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INDIVIDUAL INTERVENTIONS TO IMPROVE ADHERENCE TO PHARMACEUTICAL TREATMENT, DIET AND PHYSICAL ACTIVITY AMONG ADULTS WITH PRIMARY HYPERTENSION. A SYSTEMATIC REVIEW PROTOCOL.

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4 1 **INDIVIDUAL INTERVENTIONS TO IMPROVE ADHERENCE TO**
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6 2 **PHARMACEUTICAL TREATMENT, DIET AND PHYSICAL ACTIVITY**
7
8 3 **AMONG ADULTS WITH PRIMARY HYPERTENSION. A SYSTEMATIC**
9
10 4 **REVIEW PROTOCOL.**

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40

41 39 **ABSTRACT**

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44 40 **Introduction.** Hypertension is a chronic disease with 31% worldwide prevalence in
45
46 41 adults. It has been associated with non-adherence to therapeutic regime with a
47
48 42 negative impact on the prognosis of the disease and healthcare associated costs. The
49
50 43 previous makes it necessary to identify effective interventions to improve adherence
51
52 44 among this population. The objective of this protocol is to describe the methodology
53
54 45 in a systematic review that will evaluate the effect of individual interventions to
55
56 46 improve adherence to the prescribed pharmacologic treatment, diet and physical
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1
2
3 47 activity in adults with primary hypertension.
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5

6 48 **Methods and analysis:** Systematic search of randomized and non-randomized
7
8 49 clinical trials will be conducted in six databases (PubMed/MEDLINE, BVS,
9
10 50 CINAHL, Embase, Cochrane and Scopus). Studies in humans, published between
11
12 51 2009 and 2019, will be included, without language restrictions. The primary
13
14 52 outcome will be a change in adherence measures to pharmacological treatment, diet
15
16 53 and physical activity, evaluated through direct and indirect methods. Risk of bias,
17
18 54 data synthesis, and analysis by subgroups will be evaluated by means of Review
19
20 55 Manager, RevMan 5.3 and Stata 14, in case the criteria for meta-analysis are met.
21
22
23
24

25 56 **Ethics and dissemination.** Information to be analyzed is of a grouped nature, and
26
27 57 given that it sources from published studies, no ethics committee approval is
28
29 58 required. Results will be published in scientific journals, and through conferences,
30
31 59 seminars, congresses, and symposiums. Copyrights will be respected by
32
33 60 corresponding accrediting through the system of bibliographic references.
34
35
36

37 61 Key words: Hypertension, interventions, adherence, diet, exercise, adults
38
39

40 62 Register in PROSPERO (in process): identification number 147655 (7 December,
41
42 63 2019).
43
44

45 64 **Strengths and limitations of this study**

46
47
48 65 _The procedures of the study will be conducted in an independent and blinded
49
50 66 manner by at least two reviewers.
51

52
53 67 _Bibliographic search will have no language restriction.
54

55
56 68 _Ample modality of individual interventions will be included, and adherence will be
57
58 69 evaluated globally (pharmacological treatment, diet and physical activity).
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3 70 _Variability in adherence measures can be associated with high heterogeneity, which
4
5 71 may lead to conduct analysis by sub-groups and meta-regressions.
6

7
8 72 _The study will be conducted by an interdisciplinary group.
9

10 73 **INTRODUCTION**

11 12 13 74 **Description of the condition**

14
15 75 According to the guidelines of the European Societies of Cardiology and
16
17 76 Hypertension (ESC/ESH) 2018, for diagnosis and treatment of hypertension the
18
19 77 presence of hypertension is defined with values equal to or over 140 mmHg for
20
21 78 arterial systolic pressure, or 90 mmHg for arterial diastolic pressure [1]. It is the most
22
23 79 common chronic non-communicable disease, and it has been described as one of the
24
25 80 main risk factors associated with cardiovascular morbimortality worldwide [2]. Its
26
27 81 occurrence around the world stands at 31.0% (CI 95%: 30.0-32.2), and in low-to-
28
29 82 middle-income countries, at 31.5% (CI 95%: 30.2-32.9), or 1, 04 billion adults [3].
30
31 83 As to incidence, a follow-up study in young adults, (median age 33), for over two
32
33 84 decades estimated an incidence rate of 58.6 cases per 100,000 people (CI 95%: 52.8-
34
35 85 64.9) [4]. According to the World Health Organization (WHO), hypertension in
36
37 86 general increases risk of ischemic cardiopathy by three or four [5].
38
39
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41
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43

44 87 Additionally, prospective studies have shown hypertension to be one of the risk
45
46 88 factors with the highest levels (31.0%) of contribution to incidence of cardiovascular
47
48 89 events, followed by hypercholesterolemia (27.0%) and smoking (18.0%) [6]. Also,
49
50 90 inadequate control of hypertension has been documented to be associated with
51
52 91 58.0% ischemic stroke, 50.0% hemorrhagic stroke, 55.0% ischemic cardiopathies,
53
54 92 and 58.0% of other forms of cardiovascular disease [7]. Regarding disability-
55
56 93 adjusted life years lost, hypertension is the main reason worldwide, rising from 95.9
57
58 94 million to 143.01 million between 1990 and 2015 [8].
59
60

1
2
3 95 Although efficacious drugs exist [9, 10] that actuate against the disease and prevent
4
5 96 its complications, only half the individuals treated achieve proper control of
6
7 97 hypertension (11), and many will abandon treatment without consulting with the
8
9 98 doctor [9], a fact attributable largely to non-adherence and self-management [12].

10 99 Non-adherence to therapeutic regime is a worldwide phenomenon with grave
11
12 100 repercussions that, according to the WHO is the consequence of multiple factors and
13
14 101 is present in almost all patients with chronic diseases who show high rates of non-
15
16 102 compliance [5, 13, 14]. As to hypertension patients, prevalence of adherence to
17
18 103 pharmacologic treatment is variable, ranging between 24.1% and 92.7% [15], while
19
20 104 for life-style-related aspects, non-compliance figures for physical exercise and diet
21
22 105 stand at 68.8% and 30.9%, respectively [16]. The high prevalence of hypertension,
23
24 106 non-adherence to therapeutic regime, and the costs arising from associated
25
26 107 disabilities, call for search of interventions that will solve this problem efficaciously.

108 **Description of the intervention**

109 Adherence to therapeutic regime is defined as “the degree to which a person’s
110
111 behavior regarding medication intake, proper diet regime and modification of life
112
113 habits fits the recommendations of their health care provider” [5], and they include
114
115 both the pharmaceutical and non-pharmaceutical component.

116 The WHO acknowledges the need to implement effective strategies to achieve
117
118 changes in health results, because despite advances in treatment of chronic diseases,
119
120 and research into the problem of adherence, non-adherence remains the single most
121
122 important reason for unreached hypertension control [17–19]. In this sense, the
123
124 health team in charge of Primary Health Care (PHC) plays a key role in facing this
125
126 problem [20, 21] through individual teaching that may be offered thru educational,

1
2
3 119 behavioral, and affective interventions, or a combination of the previous,
4
5 120 (multifaceted) [22,23]. Although diverse studies [22–32] have shown their efficacy
6
7 121 to improve adherence and hypertension control, a focus is required not only on the
8
9 122 pharmacologic component, but also on life habits related to cardiovascular risk, like
10
11 123 physical activity and diet [8, 22,31].
12
13
14

15 124 **How the intervention might work**

16
17
18 125 Different theoretical models exist to explain the phenomenon of non-adherence to
19
20 126 therapeutic regime among chronic disease patients, like the theory of cognition and
21
22 127 self-efficacy, and the models of belief in health, behavioral changes, motivation, and
23
24 128 self-regulation [34-36]. Self-management has been highlighted recently; it offers
25
26 129 chronic disease patients a series of supports to improve confidence, with a positive
27
28 130 effect on adherence to therapeutic regime [12, 36–38].
29
30
31

32 131 Scientific evidence suggests that interventions developed by the health team to
33
34 132 increase adherence to therapeutic regime in hypertension patients have focused
35
36 133 mainly on the pharmacologic component, with an emphasis on not only pedagogic
37
38 134 component with an individual focus, but also involving other dimensions like
39
40 135 conduct and affective factors, or in some cases, combinations of the above
41
42 136 mentioned aspects, and they are denominated multifaceted [10, 39, 40].
43
44
45

46 137 **OBJECTIVES**

47
48
49 138 This article describes the protocol for a systematic review that will evaluate the
50
51 139 effects of individual interventions to improve adherence to recommendations of the
52
53 140 health provider's team regarding medication treatment, diet and physical activity
54
55 141 among adults with primary hypertension.
56
57
58

59 142 **METHODS AND ANALYSIS**

1
2
3 143 **Eligibility criteria of the studies in this review**
4

5
6 144 They were defined in accordance with the criteria included in the PICOT question.
7

8
9 145 **Participants (P)**
10

11 146 Adult people aged 18 or older, with primary hypertension diagnosis defined with
12 147 systolic blood pressure (SAP) ≥ 140 mmHg or diastolic blood pressure (DAP) ≥ 90
13 148 mmHg, currently receiving PHC or that of a health provider's team, who are also
14 149 undergoing hypertension treatment. Pregnant women, hospitalized people or with
15 150 secondary hypertension will be excluded.
16
17
18
19
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21
22

23 151 Primary hypertension is defined as that whose primary origin cause is unknown, and
24 152 taken to be linked to genetics, diet, sedentary lifestyle and obesity [41, 42].
25
26
27
28

29 153 On the other hand, secondary hypertension is that resulting from diseases affecting
30 154 other organs and systems [42, 43].
31
32
33

34 155 **Types of interventions (I)**
35

36 156 The different intervention types are specified next:
37
38

39 157 -Classification: Educational, behavioral, affective or multifaceted interventions
40 158 oriented toward the individual will be included.
41
42
43
44

45 159 -Application scenario: outpatient or health provider patient.
46
47

48 160 -Methodology: in-person and non-in-person strategies.
49

50 161 -Personnel applying the intervention: interventions led by any health team member
51 162 will be included.
52
53

54 163 -Objective: improve adherence to medication treatment, diet, and, or physical
55 164 activity.
56
57
58
59
60

1
2
3 **165 Comparison (C)**
4

5
6 **166** No comparator will be included, as the objective is to evaluate the effect of the
7
8 **167** different interventions, rather than of one in particular in any specific manner.
9

10
11 **168 Types of outcome measures (O)**
12

13
14 **169 - Primary outcomes**
15

16
17 **170** The main result will be the difference of proportions or means in adherence to
18
19 **171** pharmacologic treatment, diet and physical activity [44-46] pre and post
20
21 **172** intervention. Measurements can be obtained through direct and indirect methods
22
23
24 **173 (Example Table 1).**

25
26 **174** Table 1. Direct and indirect methods reported in literature to evaluate adherence to
27
28
29 **175** therapeutic regime.
30

Pharmacologic treatment	Diet	Prescribed Activity	Physical
Tablet Counting	Degree of adherence to diet DASH*	Accelerometry changes	International Physical Activity Questionnaire (IPAQ)
Questionnaires (Morisky-Green, MARS, SMAQ)*	Anthropometric changes (IMC, ICC)*		
Electronic monitoring	Lipid profile changes		
Concentration of pharmaceutical or its metabolite in bodily fluids (blood, urine)		Strain test	

Directly observed therapy		Six-minute-walk test
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176 MARS (Medication Adherence Report Scale), SMAQ (Simplified Medication
 177 Adherence Questionnaire), DASH (Dietary Approaches to Stop Hypertension), BMI
 178 (Body Mass Index), WHI (Waist-Hip Index.).

179 **-Secondary outcomes**

- 180 • Percentage of participants with blood pressure control.
- 181 • Rate or proportion of morbimortality by major cardiovascular events (ischemic
 182 disease and stroke).
- 183 • Incremental rate of cost-effectiveness or cost-efficacy, cost-usefulness of
 184 interventions.

185 Self-reported outcomes such as quality of life and burden of disease.

186 **Types of studies (t)**

187 This review will include randomized and non-randomized clinical trials that have
 188 had a comparison group (usual treatment or placebo) related to pharmacologic
 189 treatment, diet and physical activity in people with primary hypertension.

190 **Search methods for identification of studies**

191 Electronic search

192 Systematic electronic search strategy will be designed aiming to locate and retrieve
 193 those studies meeting the inclusion criteria established in the PICOt question in the
 194 following databases: PubMed/MEDLINE, BVS, CINAHL, Embase, Cochrane and
 195 Scopus.

196 Next is an advanced, independent search for interventions for each event

197 (medication, diet and physical activity) by means of combination of controlled and
 198 free language terms. Search strategies will adapt to database characteristics. The
 199 following restrictions will apply: studies conducted in humans, published along
 200 2009-2019. Finally, search process record will be kept for each information source.
 201 (See Table 2. Search Strategy).

202 **Table 2. Search strategy PICOt**

	Participants/patients (P)	Intervention (I)	Outcomes (O)	Type studio (t) **
Pharmacological treatment	((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension [Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR behaviour therapy [tiab]	"Treatment Adherence and Compliance"[Mesh] OR Adherence[tiab] OR compliance[tiab] OR Nonadherence[tiab] OR Noncompliance [tiab] OR Non-Adherence[tiab] OR Non-Compliance[tiab] OR medication intake adherence[tiab] OR drug therap*[tiab] OR medication therapy management[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized* [tiab] OR Non-Randomized [tiab] OR Quasi-Experimental [tiab]

Diet	((((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension[Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms])))	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR behaviour therapy [tiab]	"Diet" [MeSH] OR diet [tiab] OR dietar*[tiab] OR food*[tiab] OR nutrition*[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized* [tiab] OR Non-Randomized [tiab] OR Quasi-Experimental [tiab]
Exercise	((((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension[Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab]	"Exercise" [MeSH] OR Exercise*[tiab] OR Physical Activit*[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

	("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR behaviour therapy [tiab]		OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized* [tiab] OR Non-Randomized [tiab] OR Quasi-Experimental [tiab]
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203 Filters: Publication date from 2009/01/01 to 2019/11/

204 **Searching other resources**

205 The search will include the clinical trials registers identified in the following
 206 databases: ClinicalTrials.org, BVS (doctoral theses), International Clinical Trials
 207 Registry Platform (ICTRP, OMS), Open Access Theses and Dissertations (OATD).

208 **Data collection and analysis**

209 Selection of studies

210 Search will be conducted independently by two researchers assigned per database
 211 (DP, JS, PS, JH, ST, CE, LL, LR) following the strategy set. Documents retrieved
 212 in this first phase will go to folders classified by topic and database on EndNote.
 213 Then, a reviewer (CE) will eliminate duplicates and export each single study to
 214 Rayyan QCRI to evaluate eligibility criteria. This stage will determine eligibility of
 215 the studies by means of blinded review procedure, based on titles and summaries, to
 216 be conducted by seven reviewers (DP, JS, JH, ST, CE, LL, LR) on Rayyan QCRI
 217 platform. Once the process is completely finished by every reviewer, the blind will
 218 be lifted to again review those studies lacking consensus. If disagreement stands, an
 219 external evaluator's (LV, PS, IT, FG) intervention will solve discrepancies.

1
2
3 220 In case disagreement persists, the whole study text will be loaded to an independent
4
5 221 ledger on Rayyan OCRI, to be reviewed once more, blinded. Elimination of every
6
7 222 document must be justified in this phase.
8
9

10 223 When consensus is reached about inclusion of studies, upon review of titles and
11
12 224 summaries, the whole text will be reviewed, selecting those to include in the
13
14 225 qualitative synthesis. To ease eligibility process, a table with exclusion criteria will
15
16 226 be produced, and its results will be documented following the PRISMA flow
17
18 227 diagram. (See Figure 1).
19
20

21 22 228 **Data extraction and management**

23
24
25 229 Two independent evaluators will retrieve the information using formats designed by
26
27 230 Cochrane for extraction of results from the studies included (categorical or
28
29 231 continuous data). Then, validation in duplicate will be made to prevent mistakes.
30
31 232 This process will be made on Epidata.
32
33

34 35 233 **Assessment of risk of bias in included studies**

36
37
38 234 Two independent reviewers will carry out evaluation of the methodological quality
39
40 235 of the articles.

41
42
43 236 The domains and criteria established by the Cochrane [47] group will be followed,
44
45 237 and they correspond to the following:

46
47
48 238 Selection bias: random assignment and selection of participants.

49
50
51 239 Performance bias: corresponds to blinding of investigators and participants.

52
53
54 240 Detection bias: corresponds to blinding of the intervention assessment.

55
56
57 241 Attrition bias: it refers to losses in participants and information.

58
59
60 242 Reporting bias: it refers to selection of the report.

1
2
3 243 Other bias: for example, the intent to treat, for conflict of interest.
4

5
6 244 Risk degree will be evaluated for each domain as: “low risk”, “high risk” or “unclear”.
7

8
9 245 To evaluate evidence degree of the studies, the GRADE [48] system will be used,
10

11 246 availing of four categories: “high quality”, “moderate quality”, “low quality” and
12

13 247 “very low quality”.
14

15
16 248 In case of discrepancies regarding these procedures, a third reviewer will intervene. The
17

18 249 authors of studies with a high risk of bias or incomplete information will be contacted
19

20 250 to clarify pertinent aspects and in case of no reply or if the information available does
21

22 251 not allow it, they will be included in the systematic review description, but not in the
23

24 252 meta-analysis.
25

26 253 **Measures of treatment effect** 27

28 254 Instead of adherence measuring availing of just one method, other direct and indirect
29

30 255 methods will be included (Table 1).
31

32 256 Also, taking into account that interventions can be varied and have a direct influence
33

34 257 on results obtained, they will be classified according to the designed method and the
35

36 258 number of strategies utilized. In the case of continuous data, the change estimator in the
37

38 259 measures will be recorded with its respective dispersion measure.
39

40 260 For categorical data, absolute and relative frequency measures, or effect measures
41

42 261 reported as RR, HR, OR, NNT, RAR, will be reported with 95% confidence interval.
43

44 262 **Unit analysis issues** 45

46 263 As previously mentioned, high variability exists in the methods to evaluate adherence
47

48 264 to therapeutic regime (Table 1), and it can prevent both information grouping for
49

50 265 quantitative analysis and adequate control by heterogeneity sources.
51
52
53
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56
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60

266 **Dealing with missing data**

267 In case of identifying missing data, the study authors will be contacted to obtain it
268 for analysis; in case of no reply, sensitivity analysis will be conducted eliminating
269 this kind of publications.

270 **Assessment of heterogeneity**

271 Heterogeneity will be evaluated by means of the Chi^2 ($p < 0.05$), Q Cochrane (over
272 25%) and I^2 (over 50%) [49] tests, and in case it is considerable, random-effects model
273 will be estimated. Heterogeneity sources (type and duration of intervention, population,
274 region or country, sociodemographic variables, effect measures, etc.), will be explored
275 in a subgroup analysis and/or meta regressions.

276 **Assessment of reporting bias**

277 Publication bias will be determined with funnel plot as the graphic method, and bias
278 numeric evaluation will be run through Egger and Begg [50] asymmetry tests.

279 **Data synthesis**

280 Data synthesis and statistical analyses will be performed by means of Cochrane Review
281 Manager, and meta-analysis thru RevMan 5.3 [51] and Stata 15 [52], if the criteria to do
282 so are met.

283 **Subgroup analysis and sources of heterogeneity**

284 If possible, analysis of subgroups or meta-regressions will be carried out according to
285 type of: measuring, intervention, participants at study start-up (e.g. controlled and non-
286 controlled patients), and study; also sex, age groups and other sociodemographic
287 features of interest that may explain differences in the results.

288 Sensitivity analysis

289 Sensitivity analysis will be conducted to examine bias risk effect through evaluation
290 of study feature changes in the funnel plot graph; next, analyses will be conducted
291 excluding those studies with the most and least weight on the effect measure,
292 observing the change in the punctual estimator, and those statistically significant will
293 be reported.

294 Patient and Public Involvement

295 Not patient involved.

296 DISCUSSION

297 Review results will be useful in directing the usual clinical practice of health providers
298 because it enables follow-up of hypertension out-patients.

299 Identification of interventions with the most effectiveness to improve therapeutic
300 adherence, understood as a multi-factor phenomenon involving life-styles changes, will
301 lead to reduction of the disease and economic burden of hypertension. The existence of
302 multiple methods to measure adherence enables detection of high heterogeneity.

303 However, adequate analysis of its main sources will be relevant to adapt interventions in
304 function of context and available resources (human, technical, and financial).

305 Ethics and dissemination

306 This is a systematic review study, where the source of information will be documents
307 published in scientific databases, without human participation, so there will be no need
308 for approval of an ethics committee. The results will be disseminated in scientific
309 journals, as well as in other media, such as: conferences, seminars, congresses or
310 symposia. In addition, copyright will be respected, giving the corresponding credit

1
2
3 311 through the bibliographic reference system.
4

5
6 312 Figure 1. Flow Diagram, process of the systematic review
7

8
9 313 **Acknowledgements**

10
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26
27 321 study conception or design.
28
29

30
31 322 **Authors' contributions**

32
33 323 DP contributed with the study conception. DP, JS, LR, wrote the manuscript. Every

34
35 324 author reviewed and contributed observations to the text.
36
37

38
39 325 Search strategy will be conducted DP, JS, PS, CE, LV and it will be reviewed and

40
41 326 adjusted by every author. It will be applied by DP, JS, PS, CE, JH, ST, LR, and LL.
42
43

44
45 327 Retrieval of data from the studies included, bias evaluation, and synthesis will be

46
47 328 developed by DP, JS, JH, ST, LL, and LR. Analyses will be the work of DP, JS, JH,

48
49 329 ST, LL, LR, FG, and LV.
50
51

52
53 330 Authors PS, LV, IT, and FG, will both make sure no errors will be introduced along

54
55 331 the different stages or review, and arbitrate disagreement.
56
57

58
59 332 Writing of manuscripts product of the systematic review will be agreed on and

60 333 distributed among the different authors by topic (pharmacologic adherence, diet and

1
2
3 334 physical activity).

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5
6 335 Approval by the authors of the final version of this manuscript was unanimous.

7
8
9 336 **Conflicts of interest**

10
11 337 **None**

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14 338 **REFERENCIAS**

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For peer review only

Table 2. Search strategy PICOt

	Participants/patients (P)	Intervention (I)	Outcomes (O)	Type studies (t) **
Pharmacological treatment	(((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension [Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR behaviour therapy [tiab]	"Treatment Adherence and Compliance"[Mesh] OR Adherence[tiab] OR compliance[tiab] OR Nonadherence[tiab] OR Noncompliance[tiab] OR Non-Adherence[tiab] OR Non-Compliance[tiab] OR medication intake adherence[tiab] OR drug therap*[tiab] OR medication therapy management[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized* [tiab] OR Non-Randomized [tiab] OR Quasi-experimental [tiab]
Diet	(((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension[Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR behaviour therapy [tiab]	"Diet" [MeSH] OR diet [tiab] OR dietar*[tiab] OR food*[tiab] OR nutrition*[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized* [tiab] OR Non-Randomized [tiab] OR Quasi-experimental [tiab]

Exercise	((((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension[Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR behaviour therapy [tiab]	"Exercise" [MeSH] OR Exercise*[tiab] OR Physical Activit*[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized*[tiab] OR Non-Randomized [tiab] OR Quasi-experimental [tiab]
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Filters: Publication date from 2009/01/01 to 2019/11/

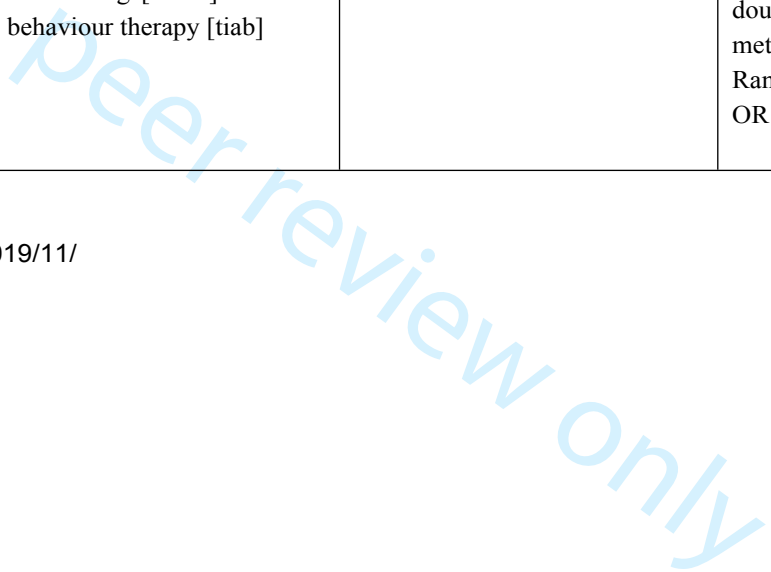
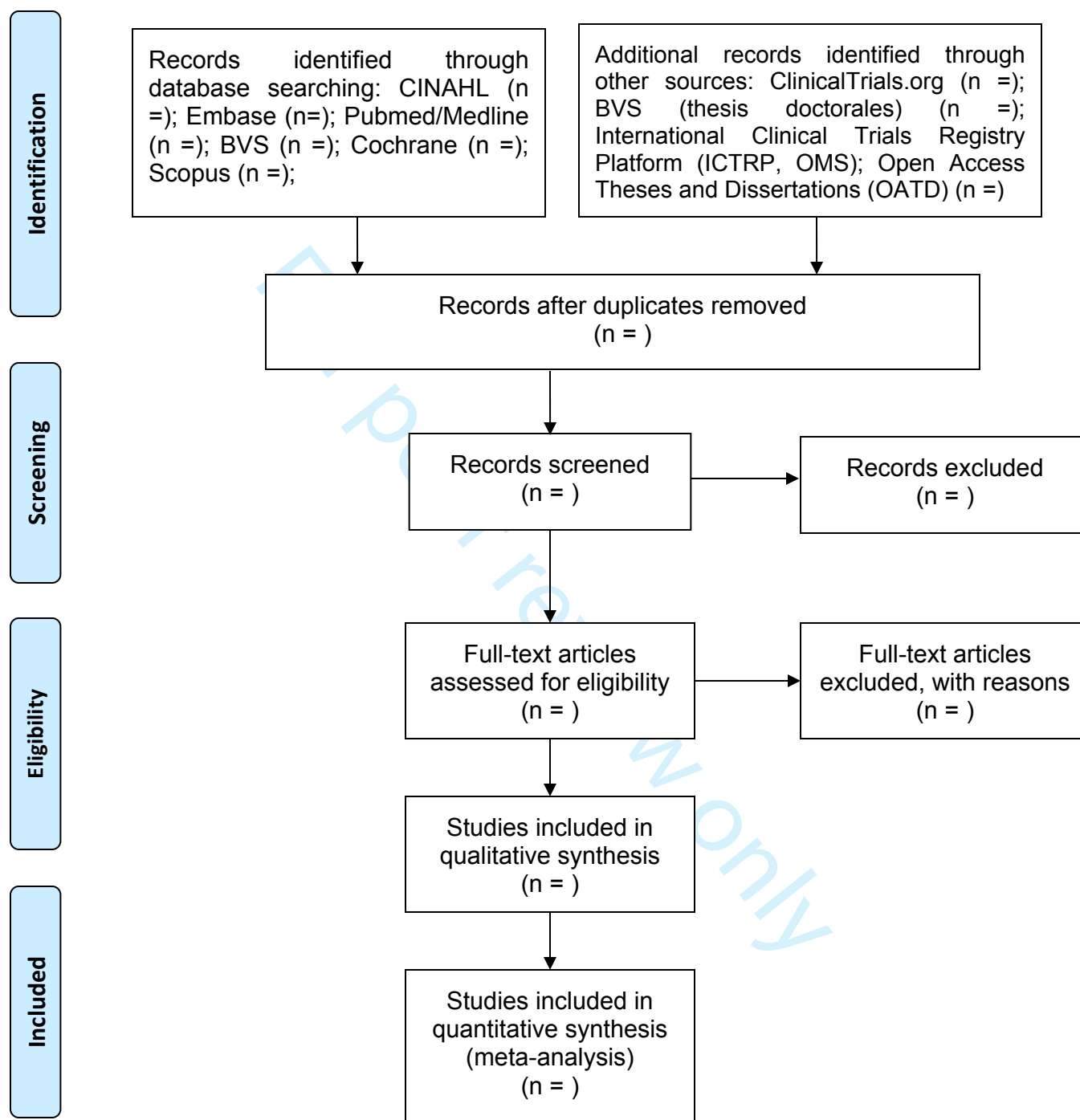


Figure 1. Flow Diagram, process of the systematic review



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	X		3-4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		X	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		62-63
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		5-38
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		322-335
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		NA	
Sources					
Sources	5a	Indicate sources of financial or other support for the review	X		317-321
Sponsor	5b	Provide name for the review funder and/or sponsor		NA	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	X		320-321
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		73-136
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		137-189
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
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	X		137-189
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	X		190-207
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	X		201-203
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		208-227
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)	X		208-227
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	X		228-232
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	X		253-261
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		168-185
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	X		233-252
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		279-282
	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)	X		271-275
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		283-293
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		280-282
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		233-252
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		244-247

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INDIVIDUAL INTERVENTIONS TO IMPROVE ADHERENCE TO PHARMACEUTICAL TREATMENT, DIET AND PHYSICAL ACTIVITY AMONG ADULTS WITH PRIMARY HYPERTENSION. A SYSTEMATIC REVIEW PROTOCOL.

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1
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4 1 **INDIVIDUAL INTERVENTIONS TO IMPROVE ADHERENCE TO**
5
6 2 **PHARMACEUTICAL TREATMENT, DIET AND PHYSICAL ACTIVITY**
7
8 3 **AMONG ADULTS WITH PRIMARY HYPERTENSION. A SYSTEMATIC**
9
10 4 **REVIEW PROTOCOL.**
11
12

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41 **ABSTRACT**

42 **Introduction.** Hypertension is a chronic disease with 31% worldwide prevalence in

43 adults. It has been associated with non-adherence to therapeutic regime with a

44 negative impact on the prognosis of the disease and healthcare associated costs. The

45 previous makes it necessary to identify effective interventions to improve adherence

46 among this population. The objective of this protocol is to describe the methods for

1
2
3 47 a systematic review that will evaluate the effect of individual interventions to
4
5 48 improve adherence to the prescribed pharmacologic treatment, diet and physical
6
7 49 activity in adults with primary hypertension.
8
9

10 50 **Methods and analysis:** A systematic search of studies will be conducted in
11
12 51 PubMed/MEDLINE, BVS, CINAHL, Embase, Cochrane and Scopus databases.
13
14 52 Randomized and non-randomized clinical studies conducted in human beings,
15
16 53 published from 01/01/2009 to 12/13/2019, will be included, with no language
17
18 54 restriction. Adherence to pharmacologic treatment, diet and physical activity,
19
20 55 measured by direct and indirect methods, will be the primary outcome. Two
21
22 56 independent reviewers will select relevant studies and will extract the data following
23
24 57 the Cochrane's Handbook for Systematic Reviews of Approach and the Preferred
25
26 58 Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P).
27
28 59 Methodologic quality will be evaluated by the ROBIS-2 Scale. Risk of bias will also
29
30 60 be evaluated, and if the criteria are met, a meta-analysis will be finally performed.
31
32
33
34
35

36 61 **Ethics and dissemination.** Information to be analyzed is of a grouped nature, and
37
38 62 given that it sources from published studies, no ethics committee approval is
39
40 63 required. Results will be published in scientific journals, and through conferences,
41
42 64 seminars, conferences, and symposiums. Copyrights will be respected by
43
44 65 corresponding accrediting through the system of bibliographic references.
45
46
47

48 66 Key words: hypertension, interventions, adherence, diet, exercise, adults.
49

50
51 67 Register in PROSPERO: CRD42020147655
52

53 68 **Strengths and limitations of this study**

54
55
56 69 _The procedures of the study will be conducted in an independent and blinded
57
58 70 manner by at least two reviewers.
59
60

1
2
3 71 _Bibliographic search will have no language restriction.
4

5
6 72 _Ample modality of individual interventions will be included, and adherence will be
7
8 73 evaluated globally (pharmacological treatment, diet and physical activity).
9

10
11 74 _Variability in adherence measures can be associated with high heterogeneity, which
12
13 75 may lead to conduct analysis by sub-groups and meta-regressions.
14

15
16 76 _The study will be conducted by an interdisciplinary group.
17

18 77 **INTRODUCTION**

19 20 21 78 **Description of the condition**

22
23 79 According to the guidelines of the European Societies of Cardiology and
24
25 80 Hypertension (ESC/ESH) 2018, for diagnosis and treatment of hypertension, it is
26
27 81 defined with values equal to or over 140 mmHg for systolic blood pressure (SBP),
28
29 82 or 90 mmHg for diastolic blood pressure (DBP) [1]. It is the most common chronic
30
31 83 non-communicable disease, and it has been described as one of the main risk factors
32
33 84 associated with cardiovascular morbidity and mortality worldwide [2]. Its
34
35 85 occurrence around the world stands at 31.0% (CI 95%: 30.0-32.2), and in low-to-
36
37 86 middle-income countries, at 31.5% (CI 95%: 30.2-32.9), or 1.04 billion adults [3].
38
39 87 As to incidence, a follow-up study in young adults, (median age 33), for over two
40
41 88 decades estimated an incidence rate of 58.6 cases per 100,000 people (CI 95%: 52.8-
42
43 89 64.9) [4]. According to the World Health Organization (WHO), hypertension
44
45 90 increases the risk of ischemic cardiopathy by three or four times and between two
46
47 91 and three times for general cardiovascular risk [5] .
48
49

50
51
52
53
54 92 Additionally, prospective studies have shown hypertension to be one of the risk
55
56 93 factors with the highest levels (31.0%) of contribution to incidence of cardiovascular
57
58 94 events, followed by hypercholesterolemia (27.0%) and smoking (18.0%) [6]. Also,
59
60

1
2
3 95 inadequate control of hypertension has been documented to be associated with
4
5 96 58.0% ischemic stroke, 50.0% hemorrhagic stroke, 55.0% ischemic cardiopathies,
6
7 97 and 58.0% of other forms of cardiovascular disease [7]. Regarding disability-
8
9
10 98 adjusted life years lost, hypertension is the main reason worldwide, rising from 95.9
11
12 99 million to 143.01 million between 1990 and 2015 [8].

13
14
15 100 Although efficacious drugs exist [9,10] that actuate against the disease and prevent
16
17 101 its complications, only half the individuals treated achieve proper control of
18
19 102 hypertension [11], and many will abandon treatment without consulting with the
20
21 103 doctor [9], a fact attributable largely to non-adherence and self-management [12]

22
23
24
25 104 Non-adherence to therapeutic regime is a worldwide phenomenon with grave
26
27 105 repercussions that, according to the WHO is the consequence of multiple factors and
28
29 106 is present in almost all patients with chronic diseases who show high rates of non-
30
31 107 compliance [5,13–15].

32
33
34
35 108 As to hypertension patients, prevalence of adherence to pharmacologic treatment is
36
37 109 variable, ranging between 24.1% and 92.7% [16], while for life-style-related aspects,
38
39 110 non-compliance figures for physical exercise and diet stand at 68.8% and 30.9%,
40
41 111 respectively [17].

42
43
44 112 Direct and indirect methods exist to assess adherence (See Table 1), and using one
45
46 113 or the other can result in advantages and disadvantages related to objectivity and
47
48 114 cost, [18]. Scientific literature shows that hypertension control takes both,
49
50 115 pharmacologic and non-pharmacologic interventions, which makes it fundamental
51
52 116 to measure adherence to all and every intervention, so as to identify the most
53
54 117 effective strategy to achieve optimal adherence level to not only medication intake
55
56 118 by patients, but also physical activity parameters that will lead to positive results in
57
58
59
60

1
2
3 119 hypertension control, for diminished consequences on health and health system's
4
5 120 costs [19,20].
6
7

8 121 Regarding the previous, several studies have shown the clinical benefits of adherence
9
10 122 to pharmacologic treatment, diet and exercise [17,21,22] diminished risk of clinical
11
12 123 events such as death and myocardial infarction hospitalization, heart failure, or stroke
13
14 124 [23]. In the same way, the higher the compliance with DASH (Dietary Approaches to
15
16 125 Stop Hypertension) [24,25], the lower the levels of mortality arising from all causes
17
18 126 including cardiovascular disease. Likewise, adherence to diet consistent with dietary
19
20 127 guidelines has been associated with lower metabolic syndrome risk prevalence, and
21
22 128 some of its factors, such as hypertension [26,27]. As to physical activity and exercise,
23
24 129 lack of physical activity has been reported as a factor in non-hypertension control,
25
26 130 entailing higher cardiovascular risk [28–30].
27
28
29
30

31 131 In terms of economic impact, studies conducted by Weaver et al, [31] estimated the
32
33 132 cost attributable to hypertension in Alberta (Canada) by 2010 at CAD\$1.4 billion,
34
35 133 and for the whole of Canada, at CAD\$13.9 billion for the same period. The same
36
37 134 study foresees this figure to go up to CAD\$20.5 billion along 2020, due to
38
39 135 demographic changes, raised prevalence, and higher per-patient costs, adding that
40
41 136 hypertension represents around 10.2% of Canada's sanitary budget. The same
42
43 137 authors, in a systematic review, hold the cost associated to hypertension and specific
44
45 138 cardiovascular disease episode, which showed uniform intra-studies figures, to reach
46
47 139 between US\$500 and \$1,500 in low-to-mid-income countries, while costs for
48
49 140 cerebrovascular accident and coronary disease exceeded \$5,000 per episode [32].
50
51
52
53

54
55 141 The high prevalence of hypertension, non-adherence to therapeutic regime, the
56
57 142 clinical implications and the costs related to disability associated with hypertension
58
59 143 make it necessary to identify interventions that can efficaciously solve this problem
60

1
2
3 144 and can be adapted to the diverse scenarios of Primary Health Care (PHC) centers.
4
5

6 145 **Description of the intervention** 7

8
9 146 Adherence to therapeutic regime is defined as “the degree to which a person’s
10
11 147 behavior regarding medication intake, proper diet regime and modification of life
12
13 148 habits fits the recommendations of their health care provider” [5], and they include
14
15
16 149 both, the pharmaceutical and non-pharmaceutical component.
17

18
19 150 The WHO acknowledges the need to implement effective strategies to achieve
20
21 151 changes in health results, because despite advances in treatment of chronic diseases,
22
23 152 and research into the problem of adherence, it remains the single most important
24
25 153 reason for unreached blood pressure control [33–35].
26
27

28
29 154 In this sense, the health team in charge of PHC plays a key role in facing this
30
31 155 problem [36,37] through individual teaching that may be offered thru educational,
32
33 156 behavioral, and affective interventions, or a combination of the previous,
34
35 157 (multifaceted) [38,39]. Although diverse studies [38–48] have shown their efficacy
36
37 158 to improve adherence and hypertension control, a focus is required not only on the
38
39 159 pharmacologic component, but also on life habits related to cardiovascular risk, like
40
41
42 160 physical activity and diet [44, 46, 48, 49].
43
44

45 161 **How the intervention can work** 46

47
48 162 There are different theoretical models to explain the phenomenon of adherence to
49
50 163 therapeutic regime in chronic disease patients, based mainly on individual health
51
52 164 behavior models [50] like the theories of cognition and self-efficacy, models of
53
54 165 belief in health, behavioral changes, motivation, and self-regulation [51–53]. Self-
55
56 166 management has been recently highlighted; it offers the chronic disease patient a
57
58
59 167 series of support measures to improve confidence, with positive effect on adherence
60

1
2
3 168 to therapeutic regime[12,53–55]. Although some authors have found intervention
4
5 169 based on individual health models to be more effective in different degrees[56], the
6
7 170 intention of this review is finding individual interventions that will improve
8
9
10 171 adherence to therapeutic regime in patients with hypertension, independently of the
11
12 172 theoretical model proposed by the authors, implicitly or explicitly.

13
14
15 173 Scientific evidence suggests that interventions developed by the health team to
16
17 174 increase adherence to therapeutic regime in patients with hypertension have focused
18
19
20 175 mainly on the pharmacologic component, with an emphasis on not only pedagogic
21
22 176 component with an individual focus, but also involving other dimensions like conduct
23
24 177 and affective factors, or in some cases, combinations of the above mentioned aspects,
25
26
27 178 and they are denominated multifaceted [10,57,58], which calls for research not only
28
29 179 in pharmacological, but also non-pharmacological aspects of adherence.

30 31 32 180 **OBJECTIVES**

33
34
35 181 This article describes the protocol for a systematic review that will evaluate the
36
37 182 effects of individual interventions to improve adherence to recommendations of the
38
39 183 PHC team regarding medication treatment, diet and physical activity among adults
40
41 184 with primary hypertension.

42 43 44 185 **METHODS AND ANALYSIS**

45 46 47 186 **Eligibility criteria of the studies in this review**

48
49
50 187 They were defined according to the criteria included in the PICOt question.

51 52 53 188 **Participants (P)**

54
55
56 189 Adult people aged 18 or older, with primary hypertension diagnosis defined with SBP
57
58 190 ≥ 140 mmHg or DBP ≥ 90 mmHg, or according to the definition used by the authors of
59
60

1
2
3 191 the studies; who are receiving health care from a PHC team that normally includes
4
5 192 medical doctors, nurses, nutritionists, etc., and whose aim is providing interventions of
6
7 193 promotion of health, prevention of cardio-cerebrovascular events; patients who are
8
9 194 covered by some modality of antihypertensive treatment.

10
11
12
13 195 Pregnant women, inpatients or those with secondary hypertension will be excluded.

14
15
16 196 Primary hypertension is defined as that whose primary origin cause is unknown, and
17
18 197 taken to be linked to genetics, diet, sedentary lifestyle and obesity [59,60].

19
20
21 198 On the other hand, secondary hypertension is that resulting from diseases affecting
22
23 199 other organs and systems [60,61]. In this review, identification will be made according
24
25 200 to the criteria defined by the authors of the studies.

26 27 28 201 **Types of interventions (I)**

29
30
31 202 Interventions meeting these criteria will be included in this review:

32
33
34 203 1. Classification: Educational, behavioral, affective or multifaceted interventions
35
36 204 oriented toward the individual will be included.

37
38
39 205 2. Application scenario: institutional and extramural

40
41
42 206 3. Methodology: in-person strategies like individual home visits, attention at PHC
43
44 207 and similar centers. Non-in-person, like text messages, phone calls, videos and health
45
46 208 applications, among others.

47
48
49 209 4. Personnel applying the intervention: interventions led by any health team member
50
51 210 (nurses, medical doctors, pharmacologists, nutritionists, and physiotherapists, etc.)
52
53 211 will be included.

54
55
56
57 212 5. Objective: improve adherence to medication treatment, diet, and, or physical
58
59 213 activity.

1
2
3 214 The following will be specifically considered for each intervention type:
4
5

6 215 -Physical activity and exercise: all those interventions directed by health
7
8 216 professionals, intent on promotion physical activity understood as every human body
9
10 217 motion driven by skeletal muscles generating energy expenditure superior to basal
11
12 218 expenditure, including moderate intensity [62] aerobic dynamics (walking, running,
13
14 219 cycling or swimming) for at least 30 minutes 5 to 7 weekly days (150 min/wk), or
15
16 220 vigorous intensity cardio-respiratory exercises no less than 20 minutes for 3 days (75
17
18 221 min/wk), or a combination of moderate and intense activity to achieve energy
19
20 222 expenditure of between 500 – 1000 metabolic equivalents (METs) [62[63]]. Physical
21
22 223 activity includes exercising, a structured, planned activity repeated in time so as to
23
24 224 improve or preserve some physical aptitude elements, [64].
25
26
27
28

29 225 -Diet: interventions aiming to control caloric necessity, obesity indexes, lipid
30
31 226 profile, or specific recommendations of clinical practice guidelines, like restricted
32
33 227 intake of salt, sugar, and fats among others, in arterial hypertension patients[1,62].
34
35
36

37 228 -Pharmacologic: interventions related to promotion or improvement of adherence to
38
39 229 medication prescribed for hypertension control by individuals or participants.
40
41

42 230 **Comparison (C)**

43
44
45 231 No comparator will be included, as the objective is to evaluate the effect of the
46
47 232 different interventions, rather than of one in particular in any specific manner.
48
49

50 233 **Types of outcome measures (O)**

51 52 53 234 ***Primary outcomes**

54
55
56 235 The main outcome will be the difference of proportions or means in adherence to
57
58 236 pharmacologic treatment, diet and physical activity [18,19,65,66] pre and post
59
60

237 intervention. Measurements can be obtained through direct and indirect methods
 238 (Table 1).

239 **Table 1. Direct and indirect methods reported in literature to evaluate**
 240 **adherence to therapeutic regime.**

Pharmacologic treatment	Diet	Prescribed physical activity
Tablet Counting	Degree of adherence to DASH* diet	Accelerometry changes International Physical Activity Questionnaire (IPAQ)
Questionnaires (Morisky-Green, MARS, SMAQ)*	Anthropometric changes (IMC, ICC)*	
-Medication-contained electronic microchip[19] -Electronic monitors of medication -Rates of prescription refills [19] -Measure of clinical response or physiologic markers[19] -Patient's diaries[19]	Lipid profile changes	
Concentration of pharmaceutical or its metabolite in bodily fluids		Strain test

(blood, urine)		
Directly observed therapy		Six-minute walk test

241 MARS (Medication Adherence Report Scale), SMAQ (Simplified Medication
 242 Adherence Questionnaire), DASH (Dietary Approaches to Stop Hypertension), BMI
 243 (Body Mass Index), WHI (Waist-Hip Index.).

244 ***Secondary outcomes**

- 245 • Percentage of participants with controlled hypertension.
- 246 • Rate or proportion of morbidity-mortality by major cardiovascular events
 247 (ischemic disease and stroke).
- 248 • Incremental rate of cost-effectiveness or cost-efficacy, cost-usefulness of
 249 interventions.
- 250 • Self-reported outcomes such as quality of life and burden of disease.

251 **Types of studies (t)**

252 This review will include randomized and non-randomized clinical trials that have
 253 had a comparison group (usual treatment or placebo) related to pharmacologic
 254 treatment, diet and physical activity in adults with primary hypertension.

255 **Search methods for identification of studies**

256 Electronic search

257 A systematic electronic search strategy will be designed to identify those studies meeting
 258 the inclusion criteria established in the PICOt question in the following databases:
 259 PubMed/MEDLINE, BVS, CINAHL, Embase, Cochrane and Scopus. The date
 260 established for the search was from 01/01/2009 to 12/13/2009, and the date to start out

261 and finish this review, according to the record by PROSPERO is from 11/30/2019 to
 262 06/30/2021.

263 Next is an advanced, independent search for interventions for each event
 264 (medication, diet and physical activity) by a combination of controlled and free
 265 language terms. Search strategies will adapt to database characteristics. The
 266 following restrictions will apply: studies conducted in humans, published along
 267 2009-2019. Finally, search process record will be kept for each information source.
 268 (Table 2).

269 **Table 2. Search strategy PICOT**

	Participants/patients (P)	Intervention (I)	Outcomes (O)	Type of study (t) **
Pharmacologic treatment	((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension [Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh]) OR "Health Education"[Mesh] OR "Patient Education as Topic"[Mesh] OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR	"Treatment Adherence and Compliance"[Mesh] OR Adherence [tiab] OR compliance [tiab] OR Nonadherence [tiab] OR Noncompliance [tiab] OR Non-Adherence [tiab] OR Non-Compliance [tiab] OR medication intake	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind

		behaviour therapy [tiab]	adherence [tiab] OR drug therap*[tiab] OR medication therapy management[tiab]	method [tiab] OR placebo* [Title/Abstract] Non Randomized* [tiab] OR Non-Randomized [tiab] OR Quasi-Experimental [tiab]
Diet	((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension[Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh] OR "Health Education"[Mesh] OR "Patient Education as Topic"[Mesh] OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR behaviour therapy [tiab]	"Diet" [MeSH] OR diet [tiab] OR dietar*[tiab] OR food*[tiab] OR nutrition*[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized*

				[tiab] OR Non-Randomized [tiab] OR Quasi-Experimental [tiab]
Exercise	((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension[Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh]) OR "Health Education"[Mesh] OR "Patient Education as Topic"[Mesh] OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR OR behaviour therapy [tiab]	"Exercise" [MeSH] OR Exercise*[tiab] OR Physical Activity*[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized*

				[tiab] OR Non-Randomized [tiab] OR Quasi-Experimental [tiab]
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270 Filters: Publication date from 01/01/2009 to 12/13/2019.

271 **Eligibility criteria**

272 The following inclusion criteria will be applied: studies conducted in humans,
273 published from 01/01/2009 to 12/13/2019 in the English, Spanish and Portuguese
274 languages. The reason to have chosen these languages is that in a preliminary search
275 strategy, in which language was not restricted, a low percentage was found in other
276 languages (less than 1%)

277 **Searching other resources**

278 In order to reduce publication bias, the review will include the clinical trials records
279 identified in the following bases: ClinicalTrials.org, BVS (doctoral theses),
280 International Clinical Trials Registry Platform (ICTRP, OMS), Open Access Theses
281 and Dissertations (OATD).

282 **Data collection and analysis**

283 Selection of studies

284 Search will be conducted independently by two researchers assigned per database (DP,
285 JS, PS, JH, ST, CE, LL, LR) following the strategy set, previously defined in Table 2.

286 Documents retrieved in this first phase will go to folders classified by topic and
287 database on EndNote. Then, a reviewer (CE) will eliminate duplicates and export each
288 unique study to Rayyan QCRI to evaluate eligibility criteria.

289 In the screening phase, selection of studies will be determined thru a blinded and

1
2
3 290 independent reviewing procedure based on titles and abstracts, to be carried out by
4
5 291 seven reviewers (DP, JS, JH, ST, CE, LL, LR) two reviewers per topic, and one in
6
7 292 charge of blinding on the Rayyan QCRI platform. Each reviewer will classify the
8
9 293 articles as included, excluded or dubious. Once each pair of reviewers completes this
10
11 294 process, the blinding will be lifted and those studies lacking consensus will be
12
13 295 reevaluated, reactivating the blind. Articles classified as dubious will be subjected to
14
15 296 a new independent review, by title and abstract. In case disagreement continues on
16
17 297 conflicted articles, an external evaluator (LV, PS, IT, FG) will resolve the discrepancy
18
19 298 by determining inclusion or exclusion of documents. Studies in discrepancy will be
20
21 299 exported to the Rayyan QCRI (CE) platform, to be reassessed blinded.

22
23
24
25
26 300 Upon achievement of consensus on studies to include in the screening phase, they will
27
28 301 go thru eligibility phase, where each reviewer team will evaluate the full text
29
30 302 independently, selecting those articles to be included in the qualitative synthesis. In
31
32 303 case of discrepancy, the same procedure by third reviewer described in the screening
33
34 304 phase, will be conducted. In order to facilitate the eligibility process, a table will be
35
36 305 produced with the inclusion and exclusion criteria, and the results will be documented
37
38 306 following the PRISMA flow chart (**Figure 1**).

307 **Data extraction and management**

308 Data extraction will be carried out independently by two reviewers, availing of the
309 formats established by Cochrane for categorical or continuous data, and any
310 difference will be settled or solved by a third investigator, as the case may be. For
311 data processing, a pilot test will be run among reviewers to guarantee the quality of
312 data extraction, and if necessary, pertaining adjustments will be made to the formats
313 before definitive extraction of information.

1
2
3 314 Then, validation will be carried out in duplicate to avoid typos in the information
4
5 315 extracted. This process will be conducted on Epidata.
6
7

8 316 Whenever the full text of the article cannot be accessed, or supplementary
9
10 317 information on results is required, authors will be contacted for information.
11
12

13 318 **Assessment of risk of bias in included studies**

14
15
16 319 Two independent reviewers will carry out evaluation of the methodological quality of
17
18 320 the articles for each topic, and in case of discrepancy, a third reviewer will settle
19
20 321 differences.
21
22

23
24 322 Dominiions and criteria established by the Cochrane [67] team will be followed using
25
26 323 the ROBIS-2 scale, for both experimental and quasi-experimental, corresponding as
27
28 324 follows:
29
30

- 31 325 • Selection bias: random assignment and selection of participants.
32
33
34 326 • Execution bias: corresponds to blinding of investigators and participants.
35
36
37 327 • Detection bias: corresponds to blinding of the intervention evaluators.
38
39
40 328 • Attrition bias: it refers to losses in participants and information.
41
42
43 329 • Reporting bias: it refers to selection of the report.
44
45
46 330 • Other bias: for example, the intent to try, out of conflict of interest.
47
48

49 331 Risk degree will be evaluated for each domain as “low risk”, “high risk” or “unclear”.

50
51 332 To evaluate evidence degree of the studies, the GRADE [68] system will be used,
52
53 333 availing of four categories: “high quality”, “moderate quality”, “low quality” and
54
55 334 “very low quality”.
56
57

58
59 335 In case of discrepancies regarding these procedures, a third reviewer will intervene. The
60

1
2
3 336 authors of studies with a high risk of bias or incomplete information will be contacted
4
5 337 to clarify pertinent aspects and in case of no reply or if the information available does
6
7 338 not allow it, they will be included in the systematic review description, but not in the
8
9
10 339 meta-analysis.

11 12 13 340 **Measures of treatment effect**

14
15 341 Instead of adherence measuring availing of just one method, other direct and indirect
16
17 342 methods will be included (Table 1).

18
19
20
21 343 Also, taking into account that interventions can be varied and have a direct influence
22
23 344 on results obtained, they will be classified according to the designed method and the
24
25 345 number of strategies utilized. In the case of continuous data, the change estimator in the
26
27 346 measures will be recorded with its respective dispersion measure.

28
29
30 347 For categorical data, absolute and relative frequency measures, or effect measures
31
32 348 reported as RR, HR, OR, NNT, RAR, will be reported with their 95% confidence
33
34 349 interval.

35 36 37 38 350 **Unit analysis issues**

39
40
41 351 As previously, mentioned, high variability exists in the methods to evaluate adherence
42
43 352 to therapeutic regime (Table 1), and this can prevent both information grouping for
44
45 353 quantitative analysis and adequate control by heterogeneity sources.

46 47 48 354 **Dealing with missing data**

49
50
51 355 In case of identifying missing data, the authors will be contacted to obtain it for
52
53 356 analysis; in case of no reply, sensitivity analysis will be conducted eliminating this
54
55 357 kind of publications.

56 57 58 358 **Assessment of heterogeneity**

59
60

1
2
3
4 359 Heterogeneity will be evaluated using the Chi^2 ($p < 0.05$), Q Cochrane (over 25%) and
5
6 360 I^2 (over 50%) [69] tests, and in case it is considerable, random-effects models will be
7
8 361 estimated. Heterogeneity sources (type and duration of intervention, population, region
9
10 362 or country, sociodemographic variables, effect measures, etc.), will be explored in a
11
12 363 subgroup analysis and/or meta regressions.

16 364 **Assessment of reporting bias**

17
18
19 365 Publication bias will be determined with funnel plot as the graphic method, and bias
20
21 366 numeric evaluation will be run through Egger and Begg [70] asymmetry tests.

24 367 **Data synthesis**

25
26
27 368 Data synthesis and statistical analyses will be performed by means of Cochrane Review
28
29 369 Manager, and meta-analysis thru RevMan 5.3 [71] and Stata 15 [72], if the criteria to do
30
31 370 so are met.

32
33
34 371 Otherwise, results will be grouped according to review topics (diet, physical activity and
35
36 372 pharmacological component), intervention type, methods used to measure adherence,
37
38 373 study design, and the effect size of the measures reported will be presented. In general
39
40 374 terms, in order to communicate the qualitative findings, the following aspects will be
41
42 375 extracted from each study, as recommended by Cochrane[73]: authors, publication year,
43
44 376 language, location, study design, intervention, comparer, results, etc.

49 377 **Subgroup analysis and sources of heterogeneity**

50
51
52 378 If possible, analysis of subgroups or meta-regressions will be carried out according to
53
54 379 type of: measuring, intervention, participants at the baseline (e.g. controlled and non-
55
56 380 controlled patients), and study; also sex, age groups and other sociodemographic
57
58 381 characteristics of interest that may explain differences in the results.

1
2
3 **382 Sensitivity analysis**
4

5
6 383 Sensitivity analysis will be conducted to examine bias risk effect through evaluation
7
8 384 of study feature changes in the funnel plot graph; next, analyses will be conducted
9
10 385 excluding those studies with the most and least weight on the effect measure,
11
12 386 observing the change in the punctual estimator, and those statistically significant will
13
14
15 387 be reported.
16

17
18 **388 Patient and public involvement**
19

20
21 389 Not patient involved.
22

23
24 **390 DISCUSSION**
25

26
27 391 Review results will be useful in directing the usual clinical practice of PHC providers
28
29 392 because it enables follow-up of hypertension ambulatory patients. Identification of
30
31 393 interventions with the most effectiveness to improve therapeutic adherence, understood
32
33 394 as a multi-factor phenomenon involving life-styles changes, will lead to reduction of the
34
35 395 disease and economic burden of arterial hypertension.
36
37

38
39 **396 Limitations of the review**
40

41
42 397 As we has been previously mentioned in this text, it is highly likely that no general
43
44 398 summary measure like meta-analysis will be obtained, explained by the high
45
46 399 heterogeneity of the interventions, as a consequence of the lack of a control group, the
47
48 400 presence of three topics or areas (medication, diet, exercise), as well as the different
49
50 401 methods to assess adherence, among others. However, adequate analysis of their main
51
52 402 sources will be relevant to adapt interventions in function of context and available
53
54 403 resources (human, technical, and financial).
55
56

57
58 **404 Ethics and dissemination**
59
60

1
2
3 405 This is a systematic review study, where the source of information will be documents
4
5 406 published in scientific databases, without human participation, so there will be no need
6
7 407 for approval of an ethics committee. The results will be disseminated in scientific
8
9 408 journals, as well as in other media, such as conferences, seminars, congresses or
10
11 409 symposia. In addition, copyright will be respected, giving the corresponding credit
12
13 410 through the bibliographic reference system.
14
15

16
17 411 **Figure 1. Systematic review flowchart.**

18
19
20 412 **Acknowledgements**

21
22
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28
29

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38
39 420 study conception or design.
40
41

42
43 421 **Authors' contributions**

44
45
46 422 DP contributed with the study conception. DP, JS, LR, wrote the manuscript. Every
47
48 423 author reviewed and contributed observations to the text.
49

50
51 424 Search strategy will be conducted DP, JS, PS, CE, LV and it will be reviewed and
52
53 425 adjusted by every author. DP, JS, PS, CE, JH, ST, LR, and LL will apply it.
54

55
56 426 Retrieval of data from the studies included, bias evaluation, and synthesis will be
57
58 427 developed by DP, JS, JH, ST, LL, and LR. Analyses will be the work of DP, JS, JH,
59
60

1
2
3 428 ST, LL, LR, FG, and LV.
4

5
6 429 Authors PS, LV, IT, and FG, will both make sure no errors will be introduced along
7
8 430 the different stages or review, and arbitrate disagreement.
9

10
11 431 Writing of manuscripts product of the systematic review will be agreed on and
12
13 432 distributed among the different authors by topic (pharmacologic adherence, diet and
14
15 433 physical activity).
16

17
18 434 Approval by the authors of the final version of this manuscript was unanimous.
19

20
21 435 **Conflicts of interest**
22

23
24 436 **None**
25

26
27 437 **REFERENCIAS**
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Figure 1. Flow Diagram, process of the systematic review

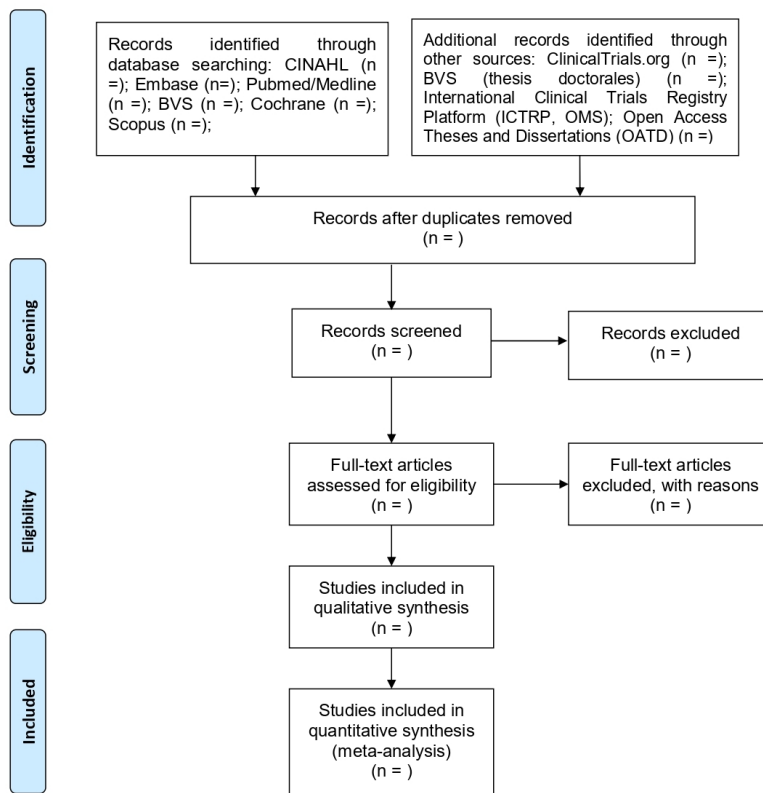


Figure 1: Flow Diagram, process of the systematic review

107x139mm (300 x 300 DPI)

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	X		3-4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		NA	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		67
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		5 to 40
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		421 to 434
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		NA	
Sources					
Sources	5a	Indicate sources of financial or other support for the review	X		416 to 420
Sponsor	5b	Provide name for the review funder and/or sponsor		NA	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		NA	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		77 to 179
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		180 to 250
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
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	X		251 to 255; 271 to 276
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	X		255 to 270; 277 to 281
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	X		269 to 270
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		282 to 306
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)	X		282 to 306
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	X		307 to 317
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	X		340 to 349
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		233 to 250
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	X		318 to 339
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		367 to 376
	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)	X		358 to 363
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		377 to 387
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		367 to 370
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		364 to 366
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		332 to 334

BMJ Open

INDIVIDUAL INTERVENTIONS TO IMPROVE ADHERENCE TO PHARMACEUTICAL TREATMENT, DIET AND PHYSICAL ACTIVITY AMONG ADULTS WITH PRIMARY HYPERTENSION. A SYSTEMATIC REVIEW PROTOCOL.

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Article Type:	Protocol
Date Submitted by the Author:	14-Nov-2020
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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine, Epidemiology, Research methods
Keywords:	Hypertension < CARDIOLOGY, NUTRITION & DIETETICS, EPIDEMIOLOGY, PRIMARY CARE, PUBLIC HEALTH

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4 1 **INDIVIDUAL INTERVENTIONS TO IMPROVE ADHERENCE TO**
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6 2 **PHARMACEUTICAL TREATMENT, DIET AND PHYSICAL ACTIVITY**
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8 3 **AMONG ADULTS WITH PRIMARY HYPERTENSION. A SYSTEMATIC**
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10 4 **REVIEW PROTOCOL.**

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46 41 **ABSTRACT**

47
48
49 42 **Introduction.** Hypertension is a chronic disease with 31% worldwide prevalence in
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51 43 adults. It has been associated with non-adherence to therapeutic regime with a
52
53 44 negative impact on the prognosis of the disease and healthcare associated costs. So,
54
55 45 it is necessary to identify effective interventions to improve adherence among the
56
57 46 afflicted population. The objective of this protocol is to describe the methods for a
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1
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3 47 systematic review that will evaluate the effect of individual interventions so as to
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5 48 improve adherence to the prescribed pharmacologic treatment, as well as to
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7 49 prescribed diet and physical activity in adults with primary hypertension.
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9

10 **Methods and analysis:** A systematic search of studies will be conducted in
11
12 PubMed/MEDLINE, BVS, CINAHL, Embase, Cochrane and Scopus databases.
13
14 Randomized and non-randomized clinical studies conducted in human beings,
15
16 52 published from 01/01/2009 to 12/13/2019, are to be included, in any language.
17
18 53 Adherence to pharmacologic treatment, diet and physical activity, measured by
19
20 54 direct and indirect methods, will be the primary outcome. Two independent
21
22 55 reviewers will select relevant studies and will extract the data following the
23
24 56 Cochrane's Handbook for Systematic Reviews of Approach and the Preferred
25
26 57 Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-
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28 58 P). Methodologic quality will be evaluated using the RoB 2 and ROBINS-I Tools.
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30 59 Risk of bias will also be evaluated, and if the criteria are met, a meta-analysis will
31
32 60 be finally performed.
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39 **Ethics and dissemination.** Information to be analyzed is of a grouped nature, and
40
41 62 given that it sources are published studies, no Ethics Committee approval is required.
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43 63 Results will be published in scientific journals, and in conferences, seminars, and
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45 64 symposiums. Copyrights will be—addressed by giving due credit through
46
47 65 bibliographic references.
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51 67 Key words: hypertension, interventions, adherence, diet, exercise, adults.

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53 68 Register in PROSPERO: CRD42020147655

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56 69 **Strengths and limitations of the study**

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59 70 _The procedures of the study will be conducted in an independent and blinded
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3 71 manner by at least two reviewers.
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5
6 72 _Bibliographic search will have no language restriction.
7

8
9 73 _Ample modality of individual interventions will be included, and adherence will be
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11 74 evaluated globally (pharmacological treatment, diet and physical activity).
12

13
14 75 _Variability in adherence measures can be associated with high heterogeneity, which
15
16 76 may lead to conduct analysis by sub-groups and meta-regressions.
17

18
19 77 _The study will be conducted by an interdisciplinary group.
20

21 78 **INTRODUCTION**

22 23 24 79 **Description of the condition**

25
26 80 Hypertension or High blood pressure is one of the most frequent non-communicable
27
28 81 diseases (NCD), and it has been described as one of the main risk factors associated
29
30 82 with cardiovascular morbid-mortality worldwide.(1–3) According to the guidelines
31
32 83 of the European Societies of Cardiology and Hypertension (ESC/ESH) 2018,
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34 84 hypertension is defined as values equal to or higher than 140 mmHg for systolic
35
36 85 blood pressure (SBP), or 90 mmHg for diastolic blood pressure (DBP) measured in
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38 86 consultation.(1)
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43 87 In 2010, worldwide prevalence of hypertension were 31.0% (CI 95%: 30.0-32.2) or
44
45 88 1.39 (CI 95%: 1.34-1.44) billion adults aged ≥ 20 , and for low-to-middle-income
46
47 89 countries it was 31.5% (CI 95%: 30.2-32.9), or 1.04 billion adults.(4) According to
48
49 90 estimates, hypertension will keep increasing reaching 1.56 billion (CI 95%: 1.54-
50
51 91 1.58 billion) people in 2025. (5) As to incidence, rates have been reported of 58.6
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53 92 cases per 100,000 people, (CI 95%: 52.8-64.9) in young adults (median age 33
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55 93 years).(6)
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59 94 According to the World Health Organization (WHO), hypertension increases the risk
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3 95 of coronary heart disease by three to four times, and the risk of cardiovascular
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5 96 disease by two to three times.(7) In this regard, a study of the Global Burden of
6
7 97 Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm Hg between
8
9 98 1990 and 2015, reported that most of the SBP-related deaths were caused by
10
11 99 ischemic cardiopathy (54.5%), hemorrhagic stroke (58.3%), and ischemic stroke
12
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14 100 (50,0%).(3) Likewise, prospective studies indicate that hypertension is one of the
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17 101 risk factors with the highest contribution (31.0%) to the incidence of cardiovascular
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19 102 events, followed by hypercholesterolemia (27.0%) and smoking (18.0%).(8)

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21
22 103 Related to the loss of disability adjusted life years associated with SBP \geq 140 mmHg,
23
24 104 figures oscillated between 95.9 million (CI 95%: 87.0-104.9 million) and 143.01
25
26 105 million (CI 95%: 130.2-157.0 million) for the 1990-2015 period.(3)

27
28
29 106 Although there are effective medications(1,9–11) to treat hypertension and prevent
30
31 107 complications, a substantial proportion of cardiovascular events are attributed to poor
32
33 108 adherence and a lack of control of high blood pressure (12) In this regard, inadequate
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35 109 control of hypertension increases risk cardiovascular mortality by 1.74 times (IC 95%:
36
37 110 1.36-2.22) as compared to treated controlled hypertension.(13)

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41 111 Non-adherence to therapeutical regime is the consequence of multiple factors that
42
43 112 have been described by the WHO and are present in almost all patients with chronic
44
45 113 diseases, who show high non-compliance rates.(14,15) In terms of hypertensive
46
47 114 patients, non-compliance with pharmacologic treatment oscillates between 45.2%
48
49 115 (CI 95%: 34.4–56.1) and 63.35% (CI: 38.78–87.91) (14,15), while for factors related
50
51 116 to changes in life style, figures for non-compliance with physical activity and diet
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53 117 stand at 68.8% and 30.9%, respectively.(16)

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58 118 Scientific literature shows that reaching an optimal SBP or DBP level demands both
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3 119 pharmaceutical and non-pharmaceutical interventions, in order for patients to get to
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5 120 take medications at optimal level and adhere to diet and physical activity changes.
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8 121 Thus, they will obtain positive results in hypertension control, with a subsequent
9
10 122 reduction in the disease burden and health care costs.(17,18)

11
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13 123 Several studies have shown the clinical benefits of adherence to pharmacologic
14
15 124 treatment, diet and physical activity changes (18–20) in the reduction of risk of
16
17 125 health events such as death and hospitalization after myocardial infarction, cardiac
18
19 126 insufficiency or stroke.(20–22) In this sense, it has been inferred that the stricter the
20
21 127 compliance with Dietary Approaches to Stop Hypertension (DASH) (20,22), the
22
23 128 lower the mortality related to all causes, including cardiovascular disease. Also,
24
25 129 adherence to diet guidelines has been associated with lower prevalence of metabolic
26
27 130 syndrome and some of its factors, like hypertension.(23,24) Lack of physical activity
28
29 131 has been determined as a factor associated to non-control of hypertension, which
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31 132 leads to higher cardiovascular risk.(25)

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36 133 In terms of economic impact, studies conducted by Weaver et al,(26) estimated the
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38 134 cost attributable to hypertension in Alberta (Canada) by 2010 at CAD\$1.4 billion,
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40 135 and for the whole of Canada, at CAD\$13.9 billion for the same period, adding that
41
42 136 hypertension represents around 10.2% of Canada's health budget. The same study
43
44 137 foresees this figure to go up to CAD\$20.5 billion along 2020, due to demographic
45
46 138 changes, population ageing, and higher costs per patient. The same authors, through
47
48 139 a systematic review, estimate costs associated with hypertension and the specific
49
50 140 episode of cardiovascular disease, to oscillate between US\$500 and \$1,500 in low-
51
52 141 to-mid-income countries, while costs of stroke and coronary disease went over
53
54 142 \$5,000 per episode.(27)

1
2
3 143 High prevalence of hypertension, non-adherence to therapeutic regime, clinical
4
5 144 implications and costs associated to hypertension-related disability make it necessary
6
7 145 to find interventions that will efficaciously improve this problem while adapting to
8
9 146 the different Primary Health Care (PHC) scenarios.

147 **Description of the intervention**

148 Adherence to therapeutic regime is defined as “the degree to which a person’s
149 behavior regarding medication intake, proper diet regime and modification of life
150 habits fits the recommendations of their health care provider”(7), and they include
151 both, the pharmaceutical and non-pharmaceutical component.

152 The WHO acknowledges the need to implement effective strategies to achieve
153 changes in health results, because despite advances in treatment of chronic diseases,
154 lack of adherence to the therapeutic regimen remains the most important reason for
155 failure to control blood pressure.(7,14,28,29)

156 In this sense, the health team in charge of PHC plays a key role in facing this problem
157 (30,31) through individual teaching that may be offered through educational,
158 behavioral, and affective interventions, or a combination of the previous
159 (Multifaceted).(32,33) Although diverse studies(32–41) have shown their efficacy
160 to improve adherence and hypertension control, a focus is required not only on the
161 pharmacologic component, but also on life habits related to cardiovascular risk, like
162 physical activity and diet.(34,42)

163 There are different theoretical models to explain the phenomenon of adherence to
164 therapeutic regime in chronic disease patients, based mainly on individual health
165 behavior models (43) such as the theories of cognition and self-efficacy, models of
166 belief in health, behavioral changes, motivation, and self-regulation.(44–48) Self-

1
2
3 167 management has been recently highlighted; it offers the chronic disease patient a
4
5 168 series of support measures to improve confidence, with positive effect on adherence
6
7 169 to therapeutic regime.(49,50) Some authors have found a higher effect of
8
9
10 170 interventions based on individual health models,(51) in different degrees; however,
11
12 171 the intention of this review is to find individual interventions that will improve
13
14 172 adherence to therapeutic regime in patients with hypertension, independently of the
15
16
17 173 theoretical model proposed by the authors, implicitly or explicitly.

18
19
20 174 Scientific evidence has prioritized interventions focused mainly on adherence to the
21
22 175 pharmacologic component of hypertension treatment, using either a pedagogic,
23
24 176 behavioral or affective focus, or a combination of one or more of these focuses
25
26
27 177 (Multifaceted). Therefore, it is necessary to look into not only the pharmacologic, but
28
29 178 also the non-pharmacologic aspects of adherence to the therapeutic
30
31 179 regimen.(42,52,53)

32 33 34 180 **OBJECTIVES**

35
36
37 181 This article describes the protocol for a systematic review that will evaluate the
38
39 182 effects of individual interventions to improve adherence to recommendations of the
40
41 183 PHC team regarding medication treatment, diet and physical activity among adults
42
43
44 184 with primary hypertension.

45 46 47 185 **METHODS AND ANALYSIS**

48 49 50 186 **Eligibility criteria of the studies in this review**

51
52 187 They were defined according to the criteria included in the PICOT question.

53 54 55 188 **Participants (P)**

56
57
58 189 Adult people aged 18 or older, with diagnosis of primary hypertension defined as SBP
59
60

1
2
3 190 ≥ 140 mmHg or DBP ≥ 90 mmHg, or according to the definition used by the authors of
4
5 191 the studies; who are receiving health care from a PHC team that normally includes
6
7 192 medical doctors, nurses, nutritionists, etc., and whose aim is providing interventions of
8
9 193 promotion of health, prevention of cardio-cerebrovascular events; and patients who are
10
11 194 covered by some modality of antihypertensive treatment.
12
13
14

15 195 Pregnant women, in-patients or those with secondary hypertension will be excluded.
16

17
18 196 Primary hypertension is defined as that whose primary origin cause is unknown, and
19
20 197 taken to be linked to genetics, diet, sedentary lifestyle and obesity.(1,54)
21
22

23 198 On the other hand, secondary hypertension is due to an identifiable cause that resulting
24
25 199 from diseases affecting other organs and systems.(1) In this review, identification will
26
27 200 be made according to the criteria defined by the authors of the studies.
28
29

30 201 **Types of interventions (I)**

31
32
33 202 Interventions meeting the following criteria will be included in this review:
34

35
36 203 1. Classification: Educational, behavioral, affective or multifaceted interventions
37
38 204 oriented toward the individual will be included.
39

40
41 205 2. Application scenario: institutional and extramural
42

43
44 206 3. Methodology: in-person strategies like individual home visits, attention at PHC
45
46 207 and similar centers. Non-in-person, like text messages, phone calls, videos and health
47
48 208 applications, among others.
49

50
51 209 4. Personnel applying the intervention: interventions led by any health team member
52
53 210 (nurses, medical doctors, pharmacologists, nutritionists, and physiotherapists, etc.)
54
55 211 will be included.
56
57

58
59 212 5. Objective: improve adherence to medication treatment, diet, and, or physical
60

1
2
3 213 activity.
4
5

6 214 The following will be specifically considered for each intervention type:
7
8

9 215 -Physical activity and exercise: all those interventions directed by health
10
11 216 professionals, intent on promoting physical activity understood as every motion
12
13 217 driven by skeletal muscles generating energy expenditure superior to basal
14
15 218 expenditure, including moderate intensity(55) aerobic dynamics (walking, running,
16
17 219 cycling or swimming) for at least 30 minutes 5 to 7 weekly days (150 min/wk), or
18
19 220 vigorous intensity cardio-respiratory exercises no less than 20 minutes for 3 days (75
20
21 221 min/wk), or a combination of moderate and intense activity to achieve energy
22
23 222 expenditure of between 500 – 1000 metabolic equivalents (METs).(55,56) Physical
24
25 223 activity includes exercising, a structured, planned activity repeated in time so as to
26
27 224 improve or preserve some physical aptitude elements.(57)
28
29
30

31
32 225 -Diet: interventions aiming to control caloric necessity, obesity indexes, lipid
33
34 226 profile, or specific recommendations of clinical practice guidelines, like restricted
35
36 227 intake of salt, sugar, and fats among others, in arterial hypertension patients.(1,55)
37
38
39

40 228 -Pharmacologic: interventions related to promotion or improvement of adherence to
41
42 229 medication prescribed for hypertension control by individuals or participants.
43
44

45 230 **Comparison (C)**

46
47
48 231 No comparator will be included, given that the objective of the systematic review is
49
50 232 to evaluate the effect of different interventions, rather than of one specific in
51
52 233 particular.
53
54

55 234 **Types of outcome measures (O)**

56
57
58 235 ***Primary outcomes**
59
60

236 The main outcome will be the difference of proportions or means in adherence to
 237 pharmacologic treatment, diet and physical activity(17,58–60) pre and post
 238 intervention. Measurements can be obtained through direct and indirect methods
 239 **(Table 1).**

240 **Table 1. Direct and indirect methods reported in literature to evaluate**
 241 **adherence to therapeutic regime.**

Pharmacologic treatment	Diet	Prescribed physical activity
Tablet Counting	Degree of adherence to DASH* diet	Accelerometry changes International Physical Activity Questionnaire (IPAQ)
Questionnaires (Morisky-Green, MARS, SMAQ)*	Anthropometric changes (IMC, ICC)*	
-Medication-contained electronic microchip(17) -Electronic monitors of medication -Rates of prescription refills(17) -Measure of clinical response or physiologic markers(17) -Patient's diaries(17)	Lipid profile changes	
Concentration of		Strain test

pharmaceutical or its metabolite in bodily fluids (blood, urine)		
Directly observed therapy		Six-minute walk test

242 MARS (Medication Adherence Report Scale), SMAQ (Simplified Medication
243 Adherence Questionnaire), DASH (Dietary Approaches to Stop Hypertension), BMI
244 (Body Mass Index), WHI (Waist-Hip Index.).

245 ***Secondary outcomes**

- 246 • Percentage of participants with controlled hypertension.
- 247 • Rate or proportion of morbidity-mortality by major cardiovascular events
248 (ischemic disease and stroke).
- 249 • Incremental rate of cost-effectiveness or cost-efficacy, cost-usefulness of
250 interventions.
- 251 • Self-reported outcomes such as quality of life and burden of disease.

252 **Types of studies (t)**

253 This review will include randomized and non-randomized clinical trials that have
254 had a comparison group (usual treatment or placebo) related to pharmacologic
255 treatment, diet and physical activity in adults with primary hypertension.

256 **Search methods for identification of studies**

257 **Electronic search**

258 A systematic electronic search strategy will be designed to identify those studies meeting
259 the inclusion criteria established in the PICOt question in the following databases:

260 PubMed/MEDLINE, BVS, CINAHL, Embase, Cochrane and Scopus. The dates
 261 established for studies to be included were between 01/01/2009 and 12/13/2019, and
 262 according to the PROSPERO record the starting date for the study is 11/30/2019 and the
 263 finishing date is 06/30/2021.

264 Next activity is an advanced, independent search for interventions for each event
 265 (medication, diet and physical activity) by a combination of controlled and free
 266 language terms. Search strategies will adapt to the characteristics of each database.
 267 The following restrictions will apply: studies conducted in humans, and published
 268 between 2009 and 2019. Finally, a search process record will be kept for each
 269 information source. (Table 2).

270 **Table 2. Search strategy PICOT**

	Participants/patients (P)	Intervention (I)	Outcomes (O)	Type of studio (t) **
Pharmacologic treatment	((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension [Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh] OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[M	"Treatment Adherence and Compliance"[Mesh] OR Adherence [tiab] OR compliance[tiab] OR Nonadherence[tiab] OR Noncompliance[tiab] OR Non-Adherence [tiab] OR Non-Compliance	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR

		esh] OR "Mentoring "[Mesh] OR behaviour therapy [tiab]	ce[tiab] OR medicatio n intake adherence [tiab] OR drug therap*[tia b] OR medicatio n therapy manageme nt[tiab]	double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized* [tiab] OR Non- Randomized [tiab] OR Quasi- Experimental [tiab]
Diet	((("Essential hypertension"[MeS H Terms] OR HTN [Title/Abstract]) OR Primary Hypertension[Title /Abstract]) OR "hypertension"[Me SH Terms]) OR Hypertension[Title /Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education "[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mes h]) OR "Program Evaluation" [Mesh] OR interventio n*[tiab] OR educat*[tia b] OR prevent*[ti ab] OR "Behavior therapy"[M esh] OR "Mentoring "[Mesh] OR behaviour therapy [tiab]	"Diet" [MeSH] OR diet [tiab] OR dietar*[tia b] OR food*[tiab] OR nutrition*[tiab]	Clinical Query de Pubmed: ((clinical[Title/A bstract] AND trial[Title/Abstra ct]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random*[Title/A bstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non

				Randomized* [tiab] OR Non- Randomized [tiab] OR Quasi- Experimental [tiab]
Exercise	((("Essential hypertension"[MeSH Terms] OR HTN [Title/Abstract]) OR Primary Hypertension[Title/Abstract]) OR "hypertension"[MeSH Terms]) OR Hypertension[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT ("animals"[MeSH] AND "humans"[MeSH Terms]))	("Education"[Mesh]) OR "Health Education"[Mesh]) OR "Patient Education as Topic"[Mesh]) OR "Program Evaluation"[Mesh] OR intervention*[tiab] OR educat*[tiab] OR prevent*[tiab] OR "Behavior therapy"[Mesh] OR "Mentoring"[Mesh] OR behaviour therapy [tiab]	"Exercise" [MeSH] OR Exercise*[tiab] OR Physical Activity*[tiab]	Clinical Query de Pubmed: ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic [MeSH Terms] OR clinical trial [Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading]) OR double blind method [tiab] OR single blind method [tiab] OR placebo* [Title/Abstract] Non Randomized* [tiab] OR Non-Randomized [tiab] OR Quasi-Experimental [tiab]

271 Filters: Publication date from 01/01/2009 to 12/13/2019.

1
2
3 272 **Eligibility criteria**
4

5
6 273 The following inclusion criteria will be applied: studies conducted in humans,
7
8 274 published from 01/01/2009 to 12/13/2019 in the English, Spanish and Portuguese
9
10 275 languages. The reason to have chosen these languages is that in a preliminary search
11
12 276 strategy, in which language was not restricted, a low percentage was found in other
13
14 277 languages (less than 1%).
15
16

17
18 278 **Searching other resources**
19

20
21 279 In order to reduce publication bias, the review will include the clinical trials records
22
23 280 identified in the following databases: ClinicalTrials.org, International Clinical Trials
24
25 281 Registry Platform (ICTRP, OMS), Open Access Theses and Dissertations (OATD).
26
27

28 282 **Data collection and analysis**
29

30
31 283 Selection of studies
32

33
34 284 Search will be conducted independently by two researchers assigned per database (DP,
35
36 285 JS, PS, JH, ST, CE, LL, and LR) following the strategy set, previously defined in
37
38 286 Table 2.
39
40

41 287 Documents retrieved in this first phase will go to folders classified by topic and
42
43 288 database on EndNote. Then, a reviewer (CE) will eliminate duplicates and export each
44
45 289 unique study to Rayyan QCRI to evaluate eligibility criteria.
46
47

48
49 290 In the screening phase, selection of studies will be determined through a blinded and
50
51 291 independent reviewing procedure based on titles and abstracts, to be carried out by
52
53 292 seven reviewers (DP, JS, JH, ST, CE, LL, LR) two reviewers per topic, and one in
54
55 293 charge of blinding on the Rayyan QCRI platform. Each reviewer will classify the
56
57 294 articles as included, excluded or maybe. Once each pair of reviewers completes this
58
59
60

1
2
3 295 process, the blinding will be lifted and those studies lacking consensus will be
4
5 296 reevaluated, reactivating the blind. Articles classified as conflict and maybe will be
6
7 297 subjected to a new independent review, by title and abstract. In case disagreement
8
9 298 continues on conflicted articles, an external evaluator (LV, PS, IT, FG) will resolve
10
11 299 the discrepancy by determining inclusion or exclusion of documents. Studies in
12
13 300 discrepancy will be exported to the Rayyan QCRI (CE) platform, to be reassessed
14
15 301 blinded.

16
17
18
19 302 Upon achievement of consensus on studies to include in the screening phase, they will
20
21 303 go through eligibility phase, where each reviewer team will evaluate the full text
22
23 304 independently, selecting those articles to be included in the qualitative synthesis. In
24
25 305 case of discrepancy, the same procedure by a third reviewer described in the screening
26
27 306 phase, will be conducted. In order to facilitate the eligibility process, a table will be
28
29 307 produced with the inclusion and exclusion criteria, and the results will be documented
30
31 308 following the PRISMA flow chart (**Figure 1**).

32 33 34 35 36 309 **Data extraction and management**

37
38
39 310 Data extraction will be carried out independently by two reviewers, availing of the
40
41 311 formats established by Cochrane for categorical or continuous data, and any
42
43 312 difference will be settled or solved by a third investigator, as the case may be. For
44
45 313 data processing, a pilot test will be run among reviewers to guarantee the quality of
46
47 314 data extraction, and if necessary, corresponding adjustments will be made to the
48
49 315 formats before definitive extraction of information.

50
51
52
53 316 Then, validation will be carried out in duplicate to avoid typos in the information
54
55 317 extracted. This process will be conducted on Epidata.

56
57
58
59 318 Whenever the full text of the article cannot be accessed, or supplementary
60

1
2
3 319 information on results is required, authors will be contacted for information.
4
5

6 320 **Assessment of risk of bias in included studies**
7

8
9 321 Two independent reviewers will carry out evaluation of the methodological quality of
10
11 322 the articles for each topic, and in case of discrepancy, a third reviewer will settle
12
13 323 differences.
14

15
16 324 Dominions and criteria established by the Cochrane (61) team will be followed to
17
18 325 evaluate bias risk in the studies.
19

20
21 326 To evaluate the methodological quality of the experimental studies, RoB 2 tool will
22
23 327 be used(62), which encompasses the following 5 domains: randomization process,
24
25 328 deviations arising from the foreseen interventions, data missing from the outcomes,
26
27 329 measure of the outcomes, and selection of the results reported, which will be
28
29 330 evaluated through the signaling questions and also through an algorithm in which
30
31 331 global risk is evaluated as: low, high, and some concerns.
32
33

34
35 332 ROBINS-I tool(63) will be used for quasi-experimental studies, and it encompasses 7
36
37 333 domains to evaluate risks distributed in three parts: pre-intervention, intervention, and
38
39 334 post-intervention. In this scale, the studies risk will be reported as low risk, moderate
40
41 335 risk, serious risk, critical risk, and no information.
42
43

44
45 336 To evaluate the evidence degree of the studies, the GRADE(64) system will be used,
46
47 337 availing of four categories: “high quality”, “moderate quality”, “low quality” and
48
49 338 “very low quality”.
50
51

52
53 339 In case of discrepancies regarding these procedures, a third reviewer will intervene. The
54
55 340 authors of studies with a high risk of bias or incomplete information will be contacted
56
57 341 to clarify pertinent aspects and in case of no reply or if the information available does
58
59 342 not allow it, they will be included in the systematic review description, but not in the
60

1
2
3 343 meta-analysis.
4
5

6 344 **Measures of treatment effect**
7

8
9 345 Instead of adherence measuring availing of just one method, other direct and indirect
10
11 346 methods will be included (Table 1).
12

13
14 347 Also, taking into account that interventions can be varied and have a direct influence
15
16 348 on results obtained, they will be classified according to the designed method and the
17
18 349 number of strategies utilized. In the case of continuous data, the change estimator in the
19
20 350 measures will be recorded with its respective dispersion measure.
21
22

23
24 351 For categorical data, absolute and relative frequency measures, or effect measures
25
26 352 reported as RR, HR, OR, NNT, ARR, will be reported with their 95% confidence
27
28 353 interval.
29

30
31 354 **Unit analysis issues**
32

33
34 355 As previously mentioned, high variability exists in the methods to evaluate adherence
35
36 356 to therapeutic regime (Table 1) and this can prevent both information grouping for
37
38 357 quantitative analysis and adequate control by heterogeneity sources.
39
40

41 358 **Dealing with missing data**
42

43
44 359 In case of finding missing data, the authors will be contacted to obtain it for analysis;
45
46 360 in case of no reply, sensitivity analysis will be conducted eliminating this kind of
47
48 361 publications.
49
50

51
52 362 **Assessment of heterogeneity**
53

54
55 363 Heterogeneity will be evaluated using the Chi^2 ($p < 0.05$), Q Cochrane (over 25%) and
56
57 364 I^2 (over 50%) (65) tests, and if it is considerable, random-effects models will be
58
59
60

1
2
3 365 estimated. Heterogeneity sources (type and duration of intervention, population, region
4
5 366 or country, sociodemographic variables, effect measures, etc.), will be explored in a
6
7 367 subgroup analysis and/or meta-regressions.
8
9

10 368 **Assessment of reporting bias**

11
12
13 369 Publication bias will be determined with funnel plot as the graphic method, and bias
14
15 370 numeric evaluation will be run through Egger and Begg(66) asymmetry tests.
16
17

18 371 **Data synthesis**

19
20
21 372 Data synthesis and statistical analyses will be performed by means of Cochrane Review
22
23 373 Manager, and meta-analysis through RevMan 5.3(67) and Stata 15(68), if the criteria to
24
25 374 do so are met.
26
27

28
29 375 Otherwise, results will be grouped according to review topics (diet, physical activity and
30
31 376 pharmacological component), intervention type, methods used to measure adherence,
32
33 377 study design, and the effect size of the measures reported will be presented. In general
34
35 378 terms, in order to communicate the qualitative findings, the following aspects will be
36
37 379 extracted from each study, as recommended by Cochrane(69): authors, publication year,
38
39 380 language, location, study design, intervention, comparator, results, etc.
40
41
42

43 381 **Subgroup analysis and sources of heterogeneity**

44
45
46 382 If possible, analysis of subgroups or meta-regressions will be carried out according to
47
48 383 type of: measuring, intervention, participants at the baseline (e.g. controlled and non-
49
50 384 controlled patients), and study; also sex, age groups and other sociodemographic
51
52 385 characteristics of interest that may explain differences in the results.
53
54

55 386 **Sensitivity analysis**

56
57
58 387 Sensitivity analysis will be conducted to examine bias risk effect through evaluation
59
60

1
2
3 388 of study feature changes in the funnel plot graph; next, analyses will be conducted
4
5 389 excluding those studies with the most and least weight on the effect measure,
6
7 390 observing the change in the punctual estimator, and those statistically significant will
8
9
10 391 be reported.

11 12 13 392 **Patient and public involvement**

14
15
16 393 Not patient involved.

17 18 394 **DISCUSSION**

19
20
21 395 Review results will be useful in directing the usual clinical practice of PHC providers
22
23 396 because it enables follow-up of hypertension ambulatory patients. Identification of
24
25 397 interventions with the most effectiveness to improve therapeutic adherence, understood
26
27 398 as a multi-factor phenomenon involving life-styles changes, will lead to reduction of the
28
29 399 disease and economic burden of arterial hypertension.

30 31 32 33 400 **Limitations of the review**

34
35
36 401 As has been previously mentioned in this text, it is highly likely that no general summary
37
38 402 measure like meta-analysis will be obtained, explained by the high heterogeneity of the
39
40 403 interventions, as a consequence of the lack of a control group, the presence of three topics
41
42 404 or areas (medication, diet, exercise), as well as the different methods to assess adherence,
43
44 405 among others. However, adequate analysis of their main sources will be relevant to adapt
45
46 406 interventions in function of context and available resources (human, technical, and
47
48 407 financial).

49 50 51 52 53 408 **Ethics and dissemination**

54
55
56 409 This is a systematic review study, where the source of information will be documents
57
58 410 published in scientific databases, without human participation, so there will be no need
59
60

1
2
3 411 for approval of an Ethics Committee. The results will be disseminated in scientific
4
5 412 journals, as well as in other media, such as conferences, seminars, congresses or
6
7 413 symposia. In addition, copyright will be respected, giving the corresponding credit
8
9 414 through the bibliographic reference system.
10
11
12

13 415 **Figure 1. Systematic review flowchart.**
14
15

16 416 **Acknowledgements**

17
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19
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21
22 419 convening 771 of 2016.
23
24
25

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32
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34
35 424 study conception or design.
36
37
38

39 425 **Authors' contributions**

40
41
42 426 DP contributed with the study conception. DP, JS, LR, wrote the manuscript. Every
43
44 427 author reviewed and contributed observations to the text.
45
46

47 428 Search strategy will be conducted DP, JS, PS, CE, LV and it will be reviewed and
48
49 429 adjusted by every author. DP, JS, PS, CE, JH, ST, LR, and LL will apply it.
50
51

52 430 Retrieval of data from the studies included, bias evaluation, and synthesis will be
53
54 431 conducted by DP, JS, JH, ST, LL, and LR. Analyses will be the work of DP, JS, JH,
55
56 432 ST, LL, LR, FG, and LV.
57
58

59 433 Authors PS, LV, IT, and FG, will both make sure no errors will be introduced along
60

1
2
3 434 the different stages or review, and arbitrate disagreement.
4
5

6 435 Writing of manuscripts product of the systematic review will be agreed on and
7
8 436 distributed among the different authors by topic (pharmacologic adherence, diet and
9
10 437 physical activity).
11
12

13 438 Approval by the authors of the final version of this manuscript is to be unanimous.
14
15

16 439 **Conflicts of interest**
17

18
19 440 **None** declared
20
21

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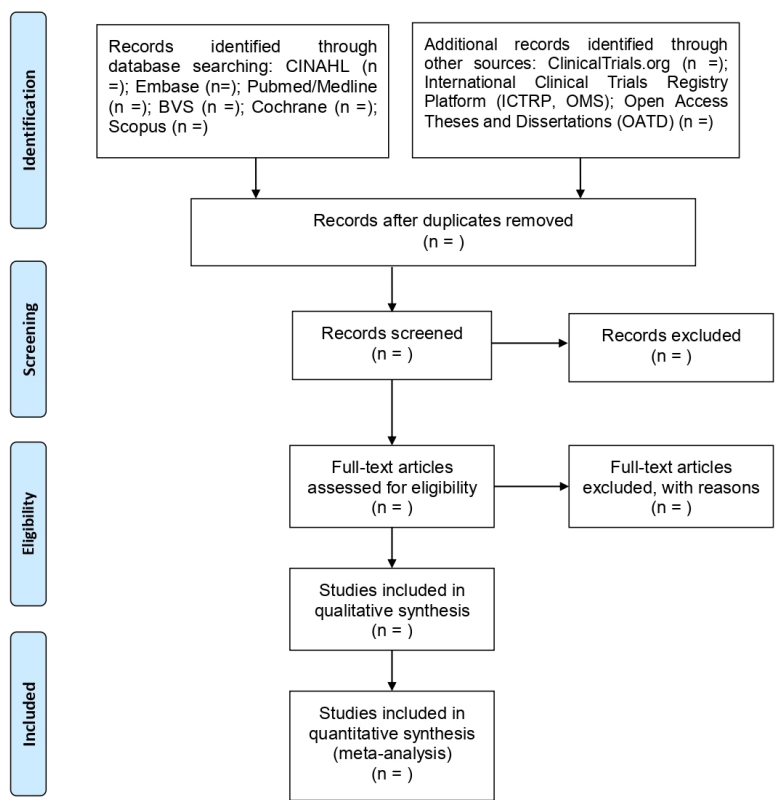
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Figure 1. Systematic review flowchart



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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	X		3-4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		NA	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		68
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		5 to 40
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		426 to 438
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		NA	
Sources					
Sources	5a	Indicate sources of financial or other support for the review	X		421 to 425
Sponsor	5b	Provide name for the review funder and/or sponsor		NA	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		NA	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		78 to 179
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		180 to 184
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
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	X		185 to 255
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	X		256 to 269; 278 to 282
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	X		270 to 277
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		283 to 309
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)	X		285 to 309
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	X		310 to 320
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	X		240 to 244
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		345 to 358
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	X		321 to 344
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		382 to 386
	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)	X		363 to 368

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		387 to 392
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		348 to 354
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		369 to 371
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		337 to 344