto University Faculty of Medicine, Oporto, Portugal

CINTESIS - Center for Health Technology and Services Research, Oporto University
Faculty of Medicine, Oporto, Portugal

Carlos Martins, carlosmartins20@gmail.com

MEDCIDS – Departamento de Medicina da Comunidade, Informação e Decisão em Saúde,
Oporto University Faculty of Medicine, Oporto, Portugal

CINTESIS - Center for Health Technology and Services Research, Oporto University
Faculty of Medicine, Oporto, Portugal

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27 All authors have completed the ICMJE uniform disclosure at
28 http://www.icmje.org/coi_disclosure.pdf and declare: financial support for the submitted
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47 **Correspondence:**

48 Dr. Luís Monteiro; Email: luismonteiro.net@gmail.com; Postal Address: Av. Infante D.
49 Henrique, 6200-506 Covilhã.

50 **Contributions:**

51 LM had the original idea for the systematic review. LM, TM, and ISS wrote the protocol
52 and reviewed the search strategy. LM, TM, ISS, MM-S, and CM reviewed the protocol.

Abstract

Introduction: Life expectancy continues to increase in developed countries. Elderly people are more likely to consume more medications and become vulnerable due to age-related changes in drugs' pharmacokinetics and pharmacodynamics. Recent studies have identified opportunities and barriers for deprescribing potentially inappropriate medications. Some computer decision support systems may improve prescribing, while improved software can reduce unnecessary prescription of tests; however, there is lack of evidence about their efficacy on deprescribing. We will systematically review the available literature to understand if computerized decision support is effective in the use of potentially inappropriate medications, thus having an impact on health outcomes.

Methods and analysis: A systematic review will be conducted using PubMed, CENTRAL, Web of Science and EMBASE databases, as well as the grey literature assessing the effectiveness of computer decision support interventions in deprescribing inappropriate medication, with an impact on health outcomes in the elderly. Two reviewers will conduct the articles 'screening, selection, and data extraction, independently and blind to each other. Eligible sources will be selected after discussing non-conformities. All extracted data from selected articles will be categorised based on the studies' participants, design and setting, methodological quality, bias and any other potential sources of heterogeneity. This review will be conducted and reported in adherence with the PRISMA statement of quality for reporting systematic reviews and meta-analyses.

Ethics and Dissemination: As a systematic review, this research is exempt from ethical approval. We intend to publish the full article in a related peer-reviewed journal and report on it at international conferences.

Keywords: Medical Informatics Applications, Deprescriptions.

Registration: PROSPERO, nr. CRD42017067021.

85 Introduction

86
87 In developed countries, the aging population is increasing (1). Caring for older adults is a
88 challenge for healthcare providers, because older patients are more likely to have
89 multimorbidities (2, 3) and to consume more medication. Polypharmacy has a negative
90 impact on senior health (4, 5) due to an increased risk of drug interactions and prescriptions
91 for potentially inappropriate medications (6). Prescribing medication for elderly patients
92 should be evidence-based; cautiousness is mandatory because seniors have changes in
93 pharmacokinetics and pharmacodynamics, and research often excludes patients who are
94 more than 65-years-old.

95 Deprescribing is defined as the “the process of withdrawal of inappropriate medication,
96 supervised by a health care professional with the goal of managing polypharmacy and
97 improving outcomes” (7).

98 In the community setting, primary care physicians/family doctors, nurses, pharmacists, and
99 other professionals must manage the continuity of senior care. Recent studies have
100 identified both opportunities and barriers for deprescribing.

101 Some computerized decision support systems may improve prescribing and software to
102 reduce unnecessary tests (8), but there is lack of evidence regarding their efficacy on
103 deprescribing. This systematic review aims to determine if computerized decision support
104 is effective in eliminating potentially inappropriate prescriptions, and establish the efficacy
105 of these interventions in the elderly in terms of health outcomes.

106

107 Methods and Analysis

108

109 *Eligibility criteria*

110 This systematic review will include interventional studies, such as experimental study
111 designs [randomized controlled studies (RCTs), non-randomized controlled studies, and
112 quasi-randomized controlled studies]. Observational studies (such as case reports, case
113 series, cross-sectional analyses, case–controls, cohorts, etc.) will not be selected.

114 Only studies including participants aged 65 years and older, who were prescribed one or
115 more regular medication, will be selected. On the other hand, studies including only

1
2
3 116 moribund, terminal, or palliative participants will be excluded. Studies published or in press
4
5 117 will be included independently of the language, year of publication, and setting in which it
6
7 118 was conducted (hospitals, nursing centres, communities, etc.).

8
9 119

10 120 ***Information sources***

11
12 121 Our sources of information will include electronic databases (namely PubMed, CENTRAL,
13
14 122 EMBASE), trial registries, different types of grey literature, and contact with specialists in
15
16 123 the field. If further data is needed, authors of the selected articles will be contacted.

17 124

18 19 125 ***Search strategy***

20
21 126 Our initial search syntax in CENTRAL will be:

22 127 1 MeSH descriptor: [Medical Informatics Applications]explode all trees

23
24 128 2.Computer decision support

25
26 129 3.MeSH descriptor: [Deprescriptions]explode all trees

27
28 130 4.MeSH descriptor: [Inappropriate Prescribing] explode all trees

29
30 131 5.#1 or #2

31
32 132 6.#3 or #4

33
34 133 7.#5 and #6

35 134

36 135 For MEDLINE, the query will be "Medical Informatics Applications"[Mesh] AND
37
38 136 ("Deprescriptions"[Mesh] OR "Inappropriate Prescribing"[Mesh]); and for
39
40 137 EMBASE('medical informatics'/exp OR 'mobile application'/exp) AND
41
42 138 ('deprescription'/exp OR 'inappropriate prescribing'/exp).

43 139

44 45 140 ***Study selection process***

46
47 141 Two authors will independently, and blinded to each other, perform the primary article
48
49 142 screening. First, they will review the title and abstract, and categorise the articles into three
50
51 143 groups: relevant, irrelevant, and unsure. Articles categorised as irrelevant by both reviewers
52
53 144 will be eliminated from the study. Then, each reviewer will review the full text of the
54
55 145 remaining articles and make a list of those to be included. The two lists will be compared

1
2
3 146 and non-conformities will be discussed. When an agreement cannot be reached, the whole
4
5 147 team of researchers will make the final decision.

6
7 148

8
9 149 ***Data management***

10 150 Once the articles to be included are selected, data will be extracted and entered into data
11
12 151 sheets independently by the two reviewers.

13 152 These two sheets, including their differences, will be checked by a third reviewer.

14 153 Any potential difference among reviewers will be discussed with the team, and if not
15
16 154 resolved, the manuscript authors will be contacted. Also, if required data are missing from
17
18 155 the article or are incomplete or unclear, inquiries will be sent to the authors.

19
20
21 156

22 157 ***Data items***

23
24 158 The following information will be extracted from each article:1) study characteristics,
25
26 159 intervention type; type of study; country, setting, duration of follow-up;2) participants,
27
28 160 number, age;3) outcomes, effect of intervention on withdrawal of potentially inappropriate
29
30 161 medication, clinical outcomes such as mortality, any reported adverse drug withdrawal
31
32 162 effects, physical health, cognitive function, psychological health parameters, quality of life
33
34 163 measurement, and value.

35
36 164

37 165 ***Risk of bias***

38 166 Two reviewers will assess, independently and blinded to each other, the risk of bias.

39 167 The Cochrane Collaboration Risk of Bias tool will be used to assess this for each study(9).

40
41
42 168

43 169 ***Data synthesis***

44
45 170 The final report will present the range of clinical decision support, as well as efficiency
46
47 171 regarding health outcomes. If studies are sufficiently homogeneous in terms of design and
48
49 172 comparisons, we will conduct regression-analyses using a random-effects model.

50 173 Each outcome will be combined and calculated using the statistical software RevMan
51
52 174 5.1(10), according to statistical guidelines referenced in the current version of the Cochrane
53
54 175 Handbook for Systematic Reviews of Interventions(11). The Mantel-Haenszel method will
55
56 176 be used for the fixed effect model if tests for heterogeneity are not significant. If statistical

1
2
3 177 heterogeneity is observed ($I^2 \geq 50\%$ or $p < 0.1$), the random effects model will be chosen. If
4
5 178 heterogeneity is substantial, we will not perform a meta-analysis; a narrative, qualitative
6
7 179 summary will be done instead.

8
9 180 Subgroups will be presented according to the setting, intervention and medication. The final
10
11 181 paper will be prepared following the Preferred Reporting Items for Systematic Reviews and
12
13 182 Meta-Analyses (PRISMA) guidelines(12, 13).

14 183 Subgroup analyses will be used to explore possible sources of heterogeneity, based on the
15
16 184 following: medications and type of software.

17 185 A systematic narrative synthesis will be provided in the text and tables to summarise and
18
19 186 explain the characteristics and findings of the studies; it will explore the relationship within
20
21 187 and between studies, in line with guidance from the Centre for Reviews and Dissemination.

22 188 In order to determine whether reporting bias is present, we will determine whether the
23
24 189 protocol of the RCT was published before recruitment of patients was initiated.

25 190 Data from RCTs will not be combined with data from other study designs. We will evaluate
26
27 191 whether selective reporting of outcomes is obvious. The quality of evidence for all
28
29 192 outcomes will be judged with the Grading of Recommendations Assessment, and the
30
31 193 Development and Evaluation working group methodology(14). We further separated
32
33 194 comparative studies with and without concurrent control groups. Forest plots will be
34
35 195 produced when three or more studies are included in a meta-analysis. Data in tables will be
36
37 196 presented by therapeutic class, based on the Anatomical Therapeutic Classification (ATC)
38
39 197 codes.

40 198

41 199 Randomized studies

42
43 200 If heterogeneity is detected, we will select the random effects model. If one or more of the
44
45 201 original studies use a cluster-randomization method, we will use generic inverse variance.

46 202

47
48 203 Dichotomous data

49
50 204 Effect sizes and 95% confidence intervals (CIs) were expressed as odds ratios (OR). When a
51
52 205 study reports zero events in both arms, it would be excluded from the meta-analysis.

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208 Discussion

209

210 Although electronic health records are common in clinical practice, there is a lack of
211 evidence of computer decision support regarding health outcomes. Deprescribing
212 potentially inappropriate medication in the elderly is particularly difficult, although
213 computer support may be an important tool. This systematic review will help identify the
214 best decision support available, as well as its limitations. Therefore, this systematic review
215 will be relevant for patients, health professionals, and policy makers.

216 References

217

- 218 1. OECD. Elderly population (indicator). doi: 10.1787/8d805ea1-en (Accessed on 26
219 February 2017) [Available from: [https://data.oecd.org/pop/elderly-
220 population.htm#indicator-chart](https://data.oecd.org/pop/elderly-population.htm#indicator-chart).
- 221 2. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al.
222 Aging with multimorbidity: a systematic review of the literature. *Ageing ResRev.*
223 2011;10(4):430-9.
- 224 3. Prazeres F, Santiago L. Prevalence of multimorbidity in the adult population
225 attending primary care in Portugal: a cross-sectional study. *BMJ open.* 2015;5(9):e009287.
- 226 4. Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health
227 outcomes associated with polypharmacy in community-dwelling older adults: a systematic
228 review. *JAm Ger Soc.* 2014;62(12):2261-72.
- 229 5. Lu WH, Wen YW, Chen LK, Hsiao FY. Effect of polypharmacy, potentially
230 inappropriate medications and anticholinergic burden on clinical outcomes: a retrospective
231 cohort study. *Can Med AssocJ.* 2015;187(4):E130-7.
- 232 6. Weng MC, Tsai CF, Sheu KL, Lee YT, Lee HC, Tzeng SL, et al. The impact of
233 number of drugs prescribed on the risk of potentially inappropriate medication among
234 outpatient older adults with chronic diseases. *J AssocPhysicians.* 2013;106(11):1009-15.
- 235 7. Reeve E, Ong M, Wu A, Jansen J, Petrovic M, Gnjjidic D. A systematic review of
236 interventions to deprescribe benzodiazepines and other hypnotics among older people. *Eur*
237 *J Clin Pharmacol.* 2017;doi:10.1007/s00228-017-2257-8.
- 238 .
- 239 8. Martins CMS, da Costa Teixeira AS, de Azevedo LFR, Sá LMB, Santos PAAP, do
240 Couto MLGD, et al. The effect of a test ordering software intervention on the prescription
241 of unnecessary laboratory tests - a randomized controlled trial. *BMC Med InformDecis.*
242 2017;17(1):20.
- 243 9. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The
244 Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Brit Med J.*
245 2011;343.

- 1
2
3 246 10. Review Manager (RevMan) Copenhagen: The Nordic Cochrane Centre, The
4 247 Cochrane Collaboration. Version 5.3 ed2014.
5 248 11. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0:
6 249 updated March 2011.
7
8 250 12. Moher D, Shamseer L, Clarke M, Gherzi D, Liberati A, Petticrew M, et al. Preferred
9 251 reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015
10 252 statement. *Syst Rev.* 2015;4(1):1.
11 253 13. Shamseer L, Moher D, Clarke M, Gherzi D, Liberati A, Petticrew M, et al. Preferred
12 254 reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015:
13 255 elaboration & explanation. *Brit Med J.* 2015;349.
14 256 14. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA,
15 257 Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and
16 258 transparent approach to making well informed healthcare choices. 1: Introduction. *Brit Med*
17 259 *J.* 2016;353.
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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"/>	2,3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" 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"/>	5; 81
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"/>	8-25
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	50-52
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"/>	39-46
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	39
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input type="checkbox"/>	N/A
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input type="checkbox"/>	<input type="checkbox"/>	87-103
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	<input type="checkbox"/>	<input type="checkbox"/>	103-105
					110-118

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
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"/>	114-118
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 type="checkbox"/>	<input type="checkbox"/>	121-123
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 type="checkbox"/>	<input type="checkbox"/>	121-123
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input type="checkbox"/>	<input type="checkbox"/>	150-155
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 type="checkbox"/>	<input type="checkbox"/>	150-155
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 type="checkbox"/>	<input type="checkbox"/>	150-155
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 type="checkbox"/>	<input type="checkbox"/>	150-155
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 type="checkbox"/>	<input type="checkbox"/>	149-152
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 type="checkbox"/>	<input type="checkbox"/>	166-167
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input type="checkbox"/>	<input type="checkbox"/>	170-197
	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 type="checkbox"/>	<input type="checkbox"/>	175
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input type="checkbox"/>	<input type="checkbox"/>	172
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input type="checkbox"/>	<input type="checkbox"/>	182

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input type="checkbox"/>	<input type="checkbox"/>	172
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input type="checkbox"/>	<input type="checkbox"/>	192

For peer review only

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Computerized decision to reduce inappropriate medication in the elderly: A systematic review with a meta-analysis protocol

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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Health informatics, Patient-centred medicine, Geriatric medicine
Keywords:	Medical Informatics Applications, Deprescriptions, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, GENERAL MEDICINE (see Internal Medicine), PRIMARY CARE

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Authors:

Luis Monteiro, luismonteiro.net@gmail.com

Faculdade de Ciências da Saúde, Universidade da Beira Interior, Covilhã, Portugal
USF Esgueira +, Aveiro, Portugal

Tiago Maricoto, tiago.maricoto@gmail.com

Faculdade de Ciências da Saúde, Universidade da Beira Interior, Covilhã, Portugal
USF Aveiro Aradas, Aveiro, Portugal

Isabel Solha, isabel.solha@gmail.com

USF Terras de Souza, Paredes, Portugal

Matilde Monteiro-Soares, matsoares@med.up.pt

MEDCIDS – *Department of Community Medicine, Information and Health Decision Sciences,*
Oporto University Faculty of Medicine, Oporto, Portugal

CINTESIS - Center for Health Technology and Services Research, Oporto University
Faculty of Medicine, Oporto, Portugal

Carlos Martins, carlosmartins20@gmail.com

MEDCIDS – Departamento de Medicina da Comunidade, Informação e Decisão em Saúde,
Oporto University Faculty of Medicine, Oporto, Portugal

CINTESIS - Center for Health Technology and Services Research, Oporto University
Faculty of Medicine, Oporto, Portugal

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47 **Correspondence:**

48 Dr. Luís Monteiro; Email: luismonteiro.net@gmail.com; Postal Address: Av. Infante D.
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Abstract

Introduction: Life expectancy continues to increase in developed countries. Elderly people are more likely to consume more medications and become vulnerable to age-related changes in drugs' pharmacokinetics and pharmacodynamics. Recent studies have identified opportunities and barriers for deprescribing potentially inappropriate medications. It is already been demonstrated that computerized decision support systems can reduce physician orders for unnecessary tests. We will systematically review the available literature to understand if computerized decision support is effective in the use of potentially inappropriate medications, thus having an impact on health outcomes.

Methods and analysis: A systematic review will be conducted using MEDLINE, CENTRAL, and EMBASE databases, as well as the grey literature assessing the effectiveness of computer decision support interventions in deprescribing inappropriate medication, with an impact on health outcomes in the elderly. The search will be performed during January and February 2018. Two reviewers will conduct the articles 'screening, selection, and data extraction, independently and blind to each other.' Eligible sources will be selected after discussing non-conformities. All extracted data from selected articles will be categorised based on the studies' participants, design and setting, methodological quality, bias and any other potential sources of heterogeneity. This review will be conducted and reported in adherence with the PRISMA statement of quality for reporting systematic reviews and meta-analyses.

Ethics and Dissemination: As a systematic review, this research is exempt from ethical approval. We intend to publish the full article in a related peer-reviewed journal and report on it at international conferences.

Keywords: Medical informatics applications, deprescriptions, potentially inappropriate medicines.

Registration: PROSPERO, nr. CRD42017067021.

Strengths and limitations of this study

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2
3 85 • This study will include the first meta-analysis on this clinical topic.
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5 86 • This protocol was written following the recently published PRISMA-P guidelines.
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7 87 • We aim to clarify whether newer technologies, such as computerized decisions, help
8
9 88 to improve clinical outcomes.
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11 89 • Studies with high heterogeneity and varying quality may limit the quality of
12
13 90 evidence for this systematic review.

91 **Introduction**

92
93 In developed countries, the aging population is increasing (1). Caring for older adults is a
94 challenge for healthcare providers, as older patients are more likely to have
95 multimorbidities (2, 3) and to consume more medication (4). Polypharmacy has a negative
96 impact on senior health (5, 6) due to an increased risk of drug interactions and prescriptions
97 for potentially inappropriate medications (4). Prescribing medication for elderly patients
98 should be evidence-based; cautiousness is mandatory, since seniors have changes in
99 pharmacokinetics and pharmacodynamics, and research often excludes patients who are
100 more than 65-years-old (7).

101 Deprescribing is defined as the “the process of withdrawal of inappropriate medication,
102 supervised by a health care professional with the goal of managing polypharmacy and
103 improving outcomes” (8).

104 In the community setting, primary care physicians/family doctors, nurses, pharmacists, and
105 other professionals must manage the continuity of senior care. Recent studies have
106 identified that interventions such as pharmaceutical care appear beneficial in reducing
107 inappropriate prescribing (9). Although family doctors want to learn more through mobile
108 technologies (10), the doctors’ perspective is that there is insufficient emphasis on geriatric
109 pharmacotherapy training (11)

110 It has already been shown that computerized decision support systems can reduce
111 physicians’ orders of unnecessary tests (12). This systematic review aims to determine if
112 computerized decision support is effective in reducing potentially inappropriate medicines.
113 This should better establish the efficacy of these interventions in the elderly in terms of
114 health outcomes.

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3 115 Other studies have addressed this issue(9, 13). Our study will include a meta-analysis,
4
5 116 which has not previously been done.
6

7 117 **Methods and Analysis**

8 118 9 119 *Eligibility criteria*

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11 119 *Eligibility criteria*
12 120 This systematic review will include interventional studies, such as experimental study
13
14 121 designs [randomized controlled studies (RCTs), non-randomized controlled studies, and
15
16 122 quasi-randomized controlled studies]. Observational studies (such as case reports, case
17
18 123 series, cross-sectional analyses, case–controls, and cohorts, etc.) will not be selected. We
19
20 124 will include trials in the general population and studies with older adults with particular
21
22 125 diseases.

23 126 Only studies including participants aged 65 years and older, who were prescribed one or
24
25 127 more regular medications, will be selected. On the other hand, studies including only
26
27 128 moribund, terminal, or palliative participants will be excluded. Studies published or in press
28
29 129 will be included independently of the language, year of publication, and setting in which it
30
31 130 was conducted (hospitals, nursing centres, communities, etc.). Potentially inappropriate
32
33 131 medications will be defined using the Beers Criteria (14) and STOPP/START Criteria (15)
34

35 133 *Information sources*

36 134 Our sources of information will include electronic databases (namely MEDLINE,
37
38 135 CENTRAL, EMBASE, ISI Web of science), trial registries, different types of grey
39
40 136 literature, and contact with specialists in the field. If further data is needed, authors of the
41
42 137 selected articles will be contacted. The search will be performed in January and February
43
44 138 2018. The search will have no language restrictions. We will first contact the authors to
45
46 139 ascertain if the main data are available in other languages and seek to translate whenever
47
48 140 necessary. A second search, using all identified keywords and proprietary names of
49
50 141 computerized decision support systems will then be undertaken across all included
51
52 142 databases.

53 143 *Search strategy*

54 144 Our initial search syntax in CENTRAL will be:

55
56 145 1 MeSH descriptor: [Medical Informatics Applications]explode all trees
57

- 1
2
3 146 2.Computer decision support
4
5 147 3.MeSH descriptor: [Deprescriptions]explode all trees
6
7 148 4.MeSH descriptor: [Inappropriate Prescribing] explode all trees
8
9 149 5.#1 or #2
10
11 150 6.#3 or #4
12
13 151 7.#5 and #6
14

15 153 For MEDLINE, the query will be "Medical Informatics Applications"[Mesh] AND
16 154 ("Deprescriptions"[Mesh] OR "Inappropriate Prescribing"[Mesh]) "decision support
17 155 systems, clinical"[MeSH Terms] OR clinical decision support systems [Text Word] /
18 156 "decision making, computer-assisted"[MeSH Terms] OR computer assisted decision
19 157 making[Text Word] / "medical order entry systems"[MeSH Terms] / "medication
20 158 errors"[MeSH Terms]; and for EMBASE ('medical informatics'/exp OR 'mobile
21 159 application'/exp) AND ('deprescription'/exp OR 'inappropriate prescribing'/exp).
22
23 160 Reference lists will be checked to identify additional relevant studies in the systematic
24 161 review. For ISI Web of science the query will be "Medical Informatics
25 162 Applications"[Mesh] AND ("Deprescriptions"[Mesh] OR "Inappropriate
26 163 Prescribing"[Mesh]) "decision support systems, clinical"[MeSH Terms] OR clinical
27 164 decision support systems[Text Word] /
28 165 "decision making, computer-assisted"[MeSH Terms] OR computer assisted decision
29 166 making [Text Word] / "medical order entry systems"[MeSH Terms] / "medication
30 167 errors"[MeSH Terms]."
31
32 168

34 169 ***Study selection process***

35
36 170 Two authors will independently, and blinded to each other, perform the primary article
37
38 171 screening. First, they will review the title and abstract, and categorise the articles into three
39 172 groups: relevant, irrelevant, and unsure. Articles categorised as irrelevant by both reviewers
40
41 173 will be eliminated from the study. Then, each reviewer will review the full text of the
42
43 174 remaining articles and make a list of those to be included. The two lists will be compared
44
45 175 and non-conformities will be discussed. When an agreement cannot be reached, the whole
46 176 team of researchers will come to the final decision.
47

48 177

50 178 ***Data management***

51 179 Once the articles to be included are selected, data will be extracted and entered into data
52
53 180 sheets independently by two reviewers. These two sheets, including their differences, will
54
55 181 be checked by a third reviewer. These sheets will also include the study reference,
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182 intervention type, study design, country, setting, follow-up, number of participants, age,
183 effect of intervention on reducing potential inappropriate medications, and clinical
184 outcomes.

185 Any potential difference among reviewers will be discussed with the team, and if not
186 resolved, the manuscript authors will be contacted. Also, if required data are missing from
187 the article or are incomplete or unclear, inquiries will similarly be sent to the authors.

188

189 ***Data items***

190 The following information will be extracted from each article: 1) study characteristics,
191 intervention type; type of study; country, setting, duration of follow-up; 2) participants,
192 number, age; 3) outcomes: The primary outcome is effect of intervention on withdrawal of
193 potentially inappropriate medications (discontinuation rate). The authors will give priority
194 to the following outcomes, by order of importance: mortality, hospitalization, any reported
195 adverse drug withdrawal effects, and quality of life measurements.

196

197 ***Risk of bias***

198 Two reviewers will assess, independently and blinded to each other, the risk of bias.
199 The Cochrane Collaboration Risk of Bias tool will be used to assess this for each study
200 (16).

201

202 ***Data synthesis***

203 The final report will present the available data of the computer decision to support or
204 reduce inappropriate medications in older adults.
205 Each outcome will be combined and calculated using the statistical software RevMan 5.1
206 (17), according to statistical guidelines referenced in the current version of the Cochrane
207 Handbook for Systematic Reviews of Interventions(18). If heterogeneity is substantial, we
208 will not perform a meta-analysis; thus, a narrative, qualitative summary will be done
209 instead.

210 Subgroups will be presented according to the setting, intervention, and medication. The
211 final paper will be prepared following the Preferred Reporting Items for Systematic
212 Reviews and Meta-Analyses (PRISMA) guidelines (19, 20).

213 Subgroup analyses will be used to explore possible sources of heterogeneity, based on the
214 following: medications and type of software.

215 Regarding subgroups, we assume it will be relevant to include subgroups regarding the tool
216 used by software to identify targets: STOPP/START criteria subgroup and the Beers
217 criteria. Subgroup. We will also conduct meta-regression to evaluate whether the covariates
218 have significant influence on heterogeneity.

219 The studies rated as having a high risk of bias will be included and then analysed in a sub-
220 group analysis. They will be included for the discussion topic.

221 A systematic narrative synthesis will be provided in the text and tables to summarise and
222 explain the characteristics and findings of the studies; it will explore the relationship within
223 and between studies, in line with guidance from the Centre for Reviews and Dissemination.

224 In order to determine whether reporting bias is present, we will include funnel plot and
225 statistical tests in the assessment. We will determine whether the protocol of the RCT was
226 published before recruitment of patients was initiated.

227 Data from RCTs will not be combined with data from other study designs. We will evaluate
228 whether selective reporting of outcomes is obvious. The quality of evidence for all
229 outcomes will be judged with the Grading of Recommendations Assessment, and the
230 Development and Evaluation working group methodology (21). We further separated
231 comparative studies with and without concurrent control groups. Forest plots will be
232 produced when three or more studies are included in a meta-analysis. Data in tables will be
233 presented by therapeutic class, based on the Anatomical Therapeutic Classification (ATC)
234 codes.

235 Randomized studies:

236 If heterogeneity is detected, we will select the random effects model.

237 Dichotomous data:

238 Effect sizes and 95% confidence intervals (CIs) were expressed as odds ratios (OR). When a
239 study reports zero events in both arms, we will consider using zero-cell correction methods.

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242 Ethics and Dissemination

243 As a systematic review, this research is exempt from ethical approval. We intend to publish
244 the full article in a related peer-reviewed journal and report on it at international
245 conferences.

246 Discussion

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248 Although electronic health records are common in clinical practice, there is a lack of
249 evidence of computer decision support regarding health outcomes. Deprescribing
250 potentially inappropriate medication in the elderly is particularly difficult, although
251 computer support may be an important tool. This systematic review will help identify the
252 success of computerized decision support to reduce inappropriate medication. Therefore,
253 this review will be relevant for patients, health professionals, and policy makers. One
254 potential limitation of this study will be if we find a limited number of studies with clinical
255 outcomes measured.

256 References

- 257
258 1. OECD. Elderly population (indicator). doi: 10.1787/8d805ea1-en (Accessed on 26
259 February 2017) [Available from: [https://data.oecd.org/pop/elderly-
260 population.htm#indicator-chart](https://data.oecd.org/pop/elderly-population.htm#indicator-chart).
261 2. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al.
262 Aging with multimorbidity: a systematic review of the literature. *Ageing research reviews*.
263 2011;10(4):430-9.
264 3. Prazeres F, Santiago L. Prevalence of multimorbidity in the adult population
265 attending primary care in Portugal: a cross-sectional study. *BMJ open*. 2015;5(9):e009287.
266 4. Weng MC, Tsai CF, Sheu KL, Lee YT, Lee HC, Tzeng SL, et al. The impact of
267 number of drugs prescribed on the risk of potentially inappropriate medication among
268 outpatient older adults with chronic diseases. *QJM : monthly journal of the Association of
269 Physicians*. 2013;106(11):1009-15.
270 5. Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health
271 outcomes associated with polypharmacy in community-dwelling older adults: a systematic
272 review. *Journal of the American Geriatrics Society*. 2014;62(12):2261-72.
273 6. Lu WH, Wen YW, Chen LK, Hsiao FY. Effect of polypharmacy, potentially
274 inappropriate medications and anticholinergic burden on clinical outcomes: a retrospective
275 cohort study. *CMAJ : Canadian Medical Association journal = journal de l'Association
276 medicale canadienne*. 2015;187(4):E130-7.
277 7. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized
278 controlled trials published in high-impact general medical journals: a systematic sampling
279 review. *Jama*. 2007;297(11):1233-40.

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2
3 280 8. Reeve E, D. Gnjidic, J. Long, and S. Hilmer. A systematic review of the emerging
4 281 definition of "deprescribing" with network analysis: Implications for future research and
5 282 clinical practice. *British journal of clinical pharmacology*. 2015(2015a. 80(6)):1254–68
6 283
7
8 284 9. Patterson SM, Cadogan CA, Kerse N, Cardwell CR, Bradley MC, Ryan C.
9 285 Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane*
10 286 *Database Syst Rev*. 2014;10.
11 287 10. survey PCISoW. PCI Survey: Family doctors want education on a smartphone2017.
12 288 Available from:
13 289 [https://www.dropbox.com/s/4vy5o2kdhz7ji8z/WONCA%20survey%20summary%20ACv2](https://www.dropbox.com/s/4vy5o2kdhz7ji8z/WONCA%20survey%20summary%20ACv2.pdf?dl=0)
14 290 [.pdf?dl=0](https://www.dropbox.com/s/4vy5o2kdhz7ji8z/WONCA%20survey%20summary%20ACv2.pdf?dl=0).
15
16 291 11. Cullinan S, Fleming A, O'Mahony D, Ryan C, O'Sullivan D, Gallagher P, et al.
17 292 Doctors' perspectives on the barriers to appropriate prescribing in older hospitalized
18 293 patients: a qualitative study. *British journal of clinical pharmacology*. 2014;79(5):860-9.
19 294 12. Martins CMS, da Costa Teixeira AS, de Azevedo LFR, Sá LMB, Santos PAAP, do
20 295 Couto MLGD, et al. The effect of a test ordering software intervention on the prescription
21 296 of unnecessary laboratory tests - a randomized controlled trial. *BMC Medical Informatics*
22 297 *and Decision Making*. 2017;17(1):20.
23
24 298 13. Clyne B, Fitzgerald C, Quinlan A, Hardy C, Galvin R, Fahey T, et al. Interventions
25 299 to Address Potentially Inappropriate Prescribing in Community-Dwelling Older Adults: A
26 300 Systematic Review of Randomized Controlled Trials. *Journal of the American Geriatrics*
27 301 *Society*. 2016;64(6):1210-22.
28 302 14. American Geriatrics Society 2015 Updated Beers Criteria for Potentially
29 303 Inappropriate Medication Use in Older Adults. *Journal of the American Geriatrics Society*.
30 304 2015;63(11):2227-46.
31
32 305 15. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P.
33 306 STOPP/START criteria for potentially inappropriate prescribing in older people: version 2.
34 307 *Age and ageing*. 2014;44(2):213-8.
35 308 16. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The
36 309 Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*.
37 310 2011;343.
38
39 311 17. Review Manager (RevMan) Copenhagen: The Nordic Cochrane Centre, The
40 312 Cochrane Collaboration. Version 5.3 ed2014.
41 313 18. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0:
42 314 updated March 20112011.
43 315 19. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred
44 316 reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015
45 317 statement. *Systematic Reviews*. 2015;4(1):1.
46
47 318 20. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred
48 319 reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015:
49 320 elaboration & explanation. *BMJ*. 2015;349.
50 321 21. Alonso-Coello P, Schünemann HJ, Moher J, Brignardello-Petersen R, Akl EA,
51 322 Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and
52 323 transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ*.
53 324 2016;353.
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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"/>	2,3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" 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"/>	5; 81
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"/>	8-25
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	50-52
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 checked="" type="checkbox"/>	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	39-46
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	39
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	92-113
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"/>	117-127 187-188

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
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"/>	124-127
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"/>	138-161
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"/>	138-161
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"/>	172-180
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"/>	163-170
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"/>	191-192
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"/>	183-188
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"/>	186-188
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"/>	191-192 210-211
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	195-229
	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"/>	195-229 199-200
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	204-205 208-209

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Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	212-214
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"/>	215-216
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"/>	219-221

For peer review only

BMJ Open

Computerized decision to reduce inappropriate medication in the elderly: A systematic review with a meta-analysis protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-018988.R2
Article Type:	Protocol
Date Submitted by the Author:	29-Nov-2017
Complete List of Authors:	Monteiro, Luís; Universidade da Beira Interior Faculdade de Ciências da Saúde; USF Esgueira + Maricoto, Tiago; Universidade da Beira Interior Faculdade de Ciências da Saúde; USF Aveiro Aradas Solha, Isabel; USF Terras de Souza Monteiro-Soares, Matilde; Oporto University Faculty of Medicine, MEDCIDS – Department of Community Medicine, Information and Health Decision Sciences; Oporto University Faculty of Medicine, CINTESIS - Center for Health Technology and Services Research Martins, Carlos; Oporto University Faculty of Medicine, CINTESIS - Center for Health Technology and Services Research; Oporto University Faculty of Medicine, MEDCIDS – Department of Community Medicine, Information and Health Decision Sciences
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Health informatics, Patient-centred medicine, Geriatric medicine
Keywords:	Medical Informatics Applications, Deprescriptions, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS, GENERAL MEDICINE (see Internal Medicine), PRIMARY CARE

SCHOLARONE™
Manuscripts

Title

Computerized decision to reduce inappropriate medication in the elderly: A systematic review with meta-analysis protocol

Registration: PROSPERO, nr. CRD42017067021.

Authors:

Lúis Monteiro, luismonteiro.net@gmail.com

Faculdade de Ciências da Saúde, Universidade da Beira Interior, Covilhã, Portugal
USF Esgueira +, Aveiro, Portugal

Tiago Maricoto, tiago.maricoto@gmail.com

Faculdade de Ciências da Saúde, Universidade da Beira Interior, Covilhã, Portugal
USF Aveiro Aradas, Aveiro, Portugal

Isabel Solha, isabel.solha@gmail.com

USF Terras de Souza, Paredes, Portugal

Matilde Monteiro-Soares, matsoares@med.up.pt

MEDCIDS – Department of Community Medicine, Information and Health Decision Sciences,
Oporto University Faculty of Medicine, Oporto, Portugal

CINTESIS - Center for Health Technology and Services Research, Oporto University
Faculty of Medicine, Oporto, Portugal

Carlos Martins, carlosmartins20@gmail.com

MEDCIDS – Departamento de Medicina da Comunidade, Informação e Decisão em Saúde,
Oporto University Faculty of Medicine, Oporto, Portugal

CINTESIS - Center for Health Technology and Services Research, Oporto University
Faculty of Medicine, Oporto, Portugal

Competing Interests Statement:

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8
9 34 Operational Programme.NORTE 2020, under the PORTUGAL 2020 Partnership
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11 35 Agreement, and the European Regional Development Fund (ERDF). There are no other
12
13 36 relationships or activities that could appear to have influenced the submitted work
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15 37

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24 43 R&D Unit (Reference UID/IC/4255/2013).

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31 47 Development Fund (ERDF).
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33 **Correspondence:**

34 49 Dr. Luís Monteiro; Email: luismonteiro.net@gmail.com; Postal Address: Av. Infante D.
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36 50 Henrique, 6200-506 Covilhã.
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40 **Contributions:**

41 52 LM had the original idea for the systematic review. LM, TM, and ISS wrote the protocol
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43 53 and reviewed the search strategy. LM, TM, ISS, MM-S, and CM reviewed the protocol.
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Abstract

Introduction: Life expectancy continues to increase in developed countries. Elderly people are more likely to consume more medications and become vulnerable to age-related changes in drugs' pharmacokinetics and pharmacodynamics. Recent studies have identified opportunities and barriers for deprescribing potentially inappropriate medications. It is already been demonstrated that computerized decision support systems can reduce physician orders for unnecessary tests. We will systematically review the available literature to understand if computerized decision support is effective in reducing the use of potentially inappropriate medications, thus having an impact on health outcomes.

Methods and analysis: A systematic review will be conducted using MEDLINE, CENTRAL, EMBASE and Web of Science databases, as well as the grey literature assessing the effectiveness of computer decision support interventions in deprescribing inappropriate medication, with an impact on health outcomes in the elderly. The search will be performed during January and February 2018. Two reviewers will conduct articles' screening, selection, and data extraction, independently and blind to each other. Eligible sources will be selected after discussing non-conformities. All extracted data, from the included articles, will be assessed based on studies' participants, design and setting, methodological quality, bias and any other potential sources of heterogeneity. This review will be conducted and reported in adherence with the PRISMA statement of quality for reporting systematic reviews and meta-analyses.

Ethics and Dissemination: As a systematic review, this research is exempt from ethical approval. We intend to publish the full article in a related peer-reviewed journal and present it at international conferences.

Keywords: Medical informatics applications, deprescriptions, potentially inappropriate medicines.

Registration: PROSPERO, nr. CRD42017067021.

Strengths and limitations of this study

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3 87 - We aim to clarify whether new technologies, namely computerized decision
4 88 systems, can help reducing inappropriate medication in the elderly.
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6 89 - This protocol was written following the recently published PRISMA-P guidelines.
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8 90 - We will conduct a comprehensive systematic review on this clinical topic using, if
9 possible, meta-analytic methods.
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11 92 - Studies with high heterogeneity and varying quality may limit the quality of
12 evidence for this systematic review.
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95 **Introduction**

96
97 In developed countries, aging population is increasing (1). Caring for older adults is a
98 challenge for healthcare providers, as they are more likely to have multi-morbidities (2, 3)
99 and to consume more medication (4).

100 Polypharmacy, defined as “the use of multiple drugs administered to the same patient, most
101 commonly seen in elderly patients”(5, 6), although frequent has a negative impact on senior
102 health (7, 8). There is an increased risk of drug interactions and prescriptions of potentially
103 inappropriate medications (4), changes in pharmacokinetics and pharmacodynamics and
104 limited generalization of clinical research results due to common exclusion of subjects with
105 more than 65-years-old (9). So, prescribing medication for elderly patients should be
106 evidence-based and particularly cautious.

107 In several cases it is urgent to deprescribe, this is to begin “the process of withdrawal of
108 inappropriate medication, supervised by a health care professional with the goal of
109 managing polypharmacy and improving outcomes” (10).

110 Inappropriate medication prescription, meaning “the practice of administering medications
111 in a manner that poses more risk than benefit, particularly where safer alternatives exist” (5,
112 11), can be reduced by several interventions (12). However, they are not widely known and
113 therefore used. In one hand, general practitioners report interest in learning and using more
114 mobile technologies to assist in clinical care (13); on the other they refer an insufficient
115 emphasis on geriatric pharmacotherapy training (14).

116 It has already been shown that computerized decision support systems can reduce
117 physicians’ orders of unnecessary tests (15). This systematic review aims to determine if

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3 118 computerized decision support is effective in reducing potentially inappropriate medication
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5 119 prescription in the elder population.

6 120 Other studies have addressed strategies to improve care of elderly in what concerns
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8 121 inappropriate medication prescription (12, 16). In 2013, one synthesis study identified 8
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10 122 randomized controlled trials (RCTs), 2 clusters RCTs and 2 controlled before and after
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12 123 studies (9). In 2015, another study included 12 RCTs (13). Both studies reported high
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14 124 heterogeneity on the included studies. However, these studies have not focused on
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16 125 computerized decision support systems. In addition, we consider that since the last study
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18 126 search, more adequate studies have been published and that, for the first time, a meta-
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20 127 analysis will be possible to conduct.

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23 129 **Methods and Analysis**

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25 131 *Eligibility criteria*

26 132 In this systematic review we will select 1) interventional studies, such as RCTs, non-
27
28 133 randomized controlled studies, and quasi-randomized controlled studies; 2) that include
29
30 134 participants with 65 years or more, to whom one or more regular medications were
31
32 135 prescribed and 3) assess the impact of computerized decision support systems in
33
34 136 withdrawal of potentially inappropriate medication prescription. On the other hand, studies
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36 137 including only moribund, terminal, or palliative participants will be excluded. Studies
37
38 138 published or in press will be included independently of the language, year of publication,
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40 139 and setting in which it was conducted (hospitals, nursing centres, communities, etc.).
41
42 140 Potentially inappropriate medications will be defined using the Beers Criteria (17) and
43
44 141 STOPP/START Criteria (18).

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46 143 *Information sources*

47 144 Our sources of information will include electronic databases (namely MEDLINE,
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49 145 CENTRAL, EMBASE, Web of Science), trial registries, different types of grey literature,
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51 146 and contact with specialists in the field. If further data is needed, authors of the selected
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53 147 articles will be contacted. The search will be performed in January and February 2018. The
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55 148 search will have no language restrictions. In those cases that none of the research team

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3 149 members is able to translate the included study, we will first contact the authors to ascertain
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5 150 if the main data are available in other languages and seek to translate whenever necessary.
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7 151 A second search, using all identified keywords and proprietary names of computerized
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9 152 decision support systems will then be undertaken across all included databases.
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154 *Search strategy*

155 Our initial search syntax in CENTRAL will be: 1) MeSH descriptor: [Medical Informatics
156 Applications] explode all trees; 2) Computer decision support; 3) MeSH descriptor:
157 [Deprescriptions] explode all trees; 4) MeSH descriptor: [Inappropriate Prescribing]
158 explode all trees; 5) #1 or #2; 6) #3 or #4; 7) #5 and #6.

159 For Pubmed, the query will be “(Medical Informatics Applications [MeSH Terms] OR
160 (medical AND informatics AND applications)) AND ((Deprescriptions [Mesh Terms] OR
161 deprescription OR deprescribing OR Inappropriate Prescribing [Mesh Terms] OR
162 (inappropriate AND prescribing*) OR (inappropriate AND prescription*) OR (over* AND
163 prescribing*)) OR medication errors [MeSH Terms] OR (error* AND medication) OR
164 (drug AND use AND error*) AND (decision support systems, clinical [MeSH Terms] OR
165 “clinical decision support systems” OR (clinical AND decision AND support*) OR
166 decision making, computer-assisted [MeSH Terms] OR (computer AND assisted AND
167 decision AND making) OR (medical AND computer AND assisted AND decision AND
168 making) OR medical order entry systems [MeSH Terms] OR (medical AND order entry
169 systems) OR (medications AND alert AND systems) OR “computerized physician order
170 entry systems” OR “computerized provider order entry systems” OR “computerized
171 physician order entry” OR “computerized provider order entry”).

172 For Web of Science the query will be “TS=(“Medical Informatics Applications” OR
173 (medical AND informatics AND applications)) AND TS=((Deprescriptions OR
174 deprescription OR deprescribing OR “Inappropriate Prescribing” OR (inappropriate AND
175 prescribing*) OR (inappropriate AND prescription*) OR (over* AND prescribing*)) OR
176 “medication errors”OR (error* AND medication) OR (drug AND use AND error*) AND
177 TS=(“clinical decision support systems” OR (clinical AND decision AND support*) OR
178 decision making, computer-assisted [MeSH Terms] OR (computer AND assisted AND
179 decision AND making) OR (medical AND computer AND assisted AND decision AND

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3 180 making) OR “medical order entry systems” OR (medical AND order entry systems) OR
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5 181 (medications AND alert AND systems) OR “computerized physician order entry systems”
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7 182 OR “computerized provider order entry systems” OR “computerized physician order
8
9 183 entry” OR “computerized provider order entry”).

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11 185 *Study selection process*

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13 186 Two authors will independently, and blinded to each other, perform the primary article
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15 187 screening. First, they will review the title and abstract, and categorise the articles into three
16
17 188 groups: relevant, irrelevant, and unsure. Articles categorised as irrelevant by both reviewers
18
19 189 will be eliminated from the study. Then, each reviewer will review the full text of the
20
21 190 remaining articles and make a list of those to be included. For both stages, the two lists will
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23 191 be compared and disagreements will be discussed. When an agreement cannot be reached,
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25 192 the whole team of researchers will come to the final decision.

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27 194 *Data extraction and management*

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29 195 Once the articles to be included are selected, data will be extracted and entered into data
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31 196 sheets independently by two reviewers. These two sheets, including their differences, will
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33 197 be checked by a third reviewer.

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35 198 The following information will be extracted from each article: 1) study characteristics,
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37 199 intervention type; type of study; country, setting, follow-up duration; 2) participants’
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39 200 number and age; and 3) clinical outcomes. The primary outcome to be considered is the
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41 201 effect of intervention on withdrawal of potentially inappropriate medications
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43 202 (discontinuation rate). The authors will give priority to the following outcomes, by order of
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45 203 importance: mortality, hospitalization, any reported adverse drug withdrawal effects, and
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47 204 quality of life measurements.

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49 205 Any potential difference among reviewers will be discussed with the team, and if not
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51 206 resolved, the manuscript authors will be contacted. Also, if required data are missing from
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53 207 the article or are incomplete or unclear, inquiries will similarly be sent to the authors.

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3 209 ***Risk of bias***

4 210 Two reviewers will assess, independently and blinded to each other, the risk of bias by
5 211 applying the Cochrane Collaboration Risk of Bias tool to all the included studies (19).

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10 213 ***Data synthesis***

11 214 The final report will present the available data of the computer decision to support in
12 215 reducing inappropriate medication prescription in older adults.

13 216 Each outcome will be combined and calculated using the statistical software RevMan 5.1
14 217 (20), according to statistical guidelines referenced in the current version of the Cochrane
15 218 Handbook for Systematic Reviews of Interventions (21).

16 219 If we are able to include a group of studies that are sufficiently comparable and reliable we
17 220 will conduct a meta-analysis. We consider that we should use a random effect model taking
18 221 in consideration the previous systematic reviews' results. We expect to encounter a
19 222 sufficient number of studies, reporting a sufficient number of events, but that are not
20 223 completely comparable (concerning the intervention, context and population).

21 224 If heterogeneity is severe (I^2 superior to 40-50%) and studies' results are strongly biased,
22 225 we will not perform a meta-analysis; thus, a narrative, qualitative summary will be done
23 226 instead.

24 227 Effect sizes and 95% confidence intervals (CIs) will be expressed as odds ratios (OR).
25 228 When a study reports zero events in both arms, we will consider using zero-cell correction
26 229 methods.

27 230 Subgroup analyses will be used to explore possible sources of heterogeneity, based on the
28 231 following: setting, type of software, medication and participants' clinical characteristics.

29 232 Regarding subgroups, we assume it will be relevant to include subgroups regarding the tool
30 233 used by software to identify targets: STOPP/START criteria subgroup and the Beers
31 234 criteria. We will also conduct meta-regression to evaluate whether the covariates have
32 235 significant influence on heterogeneity.

33 236 Forest plots will be produced when three or more studies are included in a meta-analysis.

34 237 Data in tables will be presented by therapeutic class, based on the Anatomical Therapeutic
35 238 Classification (ATC) codes.

239 Studies rated as having a high risk of bias will be included in the narrative synthesis but not
240 on our meta-analysis and discussed in detail.

241 A systematic narrative synthesis will be provided in the text and tables to summarise and
242 explain the characteristics and findings of the studies; it will explore the relationship within
243 and between studies, in line with guidance from the Centre for Reviews and Dissemination.
244 In order to determine whether publication bias is present, we will include funnel plot and
245 statistical tests in the assessment, namely Begg's and Egger's test.

246 We will also ascertain if each RCT had their protocol published before recruitment of
247 patients was initiated.

248 The quality of evidence for all outcomes will be judged with the Grading of
249 Recommendations Assessment, and the Development and Evaluation working group
250 methodology (22).

251 The final paper will be prepared following the Preferred Reporting Items for Systematic
252 Reviews and Meta-Analyses (PRISMA) guidelines (23, 24).

253

254 **Ethics and Dissemination**

256 As a systematic review, this research is exempt from ethical approval. We intend to publish
257 the full article in a related peer-reviewed journal and present it in international conferences.

258

259 **Discussion**

261 Although electronic health records are common in clinical practice, there is a lack of
262 evidence of computer decision support systems regarding health outcomes. Deprescribing
263 potentially inappropriate medication in the elderly is particularly difficult, although
264 computer support may be an important tool. This systematic review will help identify the
265 success of computerized decision support to reduce inappropriate medication prescription.
266 Therefore, this review will be relevant for patients, health professionals, and policy makers.
267 One potential limitation of this study will be if we find a limited number of studies with
268 considerable differences regarding their characteristics and methodology. This may impair

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3 269 our conclusions and impede meta-analysis. In addition, depending on the data available and
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5 270 obtained results we may not be able to define which is the best decision support available.
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References

1. OECD. Elderly population (indicator). doi: 10.1787/8d805ea1-en (Accessed on 26 February 2017) [Available from: <https://data.oecd.org/pop/elderly-population.htm#indicator-chart>].
2. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, et al. Aging with multimorbidity: a systematic review of the literature. *Ageing research reviews*. 2011;10(4):430-9.
3. Prazeres F, Santiago L. Prevalence of multimorbidity in the adult population attending primary care in Portugal: a cross-sectional study. *BMJ open*. 2015;5(9):e009287.
4. Weng MC, Tsai CF, Sheu KL, Lee YT, Lee HC, Tzeng SL, et al. The impact of number of drugs prescribed on the risk of potentially inappropriate medication among outpatient older adults with chronic diseases. *QJM : monthly journal of the Association of Physicians*. 2013;106(11):1009-15.
5. Grosjean J, Merabti T, Dahamna B, Kergourlay I, Thirion B, Soualmia LF, et al. Health multi-terminology portal: a semantic added-value for patient safety. *Stud Health Technol Inform*. 2011;166:129-38.
6. HeTOP [Internet]. Rouen University Hospital. 2017 [cited (SCHEME=ISO8601)2011-03-17]. Available from: http://www.hetop.eu/hetop/?la=en&q=#la=en&rr=MSH_D_019338&q=polypharmacy.
7. Fried TR, O'Leary J, Towle V, Goldstein MK, Trentalange M, Martin DK. Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. *Journal of the American Geriatrics Society*. 2014;62(12):2261-72.
8. Lu WH, Wen YW, Chen LK, Hsiao FY. Effect of polypharmacy, potentially inappropriate medications and anticholinergic burden on clinical outcomes: a retrospective cohort study. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2015;187(4):E130-7.
9. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *Jama*. 2007;297(11):1233-40.
10. Reeve E, D. Gnjidic, J. Long, and S. Hilmer. A systematic review of the emerging definition of "deprescribing" with network analysis: Implications for future research and clinical practice. *British journal of clinical pharmacology*. 2015(2015a. 80(6)):1254-68
11. HeTOP. Inappropriate prescribing [Internet]. 2017 [cited (SCHEME=ISO8601)2011-03-17]. Available from: http://www.hetop.eu/hetop/?la=en&q=&home#la=en&rr=MSH_D_057970&q=inappropriate+prescribing.
12. Patterson SM, Cadogan CA, Kerse N, Cardwell CR, Bradley MC, Ryan C. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev*. 2014;10.
13. survey PCISoW. PCI Survey: Family doctors want education on a smartphone2017. Available from: <https://www.dropbox.com/s/4vy5o2kdhz7ji8z/WONCA%20survey%20summary%20ACv2.pdf?dl=0>.

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3 318 14. Cullinan S, Fleming A, O'Mahony D, Ryan C, O'Sullivan D, Gallagher P, et al.
4 319 Doctors' perspectives on the barriers to appropriate prescribing in older hospitalized
5 320 patients: a qualitative study. *British journal of clinical pharmacology*. 2014;79(5):860-9.
6 321 15. Martins CMS, da Costa Teixeira AS, de Azevedo LFR, Sá LMB, Santos PAAP, do
7 322 Couto MLGD, et al. The effect of a test ordering software intervention on the prescription
8 323 of unnecessary laboratory tests - a randomized controlled trial. *BMC Medical Informatics
9 324 and Decision Making*. 2017;17(1):20.
10 325 16. Clyne B, Fitzgerald C, Quinlan A, Hardy C, Galvin R, Fahey T, et al. Interventions
11 326 to Address Potentially Inappropriate Prescribing in Community-Dwelling Older Adults: A
12 327 Systematic Review of Randomized Controlled Trials. *Journal of the American Geriatrics
13 328 Society*. 2016;64(6):1210-22.
14 329 17. American Geriatrics Society 2015 Updated Beers Criteria for Potentially
15 330 Inappropriate Medication Use in Older Adults. *Journal of the American Geriatrics Society*.
16 331 2015;63(11):2227-46.
17 332 18. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P.
18 333 STOPP/START criteria for potentially inappropriate prescribing in older people: version 2.
19 334 *Age and ageing*. 2014;44(2):213-8.
20 335 19. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The
21 336 Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*.
22 337 2011;343.
23 338 20. Review Manager (RevMan) Copenhagen: The Nordic Cochrane Centre, The
24 339 Cochrane Collaboration. Version 5.3 ed2014.
25 340 21. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0:
26 341 updated March 20112011.
27 342 22. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA,
28 343 Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and
29 344 transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ*.
30 345 2016;353.
31 346 23. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred
32 347 reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015
33 348 statement. *Systematic Reviews*. 2015;4(1):1.
34 349 24. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred
35 350 reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015:
36 351 elaboration & explanation. *BMJ*. 2015;349.
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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"/>	2,3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input checked="" 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"/>	5; 81
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"/>	8-25
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	50-52
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 checked="" type="checkbox"/>	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	39-46
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	39
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	92-113
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"/>	117-127 187-188

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
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"/>	124-127
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"/>	138-161
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"/>	138-161
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"/>	172-180
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"/>	163-170
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"/>	191-192
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"/>	183-188
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"/>	186-188
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"/>	191-192 210-211
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	195-229
	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"/>	195-229 199-200
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	204-205 208-209

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	212-214
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"/>	215-216
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"/>	219-221

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