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The prevalence of non-contrast CT abnormalities in reversible cerebral vasoconstriction syndrome: protocol for a systematic review and meta-analysis

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TITLE PAGE

TITLE: The prevalence of non-contrast CT abnormalities in reversible cerebral vasoconstriction syndrome: protocol for a systematic review and meta-analysis

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KEY WORDS: reversible cerebral vasoconstriction syndrome, ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage

TITLE: The prevalence of non-contrast CT abnormalities in reversible cerebral vasoconstriction syndrome: protocol for a systematic review and meta-analysis

ABSTRACT:

Introduction: Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by severe, recurrent thunderclap headaches (TCHs) and vasoconstriction of cerebral arteries that resolve within 3 months. Abnormalities on non-contrast CT (NCCT) such as ischemic strokes, intracerebral hemorrhage (ICH) and subarachnoid hemorrhages (SAH) are frequently observed on brain imaging of RCVS patients though their prevalence varies considerably between studies. The aim of this systematic review and meta-analysis is to estimate the prevalence of NCCT abnormalities seen on neuroimaging of patients with RCVS.

Methods and analysis: We will search the Medline, Embase and the Cochrane Library databases for studies on the prevalence of NCCT abnormalities on neuroimaging of RCVS patients. Search results will be screened for eligibility by title and abstract. Suitable studies will be fully reviewed and relevant data extracted using a data abstraction form. The studies will be assessed for methodological quality, risk of bias and heterogeneity. Prevalence estimates across studies will be pooled using a random-effects model and subgroup analysis will be performed to assess the impact of age, sex, publication year and study design on prevalence of vascular lesions. Sensitivity analysis will be used to investigate the robustness of the findings. This protocol has been devised using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist. **Ethics and dissemination:** Formal ethics is not required as primary data will not be collected. The findings of this study will be disseminated through a peer-reviewed publication and conference presentations. **PROSPERO registration number:** Registration is complete but under review.

ARTICLE SUMMARY:

Strengths and limitations of this study:

- This study will be the first to provide an estimate of the prevalence of NCCT abnormalities on imaging in RCVS patients.
- Risk of bias will be minimized by having 2 reviewers independently screen studies and extract data.
- The results of this study will help differentiate RCVS from illnesses that may present with similar symptoms.
- As this study will include several studies designs, including case-series and observational studies, the results have a risk of heterogeneity.

INTRODUCTION:

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by severe headaches, most often recurrent thunderclap headaches (TCHs), and segmental vasoconstriction of cerebral arteries that resolves within 3 months.(1) Patients are predominantly female, between the age of 20-50 and may present with other focal neurological symptoms related to strokes, seizures or cerebral edema.(1) RCVS has been linked to several precipitating factors including hypertension, pre-eclampsia and eclampsia, illicit substance use such as cannabis and cocaine, and multiple medications including anti-depressants, sympathomimetic drugs, triptans, immunosuppressant medications, among many others.(2) Current

1
2
3 management for RCVS involves eliminating precipitating factors, analgesic therapy and use of a calcium
4 channel block such as nimodipine or verapamil.(3)
5

6 RCVS is diagnosed based on characteristic clinical, imaging and angiographic features. Initial imaging
7 modalities include non-invasive techniques such as non-contrast computed tomography (NCCT) to
8 assess the brain parenchyma, and either computed tomography angiography (CTA) or magnetic
9 resonance angiography (MRA) to assess the vasculature.(4) Digital subtraction angiography (DSA) is
10 typically reserved for circumstances where there is a high clinical suspicion of RCVS and normal non-
11 invasive imaging.(4) Angiography typically demonstrates segmental narrowing and dilatation of the
12 cerebral arteries with a classic string-of-beads appearance, though imaging may be normal in a third of
13 patients if completed early in the course of disease.(5)
14
15

16 Imaging abnormalities such as acute ischemic stroke, intracerebral hemorrhage (ICH) and subarachnoid
17 hemorrhage (SAH) can frequently occur in RCVS making it a challenge to distinguish from other vascular
18 conditions, such as aneurysmal SAH and primary angiitis of the central nervous system (PACNS) on
19 imaging.(2) Current RCVS literature includes primarily small case series and the exact proportion of RCVS
20 patients presenting with these radiological lesions is therefore unclear. For instance, the prevalence of
21 ischemic stroke is estimated to range from 8-39% and estimates of intracerebral hemorrhage range
22 from 6-20%.(2, 6-9) We seek to better understand the imaging features of RCVS. The main objective of
23 this systematic review is to estimate the prevalence of imaging findings consistent with ischemic stroke,
24 ICH and SAH on NCCT in patients with RCVS. We hope that the results of this review will help describe
25 the initial imaging features of RCVS in order increase diagnostic certainty at presentation, and to better
26 define the population of interest for future clinical trials.
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28
29

30 **METHODS AND ANALYSIS**

31
32 This *a priori* protocol for a systematic review and meta-analysis was developed in accordance with the
33 Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist.(10)
34

35 **Eligibility Criteria**

36
37 In order to be eligible for inclusion in this systematic review, the study must meet the following:
38

39 Population: The study population will be all adult patients (≥ 18 years old) with CT-angiography or
40 equivalent (conventional angiogram or MR-angiogram) confirmed RCVS. Studies that report on other
41 illnesses apart from RCVS will be included if they also independently report on imaging findings in RCVS.
42

43 Outcome: The primary outcomes will be prevalence of imaging findings consistent with ischemic
44 strokes, ICH and SAH on NCCT. Prevalence will be reported as the proportion of cases to the number of
45 evaluated participants.
46

47 Study Design: All case-series, observational studies and clinical trials that report on prevalence of
48 imaging findings in patients with RCVS will be included.
49

50 Publication type: All case reports, abstracts conference proceedings, letters and duplicate publications
51 will be excluded, as will literature not published in the English language.
52
53

54 **Information sources**

1
2
3 Electronic searches will be conducted in Medline, Embase, and the Cochrane Register of Clinical Trials
4 from inception to May 1, 2020. Referenced of identified studies will be manually reviewed to identify
5 relevant papers missed in the database searches. Full search strategies for all databases are included in
6 the appendix.
7

8 **Search strategy**

9
10 The search will be performed by combining terms related to RCVS, neuroimaging and vascular imaging
11 abnormalities. The full search strategy can be found in Appendix 1.
12

13 **Study selection**

14
15 Covidence will be used to screen articles for inclusion. Two trained reviewers will independently screen
16 titles and abstracts for inclusion based of predefined criteria. The reviewers will meet after 10% of the
17 sample has been screened to identify, resolve and codify area of ambiguity when screening the rest of
18 the sample. Conflicts will be resolved by consensus or a third independent reviewer. Full-texts will then
19 be reviewed by two independent reviewers and final inclusion will be based on the criteria mentioned
20 above. Reasons for exclusion of eligible studies will be documented and a Preferred Reporting Items or
21 Systematic Reviews and Meta-Analyses (PRISMA) flow diagram will be used to describe the study
22 screening and selection process.
23
24
25

26 **Data extraction**

27
28 Two reviewers will independently extract information from the selected studies using a data extraction
29 form. The form will be pilot tested on a small sample of included studies and modified if it fails to
30 capture all pertinent information. Areas of disagreement between extractors will be identified and
31 clarified. Any remaining disagreements of extracted data will be resolved through consensus or an
32 independent third reviewer.
33

34 Study characteristics that will be collected include:

- 35
36 • General study information: title, name of the journal and authors, year of publication, number
37 of sites and location of the central site
- 38
39 • Study design: study duration, study design (case-series, observational or randomized trial),
40 number of patients with RCVS, mean age of patients with RCVS and male-female distribution of
41 RCVS patients.
- 42
43 • Primary outcomes of interest: prevalence of imaging findings diagnostic with acute ischemic
44 stroke on NCCT in patients with RCVS, prevalence of imaging findings diagnostic of ICH on NCCT
45 in patients with RCVS, and prevalence of imaging findings diagnostic of SAH on NCCT in patients
46 with RCVS. We will also extract and report the criteria used by each study to diagnose ischemic
47 stroke, ICH and SAH on NCCT.
48

49 **Risk of Bias Assessment**

50
51 The methodological quality of case series and observational studies shall be assessed using Newcastle-
52 Ottawa based scales that account for selection, ascertainment, causality and reporting.(11, 12) The
53 Cochrane Risk of Bias Tool for Randomized Controlled Trials will be used to assess included randomised
54 trials.(13)
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Data Synthesis

Key study characteristics and clinical findings will be synthesized and presented in tables.

Pooled prevalence of imaging features will be calculated using the inverse variance-weighted method. Random-effects meta-analysis models will be used over fixed effect models to take into account variability both within and between studies. The Q- and I² statistic will be used as measures of heterogeneity among studies.

Subgroup analysis will be done to assess the impact of specific variables on prevalence of vascular lesions. When enough data is available, we will consider age, sex, publication year and study design as grouping variables.

Sensitivity analysis will be performed to assess the robustness of the findings. We will perform sensitivity analysis by removing studies with an outlying prevalence, excluding high bias studies as well as removing by study design.

Meta-bias(es)

We will attempt to minimize publication bias by generating and examining funnel plots. Duplicate publication bias will be minimized during the study screening phase by carefully screening publications to ensure duplications do not enter the analysis.

Patient and Public Involvement

There will be no involvement of patients or the public in this review.

ETHICS AND DISSEMINATION: Formal ethics is not required as primary data will not be collected. The findings of this study will be disseminated through a peer-reviewed publication and conference presentations.

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AUTHOR CONTRIBUTIONS: RG conceived the manuscript. RG, NN, BW, DF, MS and DD wrote and reviewed the manuscript. RS devised the search strategy. All authors approved the final version of the manuscript.

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COMPETING INTERESTS STATEMENT: There are no competing interests to report.

WORD COUNT: 1336

APPENDIX:

Search strategy:

The Medline, Embase and Cochrane Central Register of Controlled Trials databases were searched on May 1, 2020 using the following search strategy:

- 1 Vasospasm, Intracranial/ or Headache Disorders, Primary/ (10841)
- 2 Vasoconstriction/ and exp Cerebrovascular Disorders/ (3047)
- 3 ((intracranial or intracereb* or intercereb* or cerebrum or cerebral or brain) and (vasoconstrict* or vasospasm*)).tw,kf. (27084)
- 4 or/1-3 (33053)
- 5 reversible.tw,kw. (331842)
- 6 4 and 5 (2251)
- 7 rcvs.tw,kw. (1936)
- 8 (Call-Fleming or benign angiopathy of the central nervous system or acute benign cerebral angiopathy or postpartum angiopathy or thunderclap headache with reversible vasospasm or migrainous vasospasm or migraine angiitis or drug-induced cerebral arteritis or drug-induced arteritis or drug-unded cerebral angiopathy or drug-induced angiopathy or CNS pseudovasculitis).tw,kw. (211)
- 9 or/6-8 (3479)
- 10 tomography, x-ray computed/ or computed tomography angiography/ (458137)
- 11 (ct or computed tomograph*).tw,kw. (1290654)
- 12 angiography/ or angiography, digital subtraction/ or cerebral angiography/ (251469)
- 13 (angiograph* or angiogram*).tw,kw. (516573)
- 14 magnetic resonance imaging/ or magnetic resonance angiography/ (966147)
- 15 (mri or magnetic resonance imag*).tw,kw. (1000047)
- 16 Ultrasonography, Doppler, Transcranial/ (9652)

1
2
3 17 transcran* doppler*.tw,kw. or (transcran* ultrasonograph* or transcran* sonograph* or
4 transcran* ultrasound*).kw. (23105)
5 18 (transcran* adj2 (ultrasonograph* or sonograph* or ultrasound*).tw. (12072)
6 19 (neuroimag* or neuro imag*).tw,kw. (131450)
7 20 or/10-19 (3168483)
8 21 9 and 20 (1694)
9 22 exp brain ischemia/ or exp stroke/ (549189)
10 23 stroke*.tw,kw. (702880)
11 24 ((brain or cerebral) adj3 isch?em*).tw. (115810)
12 25 ((brain or cerebral) and isch?em*).kf. (6322)
13 26 Brain Edema/ or Edema/ (207804)
14 27 ed?ema*.tw,kw. (310397)
15 28 intracranial hemorrhages/ or exp subarachnoid hemorrhage/ (123665)
16 29 h?emorrhag*.tw,kw. (674036)
17 30 sah.tw,kw. (26870)
18 31 (isch?em* adj2 infarct*).tw. (20021)
19 32 isch?em* infarct*.kw. (181)
20 33 or/22-32 (1923029)
21 34 21 and 33 (1386)
22 35 exp animals/ not humans/ (17829136)
23 36 34 not 35 (864)
24 37 limit 36 to english language (794)
25 **38 37 use medall (338) Medline**
26 39 reversible cerebral vasoconstriction syndrome/ (976)
27 40 ((intracranial or intracereb* or intercereb* or cerebrum or cerebral or brain) and (vasoconstrict* or
28 vasospasm*) and reversible).tw. (2142)
29 41 rcvs.tw. (1917)
30 42 (Call-Fleming or benign angiopathy of the central nervous system or acute benign cerebral
31 angiopathy or postpartum angiopathy or thunderclap headache with reversible vasospasm or
32 migrainous vasospasm or migraine angiitis or drug-induced cerebral arteritis or drug-induced arteritis or
33 drug-unded cerebral angiopathy or drug-induced angiopathy or CNS pseudovasculitis).tw. (188)
34 43 or/39-42 (3549)
35 44 *computer assisted tomography/ or computed tomographic angiography/ (175821)
36 45 (ct or computed tomograph*).tw. (1268996)
37 46 *angiography/ or exp brain angiography/ or *digital subtraction angiography/ (85232)
38 47 (angiograph* or angiogram*).tw. (502770)
39 48 magnetic resonance angiography/ or *nuclear magnetic resonance imaging/ (229626)
40 49 (mri or magnetic resonance imag*).tw. (956815)
41 50 transcranial doppler ultrasonography/ (9223)
42 51 (transcran* adj2 (ultrasonograph* or sonograph* or ultrasound* or doppler)).tw. (24783)
43 52 *neuroimaging/ or *functional neuroimaging/ (30347)
44 53 (neuroimag* or neuro imag*).tw. (121906)
45 54 or/44-53 (2625546)
46 55 43 and 54 (1606)
47 56 cerebrovascular accident/ (305682)
48 57 exp brain ischemia/ (296962)
49 58 stroke*.tw. (687694)
50 59 ((brain or cerebral) adj3 isch?em*).tw. (115810)
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3 60 brain edema/ (49139)
4 61 ed?ema*.tw. (301725)
5 62 subarachnoid hemorrhage/ (66623)
6 63 brain hemorrhage/ (112308)
7 64 h?emorrhag*.tw. (651322)
8 65 sah.tw. (26518)
9 66 (isch?em* adj2 infarct*).tw. (20021)
10 67 or/56-66 (1812092)
11 68 55 and 67 (1343)
12 69 (exp animals/ or animal experiment/) not exp humans/ (10414540)
13 70 68 not 69 (1326)
14 71 limit 70 to english language (1234)
15 72 conference abstract.pt. (3784455)
16 73 71 not 72 (883)
17 **74 73 use emczd (588) Embase**
18 75 Vasospasm, Intracranial/ or Headache Disorders, Primary/ (10841)
19 76 Vasoconstriction/ and exp Cerebrovascular Disorders/ (3047)
20 77 ((intracranial or intracereb* or intercereb* or cerebrum or cerebral or brain) and (vasoconstrict* or
21 vasospasm*)).tw,kw. (27730)
22 78 or/75-77 (33585)
23 79 reversible.tw,kw. (331842)
24 80 78 and 79 (2273)
25 81 rcvs.tw,kw. (1936)
26 82 (Call-Fleming or benign angiopathy of the central nervous system or acute benign cerebral
27 angiopathy or postpartum angiopathy or thunderclap headache with reversible vasospasm or
28 migrainous vasospasm or migraine angiitis or drug-induced cerebral arteritis or drug-induced arteritis or
29 drug-unded cerebral angiopathy or drug-induced angiopathy or CNS pseudovasculitis).tw,kw. (211)
30 83 or/80-82 (3494)
31 84 tomography, x-ray computed/ or computed tomography angiography/ (458137)
32 85 (ct or computed tomograph*).tw,kw. (1290654)
33 86 angiography/ or angiography, digital subtraction/ or cerebral angiography/ (251469)
34 87 (angiograph* or angiogram*).tw,kw. (516573)
35 88 magnetic resonance imaging/ or magnetic resonance angiography/ (966147)
36 89 (mri or magnetic resonance imag*).tw,kw. (1000047)
37 90 Ultrasonography, Doppler, Transcranial/ (9652)
38 91 transcran* doppler*.tw,kw. or (transcran* ultrasonograph* or transcran* sonograph* or
39 transcran* ultrasound*).kw. (23105)
40 92 (transcran* adj2 (ultrasonograph* or sonograph* or ultrasound*)).tw. (12072)
41 93 (neuroimag* or neuro imag*).tw,kw. (131450)
42 94 or/84-93 (3168483)
43 95 83 and 94 (1708)
44 96 exp brain ischemia/ or exp stroke/ (549189)
45 97 stroke*.tw,kw. (702880)
46 98 ((brain or cerebral) adj3 isch?em*).tw. (115810)
47 99 (brain isch?em* or cerebral isch?em*).kw. (22194)
48 100 Brain Edema/ or Edema/ (207804)
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4 104 sah.tw,kw. (26870)
5 105 (isch?em* adj2 infarct*).tw. (20021)
6 106 isch?em* infarct*.kw. (181)
7 107 or/96-106 (1923351)
8 108 95 and 107 (1398)
9 109 limit 108 to english language (1297)
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11 **110 109 use cctr (5) Cochrane**
12 111 38 or 74 or 110 (931)
13 112 remove duplicates from 111 (644)
14 **113 112 use medall (337)**
15 **114 112 use emczd (303)**
16 **115 112 use cctr (4)**
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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a - This is not an update

1 **Registration**
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3

4 [#2](#) If registered, provide the name of the registry 2 - Registration is
5 (such as PROSPERO) and registration complete on
6 number PROSPERO but under
7 review so don't have a
8 registration number yet
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16 **Authors**
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19 **Contact** [#3a](#) Provide name, institutional affiliation, e-mail 1
20 address of all protocol authors; provide
21 physical mailing address of corresponding
22 author
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29 **Contribution** [#3b](#) Describe contributions of protocol authors 6
30 and identify the guarantor of the review
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34 **Amendments**
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38 [#4](#) If the protocol represents an amendment of a N/A - no amendments
39 previously completed or published protocol,
40 identify as such and list changes; otherwise,
41 state plan for documenting important protocol
42 amendments
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50 **Support**
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53 **Sources** [#5a](#) Indicate sources of financial or other support 6
54 for the review
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1	Sponsor	#5b	Provide name for the review funder and / or	N/A - no sponsor
2			sponsor	
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5				
6	Role of sponsor	#5c	Describe roles of funder(s), sponsor(s), and /	N/A
7	or funder		or institution(s), if any, in developing the	
8			protocol	
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14	Introduction			
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16				
17	Rationale	#6	Describe the rationale for the review in the	2-3
18			context of what is already known	
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22	Objectives	#7	Provide an explicit statement of the	3
23			question(s) the review will address with	
24			reference to participants, interventions,	
25			comparators, and outcomes (PICO)	
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32	Methods			
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35	Eligibility criteria	#8	Specify the study characteristics (such as	3
36			PICO, study design, setting, time frame) and	
37			report characteristics (such as years	
38			considered, language, publication status) to	
39			be used as criteria for eligibility for the review	
40				
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48	Information	#9	Describe all intended information sources	3-4
49	sources		(such as electronic databases, contact with	
50			study authors, trial registers or other grey	
51			literature sources) with planned dates of	
52			coverage	
53				
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1	Search strategy	#10	Present draft of search strategy to be used	4, 6-9
2				
3				
4			for at least one electronic database, including	
5				
6			planned limits, such that it could be repeated	
7				
8				
9	Study records -	#11a	Describe the mechanism(s) that will be used	4
10				
11	data		to manage records and data throughout the	
12				
13	management		review	
14				
15				
16	Study records -	#11b	State the process that will be used for	4
17				
18	selection		selecting studies (such as two independent	
19				
20				
21	process		reviewers) through each phase of the review	
22				
23			(that is, screening, eligibility and inclusion in	
24				
25			meta-analysis)	
26				
27				
28				
29	Study records -	#11c	Describe planned method of extracting data	4
30				
31	data collection		from reports (such as piloting forms, done	
32				
33	process		independently, in duplicate), any processes	
34				
35			for obtaining and confirming data from	
36				
37			investigators	
38				
39				
40				
41	Data items	#12	List and define all variables for which data will	4
42				
43			be sought (such as PICO items, funding	
44				
45			sources), any pre-planned data assumptions	
46				
47			and simplifications	
48				
49				
50				
51	Outcomes and	#13	List and define all outcomes for which data	4
52				
53	prioritization		will be sought, including prioritization of main	
54				
55			and additional outcomes, with rationale	
56				
57				
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1	Risk of bias in	#14	Describe anticipated methods for assessing	4
2				
3	individual		risk of bias of individual studies, including	
4				
5	studies		whether this will be done at the outcome or	
6				
7			study level, or both; state how this information	
8				
9			will be used in data synthesis	
10				
11				
12				
13	Data synthesis	#15a	Describe criteria under which study data will	5
14				
15			be quantitatively synthesised	
16				
17				
18	Data synthesis	#15b	If data are appropriate for quantitative	5
19				
20			synthesis, describe planned summary	
21				
22			measures, methods of handling data and	
23				
24			methods of combining data from studies,	
25				
26			including any planned exploration of	
27				
28			consistency (such as I ² , Kendall's τ)	
29				
30				
31				
32				
33	Data synthesis	#15c	Describe any proposed additional analyses	5
34				
35			(such as sensitivity or subgroup analyses,	
36				
37			meta-regression)	
38				
39				
40				
41	Data synthesis	#15d	If quantitative synthesis is not appropriate,	5
42				
43			describe the type of summary planned	
44				
45				
46	Meta-bias(es)	#16	Specify any planned assessment of meta-	5
47				
48			bias(es) (such as publication bias across	
49				
50			studies, selective reporting within studies)	
51				
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1 Confidence in [#17](#) Describe how the strength of the body of N/A - This is an
2 cumulative evidence will be assessed (such as GRADE) exploratory review
3 evidence
4
5
6
7

8
9 Notes:

- 10
11
- 12 • 1b: n/a - This is not an update
 - 13
14
15 • 2: 2 - Registration is complete on PROSPERO but under review so don't have a registration
16 number yet
 - 17
18
19 • 4: N/A - no amendments
 - 20
21
22 • 5b: N/A - no sponsor
 - 23
24
25
26
27 • 17: N/A - This is an exploratory review The PRISMA-P checklist is distributed under the terms of
28 the Creative Commons Attribution License CC-BY 4.0. This checklist was completed on 13. June
29 2020 using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration
30 with [Penelope.ai](#)
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BMJ Open

The prevalence of non-contrast CT abnormalities in adults with reversible cerebral vasoconstriction syndrome: protocol for a systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-041776.R1
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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Emergency medicine, Radiology and imaging
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TITLE PAGE

TITLE: The prevalence of non-contrast CT abnormalities in adults with reversible cerebral vasoconstriction syndrome: protocol for a systematic review and meta-analysis

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TITLE: The prevalence of non-contrast CT abnormalities in adults with reversible cerebral vasoconstriction syndrome: protocol for a systematic review and meta-analysis

ABSTRACT:

Introduction: Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by severe, recurrent thunderclap headaches (TCHs) and vasoconstriction of cerebral arteries that resolve within 3 months. Abnormalities on non-contrast CT (NCCT) such as ischemic strokes, intracerebral hemorrhage (ICH) and subarachnoid hemorrhages (SAH) are frequently observed on brain imaging of RCVS patients though their prevalence varies considerably between studies. The aim of this systematic review and meta-analysis is to estimate the prevalence of NCCT abnormalities seen on neuroimaging of adult patients with RCVS.

Methods and analysis: We will search the Medline, Embase and the Cochrane Library databases for studies on the prevalence of NCCT abnormalities on neuroimaging of RCVS patients. Search results will be screened for eligibility by title and abstract. Suitable studies will be fully reviewed and relevant data extracted using a data abstraction form. The studies will be assessed for methodological quality, risk of bias and heterogeneity. Prevalence estimates across studies will be pooled using a random-effects model and subgroup analysis will be performed to assess the impact of age, sex, publication year and study design on prevalence of vascular lesions. Sensitivity analysis will be used to investigate the robustness of the findings. This protocol has been devised using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist. **Ethics and dissemination:** Formal ethics is not required as primary data will not be collected. The findings of this study will be disseminated through a peer-reviewed publication and conference presentations. **PROSPERO registration number:** CRD42020190637.

ARTICLE SUMMARY:

Strengths and limitations of this study:

- This study will be the first to provide an estimate of the prevalence of NCCT abnormalities on imaging in RCVS patients.
- Risk of bias will be minimized by having 2 reviewers independently screen studies and extract data.
- The results of this study will help differentiate RCVS from illnesses that may present with similar symptoms.
- As this study will include several study designs, including case-series and observational studies, the results have a risk of heterogeneity.

INTRODUCTION:

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by severe headaches, most often recurrent thunderclap headaches (TCHs), and segmental vasoconstriction of cerebral arteries that resolves within 3 months.⁽¹⁾ Patients are predominantly middle-aged females and may present with other focal neurological symptoms related to strokes, seizures or cerebral edema.⁽¹⁾ RCVS has been linked to several precipitating factors including hypertension, pre-eclampsia and eclampsia, illicit substance use such as cannabis and cocaine, and multiple medications including anti-depressants, sympathomimetic drugs, triptans, immunosuppressant medications, among many others.⁽²⁾ Current

1
2
3 management for RCVS involves eliminating precipitating factors, analgesic therapy and use of a calcium
4 channel blocker such as nimodipine or verapamil.(3)
5

6 RCVS is diagnosed based on characteristic clinical, imaging and angiographic features. Initial imaging
7 modalities include non-invasive techniques such as non-contrast computed tomography (NCCT) to
8 assess the brain parenchyma, and either computed tomography angiography (CTA) or magnetic
9 resonance angiography (MRA) to assess the vasculature.(4) Digital subtraction angiography (DSA) is
10 typically reserved for circumstances where there is a high clinical suspicion of RCVS and normal non-
11 invasive imaging.(4) Angiography typically demonstrates segmental narrowing and dilatation of the
12 cerebral arteries with a classic string-of-beads appearance, though imaging may be normal in a third of
13 patients if completed early in the course of disease.(5)
14
15

16 Imaging abnormalities such as acute ischemic stroke, intracerebral hemorrhage (ICH) and subarachnoid
17 hemorrhage (SAH) can frequently occur in RCVS making it a challenge to distinguish from other vascular
18 conditions, such as aneurysmal SAH and primary angiitis of the central nervous system (PACNS) on
19 imaging.(2) Current RCVS literature includes primarily small case series and the exact proportion of RCVS
20 patients presenting with these radiological lesions is therefore unclear. For instance, the prevalence of
21 ischemic stroke is estimated to range from 8-39% and estimates of intracerebral hemorrhage range
22 from 6-20%.(2, 6-9) We seek to better understand the imaging features of RCVS. The main objective of
23 this systematic review is to estimate the prevalence of imaging findings consistent with ischemic stroke,
24 ICH and SAH on NCCT in adult patients with RCVS. We hope that the results of this review will help
25 describe the initial imaging features of RCVS in order to increase diagnostic certainty at presentation,
26 and to better define the population of interest for future clinical trials.
27
28
29

30 **METHODS AND ANALYSIS**

31
32 This *a priori* protocol for a systematic review and meta-analysis was developed in accordance with the
33 Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist.(10)
34

35 **Eligibility Criteria**

36
37 In order to be eligible for inclusion in this systematic review, the study must meet the following criteria:
38

39 Population: The study population will be all adult patients (≥ 18 years old) with CT-angiography or
40 equivalent (conventional angiogram or MR-angiogram) confirmed RCVS. Studies that report on other
41 illnesses apart from RCVS will be included if they also independently report on imaging findings in RCVS.
42

43 Outcome: The primary outcomes will be prevalence of imaging findings consistent with ischemic
44 strokes, ICH and SAH on NCCT. Prevalence will be reported as the proportion of cases to the number of
45 evaluated participants.
46

47 Study Design: All case-series, observational studies and clinical trials that report on prevalence of
48 imaging findings in patients with RCVS will be included.
49

50 Publication type: All case reports, abstracts, conference proceedings, letters and duplicate
51 publications will be excluded, as will literature not published in the English language.
52
53

54 **Information sources**

1
2
3 Electronic searches will be conducted in Medline, Embase, and the Cochrane Register of Clinical Trials
4 from inception to May 1, 2020. References of identified studies will be manually reviewed to identify
5 relevant papers missed in the database searches. Full search strategies for all databases are included in
6 the supplementary file.
7

8 **Search strategy**

9
10 The search will be performed by combining terms related to RCVS, neuroimaging and vascular imaging
11 abnormalities. The full search strategy can be found in the supplementary file.
12

13 **Study selection**

14
15 Covidence will be used to screen articles for inclusion. Two trained reviewers will independently screen
16 titles and abstracts for inclusion based on predefined criteria. The reviewers will meet after 10% of the
17 sample has been screened to identify, resolve and codify areas of ambiguity when screening the rest of
18 the sample. Conflicts will be resolved by consensus of a third independent reviewer. Full-texts will then
19 be reviewed by two independent reviewers and final inclusion will be based on the criteria mentioned
20 above. Reasons for exclusion of eligible studies will be documented and a Preferred Reporting Items for
21 Systematic Reviews and Meta-Analyses (PRISMA) flow diagram will be used to describe the study
22 screening and selection process.
23
24

25 **Data extraction**

26
27 Two reviewers will independently extract information from the selected studies using a data extraction
28 form. The form will be pilot tested on a small sample of included studies and modified if it fails to
29 capture all pertinent information. Areas of disagreement between extractors will be identified and
30 clarified. Any remaining disagreements of extracted data will be resolved through consensus or an
31 independent third reviewer.
32
33

34 Study characteristics that will be collected include:

- 35
36 • General study information: title, name of the journal and authors, year of publication, number
37 of sites and location of the central site
- 38
39 • Study design: study duration, study design (case-series, observational or randomized trial),
40 number of patients with RCVS, mean age of patients with RCVS and male-female distribution of
41 RCVS patients.
- 42
43 • Primary outcomes of interest: prevalence of imaging findings diagnostic of acute ischemic stroke
44 on NCCT in patients with RCVS, prevalence of imaging findings diagnostic of ICH on NCCT in
45 patients with RCVS, and prevalence of imaging findings diagnostic of SAH on NCCT in patients
46 with RCVS. We will also extract and report the criteria used by each study to diagnose RCVS,
47 ischemic stroke, ICH and SAH on NCCT as well as the timing of imaging with respect to symptom
48 onset.
49

50 **Risk of Bias Assessment**

51
52 The methodological quality of case series and observational studies shall be assessed using Newcastle-
53 Ottawa based scales that account for selection, ascertainment, causality and reporting.(11, 12) The
54 Cochrane Risk of Bias Tool for Randomized Controlled Trials will be used to assess included randomised
55 trials.(13)
56
57
58
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60

Data Synthesis

Key study characteristics and clinical findings will be synthesized and presented in tables.

Pooled prevalence of imaging features will be calculated using the inverse variance-weighted method. Random-effects meta-analysis models will be used over fixed effect models to take into account variability both within and between studies. The Q- and I² statistic will be used as measures of heterogeneity among studies.

Subgroup analysis will be done to assess the impact of specific variables on prevalence of vascular lesions. When enough data is available, we will consider age, sex, publication year and study design as grouping variables.

Sensitivity analysis will be performed to assess the robustness of the findings. We will perform sensitivity analysis by removing studies with an outlying prevalence, excluding high bias studies as well as removing by study design.

Meta-bias(es)

We will attempt to minimize publication bias by generating and examining funnel plots. Duplicate publication bias will be minimized during the study screening phase by carefully screening publications to ensure duplications do not enter the analysis.

Patient and Public Involvement

There will be no involvement of patients or the public in this review.

ETHICS AND DISSEMINATION: Formal ethics is not required as primary data will not be collected. The findings of this study will be disseminated through a peer-reviewed publication and conference presentations.

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8. Chen SP, Fuh JL, Wang SJ, et al. Magnetic resonance angiography in reversible cerebral vasoconstriction syndromes. *Annals of neurology*. 2010;67(5):648-56.

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- 4 9. Ducros A, Fiedler U, Porcher R, et al. Hemorrhagic manifestations of reversible cerebral
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- 13 bias in randomised trials. *BMJ (Clinical research ed)*. 2011;343:d5928.
- 14

15 **AUTHOR CONTRIBUTIONS:** RG conceived the manuscript. RG, NN, BW, DF, MS and DD wrote and

16 reviewed the manuscript. RS devised the search strategy. All authors approved the final version of the

17 manuscript.

18

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21

22 **COMPETING INTERESTS STATEMENT:** There are no competing interests to report.

23

24 **WORD COUNT:** 1348

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Search strategy:

The Medline, Embase and Cochrane Central Register of Controlled Trials databases were searched on May 1, 2020 using the following search strategy:

- 1 Vasospasm, Intracranial/ or Headache Disorders, Primary/ (10841)
- 2 Vasoconstriction/ and exp Cerebrovascular Disorders/ (3047)
- 3 ((intracranial or intracereb* or intercereb* or cerebrum or cerebral or brain) and (vasoconstrict* or vasospasm*)).tw,kf. (27084)
- 4 or/1-3 (33053)
- 5 reversible.tw,kw. (331842)
- 6 4 and 5 (2251)
- 7 rcvs.tw,kw. (1936)
- 8 (Call-Fleming or benign angiopathy of the central nervous system or acute benign cerebral angiopathy or postpartum angiopathy or thunderclap headache with reversible vasospasm or migrainous vasospasm or migraine angitis or drug-induced cerebral arteritis or drug-induced arteritis or drug-unded cerebral angiopathy or drug-induced angiopathy or CNS pseudovasculitis).tw,kw. (211)
- 9 or/6-8 (3479)
- 10 tomography, x-ray computed/ or computed tomography angiography/ (458137)
- 11 (ct or computed tomograph*).tw,kw. (1290654)
- 12 angiography/ or angiography, digital subtraction/ or cerebral angiography/ (251469)
- 13 (angiograph* or angiogram*).tw,kw. (516573)
- 14 magnetic resonance imaging/ or magnetic resonance angiography/ (966147)
- 15 (mri or magnetic resonance imag*).tw,kw. (1000047)
- 16 Ultrasonography, Doppler, Transcranial/ (9652)
- 17 transcran* doppler*.tw,kw. or (transcran* ultrasonograph* or transcran* sonograph* or transcran* ultrasound*).kw. (23105)
- 18 (transcran* adj2 (ultrasonograph* or sonograph* or ultrasound*)).tw. (12072)
- 19 (neuroimag* or neuro imag*).tw,kw. (131450)
- 20 or/10-19 (3168483)
- 21 9 and 20 (1694)
- 22 exp brain ischemia/ or exp stroke/ (549189)
- 23 stroke*.tw,kw. (702880)
- 24 ((brain or cerebral) adj3 isch?em*).tw. (115810)
- 25 ((brain or cerebral) and isch?em*).kf. (6322)
- 26 Brain Edema/ or Edema/ (207804)
- 27 ed?ema*.tw,kw. (310397)
- 28 intracranial hemorrhages/ or exp subarachnoid hemorrhage/ (123665)
- 29 h?emorrhag*.tw,kw. (674036)
- 30 sah.tw,kw. (26870)
- 31 (isch?em* adj2 infarct*).tw. (20021)
- 32 isch?em* infarct*.kw. (181)
- 33 or/22-32 (1923029)
- 34 21 and 33 (1386)
- 35 exp animals/ not humans/ (17829136)
- 36 34 not 35 (864)
- 37 limit 36 to english language (794)
- 38 37 use medall (338) Medline**

1
2
3 39 reversible cerebral vasoconstriction syndrome/ (976)
4 40 ((intracranial or intracereb* or intercereb* or cerebrum or cerebral or brain) and (vasoconstrict* or
5 vasospasm*) and reversible).tw. (2142)
6 41 rcvs.tw. (1917)
7 42 (Call-Fleming or benign angiopathy of the central nervous system or acute benign cerebral
8 angiopathy or postpartum angiopathy or thunderclap headache with reversible vasospasm or
9 migrainous vasospasm or migraine angiitis or drug-induced cerebral arteritis or drug-induced arteritis or
10 drug-unded cerebral angiopathy or drug-induced angiopathy or CNS pseudovasculitis).tw. (188)
11 43 or/39-42 (3549)
12 44 *computer assisted tomography/ or computed tomographic angiography/ (175821)
13 45 (ct or computed tomograph*).tw. (1268996)
14 46 *angiography/ or exp brain angiography/ or *digital subtraction angiography/ (85232)
15 47 (angiograph* or angiogram*).tw. (502770)
16 48 magnetic resonance angiography/ or *nuclear magnetic resonance imaging/ (229626)
17 49 (mri or magnetic resonance imag*).tw. (956815)
18 50 transcranial doppler ultrasonography/ (9223)
19 51 (transcran* adj2 (ultrasonograph* or sonograph* or ultrasound* or doppler)).tw. (24783)
20 52 *neuroimaging/ or *functional neuroimaging/ (30347)
21 53 (neuroimag* or neuro imag*).tw. (121906)
22 54 or/44-53 (2625546)
23 55 43 and 54 (1606)
24 56 cerebrovascular accident/ (305682)
25 57 exp brain ischemia/ (296962)
26 58 stroke*.tw. (687694)
27 59 ((brain or cerebral) adj3 isch?em*).tw. (115810)
28 60 brain edema/ (49139)
29 61 ed?ema*.tw. (301725)
30 62 subarachnoid hemorrhage/ (66623)
31 63 brain hemorrhage/ (112308)
32 64 h?emorrhag*.tw. (651322)
33 65 sah.tw. (26518)
34 66 (isch?em* adj2 infarct*).tw. (20021)
35 67 or/56-66 (1812092)
36 68 55 and 67 (1343)
37 69 (exp animals/ or animal experiment/) not exp humans/ (10414540)
38 70 68 not 69 (1326)
39 71 limit 70 to english language (1234)
40 72 conference abstract.pt. (3784455)
41 73 71 not 72 (883)
42 **74 73 use emczd (588) Embase**
43 75 Vasospasm, Intracranial/ or Headache Disorders, Primary/ (10841)
44 76 Vasoconstriction/ and exp Cerebrovascular Disorders/ (3047)
45 77 ((intracranial or intracereb* or intercereb* or cerebrum or cerebral or brain) and (vasoconstrict* or
46 vasospasm*)).tw,kw. (27730)
47 78 or/75-77 (33585)
48 79 reversible.tw,kw. (331842)
49 80 78 and 79 (2273)
50 81 rcvs.tw,kw. (1936)
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3 82 (Call-Fleming or benign angiopathy of the central nervous system or acute benign cerebral
4 angiopathy or postpartum angiopathy or thunderclap headache with reversible vasospasm or
5 migrainous vasospasm or migraine angiitis or drug-induced cerebral arteritis or drug-induced arteritis or
6 drug-induced cerebral angiopathy or drug-induced angiopathy or CNS pseudovasculitis).tw,kw. (211)
7
8 83 or/80-82 (3494)
9 84 tomography, x-ray computed/ or computed tomography angiography/ (458137)
10 85 (ct or computed tomograph*).tw,kw. (1290654)
11 86 angiography/ or angiography, digital subtraction/ or cerebral angiography/ (251469)
12 87 (angiograph* or angiogram*).tw,kw. (516573)
13 88 magnetic resonance imaging/ or magnetic resonance angiography/ (966147)
14 89 (mri or magnetic resonance imag*).tw,kw. (1000047)
15 90 Ultrasonography, Doppler, Transcranial/ (9652)
16 91 transcran* doppler*.tw,kw. or (transcran* ultrasonograph* or transcran* sonograph* or
17 transcran* ultrasound*).kw. (23105)
18 92 (transcran* adj2 (ultrasonograph* or sonograph* or ultrasound*).tw. (12072)
19 93 (neuroimag* or neuro imag*).tw,kw. (131450)
20 94 or/84-93 (3168483)
21 95 83 and 94 (1708)
22 96 exp brain ischemia/ or exp stroke/ (549189)
23 97 stroke*.tw,kw. (702880)
24 98 ((brain or cerebral) adj3 isch?em*).tw. (115810)
25 99 (brain isch?em* or cerebral isch?em*).kw. (22194)
26 100 Brain Edema/ or Edema/ (207804)
27 101 ed?ema*.tw,kw. (310397)
28 102 intracranial hemorrhages/ or exp subarachnoid hemorrhage/ (123665)
29 103 h?emorrhag*.tw,kw. (674036)
30 104 sah.tw,kw. (26870)
31 105 (isch?em* adj2 infarct*).tw. (20021)
32 106 isch?em* infarct*.kw. (181)
33 107 or/96-106 (1923351)
34 108 95 and 107 (1398)
35 109 limit 108 to english language (1297)
36 **110 109 use cctr (5) Cochrane**
37 111 38 or 74 or 110 (931)
38 112 remove duplicates from 111 (644)
39 **113 112 use medall (337)**
40 **114 112 use emczd (303)**
41 **115 112 use cctr (4)**
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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

	Reporting Item	Page Number
Title		
Identification	#1a Identify the report as a protocol of a systematic review	1
Update	#1b If the protocol is for an update of a previous systematic review, identify as such	n/a - This is not an update

1 **Registration**

2

3

4 [#2](#) If registered, provide the name of the registry (such 2

5 as PROSPERO) and registration number

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10 **Authors**

11

12

13 **Contact** [#3a](#) Provide name, institutional affiliation, e-mail address 1

14 of all protocol authors; provide physical mailing

15 address of corresponding author

16

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20 **Contribution** [#3b](#) Describe contributions of protocol authors and 6

21 identify the guarantor of the review

22

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24

25

26 **Amendments**

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29 [#4](#) If the protocol represents an amendment of a N/A - no

30 previously completed or published protocol, identify amendments

31 as such and list changes; otherwise, state plan for

32 documenting important protocol amendments

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39 **Support**

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42 **Sources** [#5a](#) Indicate sources of financial or other support for the 6

43 review

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47 **Sponsor** [#5b](#) Provide name for the review funder and / or sponsor N/A - no

48 sponsor

49

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51

52 **Role of sponsor** [#5c](#) Describe roles of funder(s), sponsor(s), and / or N/A

53 or funder institution(s), if any, in developing the protocol

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58 **Introduction**

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1	Rationale	#6	Describe the rationale for the review in the context of	2-3
2			what is already known	
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4				
5				
6	Objectives	#7	Provide an explicit statement of the question(s) the	3
7			review will address with reference to participants,	
8			interventions, comparators, and outcomes (PICO)	
9				
10				
11				
12				
13				
14	Methods			
15				
16				
17	Eligibility criteria	#8	Specify the study characteristics (such as PICO,	3
18			study design, setting, time frame) and report	
19			characteristics (such as years considered, language,	
20			publication status) to be used as criteria for eligibility	
21			for the review	
22				
23				
24				
25				
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27				
28				
29	Information	#9	Describe all intended information sources (such as	3-4
30			electronic databases, contact with study authors, trial	
31	sources		registers or other grey literature sources) with	
32			planned dates of coverage	
33				
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35				
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37				
38				
39	Search strategy	#10	Present draft of search strategy to be used for at	4, 6-9
40			least one electronic database, including planned	
41			limits, such that it could be repeated	
42				
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46				
47	Study records -	#11a	Describe the mechanism(s) that will be used to	4
48	data		manage records and data throughout the review	
49				
50				
51	management			
52				
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54				
55	Study records -	#11b	State the process that will be used for selecting	4
56	selection process		studies (such as two independent reviewers) through	
57				
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each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)

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6	Study records -	#11c	4
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8	data collection		
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10	process		
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15	Data items	#12	4
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23	Outcomes and	#13	4
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25	prioritization		
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31	Risk of bias in	#14	4
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33	individual studies		
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41	Data synthesis	#15a	5
42			
43			
44			
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46	Data synthesis	#15b	5
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1	Data synthesis	#15c	Describe any proposed additional analyses (such as	5
2			sensitivity or subgroup analyses, meta-regression)	
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6	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe	5
7			the type of summary planned	
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12	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es)	5
13			(such as publication bias across studies, selective	
14			reporting within studies)	
15				
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19	Confidence in	#17	Describe how the strength of the body of evidence	N/A - This is an
20	cumulative		will be assessed (such as GRADE)	exploratory
21	evidence			review
22				
23				
24				
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26				

Notes:

- 1b: n/a - This is not an update
- 4: N/A - no amendments
- 5b: N/A - no sponsor
- 17: N/A - This is an exploratory review The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution License CC-BY 4.0. This checklist was completed on 13. June 2020 using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)