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Living systematic review and meta-analysis of the prostate MRI diagnostic test with PI-RADS (Prostate Imaging Reporting and Data System) assessment for the detection of prostate cancer: Study protocol

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3	1	Living systematic review and meta-analysis of the prostate MRI diagnostic test with
4	2	PI-RADS (Prostate Imaging Reporting and Data System) assessment for the detection of
5 6	-	prostate cancer: Study protocol
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58	32	System; Systematic Review
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34 Abstract

Introduction: The Prostate Imaging Reporting and Data System (PI-RADS) standardizes reporting of prostate MRI for the detection of clinically significant prostate cancer. We provide the protocol of a planned living systematic review and meta-analysis for (i) diagnostic accuracy (sensitivity and specificity), (ii) cancer detection rates of assessment categories and (iii) interreader agreement.

40 Methods and analysis: Retrospective and prospective studies reporting on at least one of the 41 outcomes of interest are included. Each step that requires literature evaluation and data 42 extraction is performed by two independent reviewers. Since PI-RADS is intended as a living 43 document itself, a 12-month update cycle of the systematic review and meta-analysis 44 planned.

This protocol is in accordance with the PRISMA-P statement. The search strategy including
databases, study eligibility criteria, index and reference test definitions, outcome definitions
and data analysis processes are detailed. A full list of extracted data items is provided.

Summary estimates of sensitivity and specificity (for PI-RADS ≥ 3 and PI-RADS ≥ 4 considered
positive) are derived with bivariate binomial models. Summary estimates of cancer detection
rates are calculated with random intercept logistic regression models for single proportions.
Summary estimates of inter-reader agreement are derived with random effects models.

Ethics and dissemination: No original patient data is collected, ethical review board approval 53 therefore is not necessary. Results are published in peer reviewed, open-access scientific 54 journals. We make the collected data accessible as supplemental material to guarantee 55 transparency of results.

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6 7	58	Strengths and limitations of this study
8 9	59	- We establish an evidence-base for the diagnostic performance (diagnostic accuracy,
10 11 12	60	cancer detection rates, inter-reader agreement) of PI-RADS that is continuously
13 14	61	updated.
15 16 17	62	- Since PI-RADS is itself intended as a living document, our data synthesis will adapt
18 19	63	accordingly if a new version of PI-RADS is released.
20 21 22	64	- The growing body of evidence will allow subgroup analyses for PI-RADS subcategories.
23 24	65	- We expect the majority of included studies to be retrospective cohort studies. This will
25 26 27	66	affect the certainty of evidence that is generated by our project.
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68 Introduction

Prostate MRI (magnetic resonance imaging) has emerged as a fundamental tool in the diagnostic pathway for prostate cancer [1]. Recently, it has been strongly recommended by international guidelines for diagnosis in various clinical settings [2,3] – including biopsy naïve patients and patients with prior negative biopsy and persistent suspicion of prostate cancer. Because of these strong recommendations, the number of prostate MRI examinations performed will substantially increase throughout the next years.

The interpretation of prostate MRI is standardized with a formal lexicon: the PI-RADS (Prostate Imaging Reporting and Data System). PI-RADS was introduced in 2012 [4], has been updated to version 2.0 (v2.0) in 2015 [5] and moved to version 2.1 (v2.1) in 2019 [6]. Analysis of T2-weighted, diffusion-weighted (DWI) and contrast enhanced images lead to assessment categories 1 to 5, for single lesions and the entire prostate. The higher the assessment category, the higher the probability of clinically significant cancer. The interpretation lexicon has been updated in each iteration of PI-RADS, meaning changes in MRI descriptor definition and influence of the single imaging sequences on final assessment categories have taken place. The PI-RADS lexicon is explicitly designed as a living document [7], meaning that the interpretation lexicon is adapted as evidence about the diagnostic performance is generated. Currently, there is still more evidence regarding the v2.0 lexicon as compared to v2.1 lexicon. Regarding diagnostic accuracy, in 2017 Woo et al. performed a meta-analysis of 21 studies (3857 patients) using PI-RADv2.0 and reported a pooled sensitivity of 89% and a pooled specificity of 73% [8]. For PI-RADSv2.1, Park et al. performed a similar analysis in 2021 and reported a pooled sensitivity of 87% and specificity of 74% [9]. This initial analysis includes data from 10 studies and 1240 patients. The cancer detection rates of PI-RADSv2.0 have been estimated with 8% for PI-RADS 2, 13% for PI-RADS 3, 40% for PI-RADS 4 and 69% for PI-RADS

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5 [10]. For v2.1 an initial systematic review and meta-analysis reported cancer detection rates
of 2% for PI-RADS 1, 4% for PI-RADS 2, 20% for PI-RADS 3, 52% for PI-RADS 4 and 89% for PIRADS 5 (lesion level analysis) [11]. The PI-RADS lexicon does, in the current edition, not give
numeric definitions of the expected cancer rates in the assessment categories. Furthermore,
no management recommendations are linked to the assessment categories.

97 To account for the continuously generated evidence of the diagnostic performance of PI-RADS 98 and expected future iterations of the lexicon (with changes in descriptor definitions and 99 assessment category definitions, and therefore expected changes in diagnostic performance), 100 we want to establish a living systematic review and meta-analysis. This living review will 101 estimate the diagnostic accuracy of the current PI-RADS (sensitivity and specificity), the cancer 102 detection rates (CDR) of the assessment categories and inter-reader agreement of category 103 assignment. We plan to perform update searches and analyses in 12-month cycles.

Our objective is the implementation of a living systematic review and meta-analysis of the diagnostic performance of prostate MRI with PI-RADS assessment (intervention, v2.1 and upcoming versions considered) for the detection of prostate cancer (outcome) in patients with suspicion for prostate cancer (participants). Diagnostic performance of prostate MRI will not be compared to another diagnostic test (comparator), reference standard is histopathology. **BMJ** Open

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10 Methods and analysis

111 Study design and registration

This is a systematic review protocol, it follows the PRISMA-P (preferred reporting items for systematic reviews and meta-analyses – protocols) guidelines and format [12]. The systematic review has been registered with PROSPERO (international prospective register of systematic reviews) [for peer review: following the recommendations of PROSPERO, registration will be made after peer review of this protocol]. The PRISMA-P checklist for our protocol is enclosed as a supplement.

118 Study eligibility criteria

We include prospective and retrospective studies reporting on the diagnostic accuracy, and/or cancer detection rates of PI-RADS and/or inter-reader agreement of PI-RADS rating, starting with PI-RADSv2.1. Studies that use older versions of the lexicon are not considered. Studies reporting on a subset of PI-RADS categories are eligible. We consider studies published as full text in English. Date restriction is applied, considered studies need to be conducted in 2019 or later, that is after the release of the current PI-RADSv2.1. Studies are still considered as eligible if included patients were examined prior to this date but have been re-interpreted by blinded readers according to the current PI-RADS.

127 Study population

Our target populations are men with suspicion for prostate cancer, either biopsy naïve or with a prior negative biopsy. Biopsy naïve patients have a higher pretest probability for clinically significant cancer [13]. Biopsy status will be considered as a covariate in our analysis. Patients with known malignancy at the date of prostate MRI or with prior treatment of the prostate are not considered eligible.

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134	Index test
135	Prostate MRI read according to the current PI-RADS (version 2.1 at the time of writing this
136	protocol) is the diagnostic test of interest. We record MRI parameters of single studies to
137	account for deviations from the proposed imaging protocol [14]. Experience of the involved
138	radiologist(s) is recorded. We document whether MRI reading is performed without
139	knowledge of the histopathological result. We investigate diagnostic performance on lesion
140	level (up to four lesions per patient are possible) and patient level (equals highest assigned
141	lesion category compared to overall histopathological result).
142	Comparators
143	Diagnostic accuracy and cancer detection rates of PI-RADS will not be compared to another
144	diagnostic test.
145	Reference Test
146	Histopathological verification of suspicious lesions and the prostate can be performed in
147	several ways. The type of targeted lesion biopsy is recorded (cognitive fusion, transrectal
148	ultrasound MRI fusion, transperineal MRI ultrasound fusion, in-bore). A systematic biopsy and
149	additional MRI-directed perilesional biopsies may also be performed. We record the type and
150	result of targeted biopsy, type of systematic biopsy (if any) and type of perilesional biopsies
151	(if any). Histopathological upgrade of targeted biopsies given the information from systematic
152	biopsy is recorded. Furthermore, analysis of prostatectomy specimen is eligible as reference
153	standard.
154	Outcomes
155	Primary outcome is the detection (sensitivity and specificity, cancer detection rates) of
156	clinically significant cancer. The most widely adapted procedure in the literature regarding PI-
157	RADS is to consider any occurrence of a histopathological Gleason pattern \geq 3+4 as clinically
	 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149 150 151 152 153 154 155 156 157

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> significant [10,11]. The PI-RADS lexicon offers a more elaborate definition, which is more challenging to establish in clinical routine: "Gleason score \geq 7, including 3+4 with prominent but not predominant Gleason 4 component, and/or volume > 0.5cc, and/or extraprostatic extension" [14]. Especially the last point is, given that histopathological verification is performed by targeted lesion biopsy ± systematic biopsy (this is the case in the majority of individual cases and studies), often not possible to establish prior to surgery. Type of definition of clinically significant cancer will be considered as a covariate. Analysis is performed on lesion level (each lesion observed in the MRI examination, up to four lesions per patient, targeted biopsy as reference standard) and patient level (highest PI-RADS category as index test, lesion and systematic biopsy and (if performed) perilesional biopsy or prostatectomy as reference standard).

Secondary outcomes are the detection (sensitivity and specificity, cancer detection rates) of insignificant cancer, any cancer, Gleason \geq 4+3 (if reported) and \geq 3+4 with cribriform growth pattern (if reported). Although the PI-RADS lexicon explicitly does not aim at the detection of clinically insignificant cancer [14], knowledge about occurrence of these cancers is still important from a public health perspective. Patients with a diagnosis of clinically insignificant cancer will be closely monitored with active surveillance, including serial PSA testing, MRI and biopsies [15]. For primary outcome and secondary outcomes, we investigate the scenarios PI-RADS \geq 3 and \geq 4 considered positive for the estimation of sensitivity and specificity.

Inter-reader agreement of lesion and patient classification with PI-RADS (Cohen's kappa-values) is defined as a secondary outcome.

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181 Information sources and search strategy

We search the following databases for published studies: MEDLINE, Embase, Cochrane 182 183 Library, ISRCTN (<u>https://www.isrctn.com/</u>). Furthermore, we search ClinicalTrials.gov, ICTRP 184 (https://www.who.int/clinical-trials-registry-platform) and Deutsches Register Klinischer Studien for ongoing studies or completed studies not (yet) published. Time restriction will be 185 applied. We consider all studies conducted from 03/2019 onwards – PI-RADSv2.1 has been 186 published at 03/2019. Bibliographies of included articles will be manually checked for further 187 eligible studies. The search strategy will be re-used for the planned update cycles in the living 188 189 systematic review framework.

Our MEDLINE search is structured as follows: ((PIRADS) OR ("PI RADS") OR ("prostate imaging reporting and data system")) AND ("2019/03/01" [Date - Publication]: "3000/12/12" [Date -Publication]). Searches of the other databases will be adapted accordingly, it will be doublechecked whether the inclusion of "PI-RADS" and "prostate imaging: reporting and data system" is relevant in the search strategies. This proposed search strategy is more inclusive than the strategy employed by Woo and colleagues for a comparable systematic review of the diagnostic accuracy of PI-RADSv2.0 [8].

¹³ 197 **Data management**

198 Search results from the different databases are combined in a dedicated software 199 environment (e.g. Rayyan, <u>https://www.rayyan.ai/</u>), duplicates will be removed. Backup 200 copies are generated after the single database searches.

³ 201 Selection process

Two independent reviewers evaluate eligibility of search results. First, selection is performed
 on title and abstract basis. Studies considered relevant (or potentially relevant) based on title
 and abstract screening are further considered based on their full text (full text screening). In

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- 5 -	205	each step, discrepancies v	vill be resolved by discussior	and by consultation of a third reviewer,
	206	if needed. The reason for	exclusion is recorded in eac	h selection step.
	207	Data collection process		
0 1 2	208	Two independent reviewe	ers extract data from the inc	cluded studies in duplicate spreadsheets
- 3 4	209	with predefined data iter	ns. We define a core set of	data items (compare for table 1 and 2,
5 6 7	210	which also list all extracte	d data items). If any items o	f this set are missing, authors of primary
9 20	211	studies are contacted (at	least twice) to obtain this m	issing data.
2 2 23	212 213	Table 1 : Extracted data it characteristics	ems – meta-data, MRI techn	lique, reference test and patient
24 25		Data item(s)	levels	explanation
26		Meta-data of study†	6	journal / year / volume / authors
27 28		Study type†	prospective or retrospective	
29			observational or	
0			interventional	
32		MRI technique, index test		
3		vendor	4	manufacturer, magnet product type
5 5		field strength+	3 Tesla, 1.5 Tesla, other	
6		sequence parameters		sequence type, slice thickness, gap.
57 18		T2w		planes obtained
9		sequence parameters		sequence type, slice thickness, gap, b-
-0 -1		DWI		values used
2		sequence parameters		sequence type, slice thickness, gap.
-3 -4		DCE		temporal resolution
5		endorectal coil used	categorical	
6 7		spasmolytic agent used	categorical	
8		number of radiologists	numerical	
9 0		involved		
51		experience of radiologists	numerical (in years)	most experienced radiologist considered
2 3		involved		for diagnostic accuracy estimation
54 54		Reference test		
5 6		target lesion biopsv	cognitive ultrasound fusion.	additionally: mean/median number of
57		technique+	MRI US fusion transrectal	biopsy cores per lesion
8			MRI US fusion	
50 50			transperineal. in-bore	

			additionally: mean/median number of
	systematic biopsy	not performed, standard 8-	additionally. mean/median number of
	technique†	12 cores, extended	systematic biopsy cores taken per
		systematic biopsy (e.g.	patient
		Ginsburg scheme),	
		template biopsy,	
14 15 16		prostatectomy specimen	
		used	
	MRI-directed perilesional	categorical	if available, mean/median number of
	biopsies		perilesional biopsies per lesion is
	Deficient characteristics		recorded
	Patient characteristics	numerical	if information for locion localization
	number of locionat	numerical	(norinheral zone and transition zone)
	number of resions		(periprieral zone and transition zone)
			reported separately, this information is
	maan/madian agat	numorical	Tecorded
	mean/median BSA+	numerical	
		numerical	
	mean/median prostate	numericai	
	volume PSA: prostate specific antigen, MR †: core data items - If missing, aut	RI: magnetic resonance imaging, US: u hors of the primary studies are contac	Itrasound. cted twice to obtain the missing data.
	volume PSA: prostate specific antigen, MR †: core data items - If missing, aut Table 2: Extracted data ite	RI: magnetic resonance imaging, US: u hors of the primary studies are contac ems - outcome data	Itrasound. cted twice to obtain the missing data.
	volume PSA: prostate specific antigen, MR †: core data items - If missing, aut Table 2: Extracted data ite Data item(s)	RI: magnetic resonance imaging, US: u hors of the primary studies are contac ems - outcome data levels	Itrasound. cted twice to obtain the missing data. explanation
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	volume PSA: prostate specific antigen, MR †: core data items - If missing, aut Table 2: Extracted data item Data item(s) Outcome data definition of csCA used	RI: magnetic resonance imaging, US: u hors of the primary studies are contac ems - outcome data levels PI-RADS Lexicon definition, other definition	Itrasound. cted twice to obtain the missing data. explanation exact definition is recorded
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	volume PSA: prostate specific antigen, MR t: core data items - If missing, aut Table 2: Extracted data ite Data item(s) Outcome data definition of csCA used number of lesions and patients with csCAt number of lesions and	RI: magnetic resonance imaging, US: u hors of the primary studies are contact ems - outcome data levels PI-RADS Lexicon definition, other definition numerical numerical	Itrasound. cted twice to obtain the missing data. explanation exact definition is recorded
	volume PSA: prostate specific antigen, MR +: core data items - If missing, aut Table 2: Extracted data ite Data item(s) Outcome data definition of csCA used number of lesions and patients with csCA+ number of lesions and patients with ncsCA	RI: magnetic resonance imaging, US: u hors of the primary studies are contact ems - outcome data levels PI-RADS Lexicon definition, other definition numerical numerical	Itrasound. cted twice to obtain the missing data. explanation exact definition is recorded
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1 2				
3 4 5				contingency tables from paper or reconstructed are recorded
6				- Scenarios PI-RADS > 3 and PI-
7 8				RADS \geq 4 considered positive are
9				examined
10 11				- data is extracted on lesion level and
12				patient level, for all extracted
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15				(csCA, ncsCA, Gleason score ≥
6				$4+3$ and $\geq 3+4$ with cribriform
7 8				growth pattern)
19		cancer detection rates†	numerical	- number of malignant cases in each
20 21				reported PI-RADS category divided
22				by all cases in each PI-RADS
23 24				category
25				 data is extracted on lesion level and
26 27				patient level, for all extracted
28				definitions of prostate cancer
29				(csCA, ncsCA, Gleason score ≥
30 31				4+3 and ≥ 3+4 with cribriform
32				growth pattern)
33 34				- subcategories in PI-RADS 3 and 4
35				are recorded separately, if
36 37				information is available
8				- for low PI-RADS categories, the
9 0				information will also be expressed
1				as negative predictive value
12 13		reader agreement†	type of obtained inter-	
14			reader agreement metric,	
15 16			numerical value of metric	
47 48 49	218 219 220	csCA: clinically significant cance †: core data items (reporting of contacted twice to obtain the n	r, ncsCA: clinically non-significant/insignif at least one defined outcome is required nissing data.	ficant cancer). If missing, authors of the primary studies are
50 51	221	Risk of bias assessment	:	
52 53	222	For the evaluation of r	isk of bias and applicability of	results (study level analysis each) the
54 55 56	223	Quality Assessment of D	Diagnostic Accuracy Studies 2 (Q	UADAS-2) framework is used [16]. Two
57 58 59	224	independent reviewers	evaluate risk of bias and application	ability of results in the domains patient
60	225	selection, index test, re	ference standard and flow and	I timing (the latter not for applicability

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evaluation). Discrepancies are resolved by discussion and by consultation of a third reviewer,
if needed. From the results of the QUADAS-2 analysis, we will infer the overall risk of bias for
obtained results. Studies are not excluded from data synthesis based on the QUADAS-2
evaluation alone.

230 Data synthesis and statistical analysis

Data describing patient populations of the included studies (e.g. mean age, mean PSA value, mean prostate volume, prior biopsy status) is presented in table format. Data synthesis of outcomes (diagnostic accuracy in terms of sensitivity and specificity, cancer detection rates, inter-reader agreement in terms of Cohen's kappa values) is performed given a set of homogeneous studies is identified. The required minimum set of homogeneous study characteristics is: (i) reading of prostate MRI is performed without knowledge of the histopathological results (ii) MRI is performed according to PI-RADS recommendations, (iii) for inter-reader agreement, comparable metrics are reported.

We derive pooled estimates of sensitivity and specificity with bivariate binomial models [17]. A summary ROC curve with a 95% confidence region is derived for graphical representation. We examine the scenarios with PI-RADS \geq 3 and PI-RADS \geq 4 considered as a positive test on lesion level and patient level (overall, four scenarios). Possible publication bias is visually assessed with funnel plots, Deek's test will be used to test for asymmetry [18]. Coupled forest plots of sensitivity and specificity and correlation between sensitivity and 1-specificity are analyzed for assessment of heterogeneity of results [19].

We expect cancer rates in the assessment categories to vary across studies; partly because of different local reading standards, partly because of local differences/thresholds for referral to prostate MRI and targeted biopsy, partly because of different pretest probabilities and thus differences in the patient cohorts examined. In other words, we assume a certain degree of

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clinical and methodological heterogeneity between studies and do not expect results to vary
because of random sampling error alone. For this reason we employ random intercept logistic
regression models for meta-analysis of single proportions to derive summary estimates for
cancer detection rates of the PI-RADS categories [20] and subcategories of PI-RADS 3 and 4.
Heterogeneity of reported cancer detection rates is assessed with Higgins' 1² statistic, with
l²>50% denoting substantial heterogeneity [19].

Meta-regression with the following covariates (if data is sufficient) is performed to examine possible causes of heterogeneity (diagnostic accuracy and cancer detection rates): type of study population (prior biopsy status), multiparametric vs biparametric MRI, definition of clinically significant cancer, type of lesion verification, lesion localization (peripheral zone vs transition zone), reader experience, pretest probability in the study population. Subgroup analyses of covariates are performed for univariate analyses.

The summary measure for inter-reader agreement (Cohen's kappa values) will be derived with a random effects model. This approach follows the method proposed by Sun [21]. We examine the role of reader experience as a covariate – two highly experienced readers can be expected to agree more often compared to two relatively unexperienced readers or two readers with different levels of experience.

267 If quantitative data synthesis is not considered appropriate for one or more defined outcomes,
 268 a synopsis of findings is given table format. Order of presentation is stratified by risk of bias
 269 and definition of clinically significant cancer used.

270 All statistical analyses are conducted using R (<u>https://www.R-project.org/</u>) [22].

271 GRADE assessment

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272 Quality of evidence per outcome is analyzed according to the GRADE (Grading of 273 Recommendations, Assessment, Development and Evaluation) System [23], results from the 274 QUADAS-2 analysis are used for risk of bias assessment in this context. Certainty of evidence 275 is rated as high, moderate, low or very low. Results are made available in a summary of 276 findings table.

277 Patient and public involvement

In the development phase of the project the Bundesverband Prostatakrebs Selbsthilfe e.V.
(https://prostatakrebs-bps.de/) was involved in defining relevant research questions. The
Bundesverband Prostatakrebs Selbsthilfe e.V. agreed to disseminate results in their network
of support groups.

283 Living review framework

We plan to implement a 12-month cycle to update our literature search, study selection and data analysis. This is because an accumulation of evidence about the diagnostic performance of PI-RADS can be expected, especially for subcategories in categories 3 and 4. Furthermore, PI-RADS is itself intended as a living diagnostic algorithm [7] – that is, new iterations can be expected. Given that the diagnostic algorithm is further adapted, changes in diagnostic accuracy can be expected. If a new version of PI-RADS is released, our literature search strategy will remain unchanged. Data collection and reporting of results will pertain to the current version of PI-RADS.

We consider the living systematic review framework suitable for our project, because the
 scope and needs address the three demands as expressed in the initial discussion of living
 systematic reviews by Elliott et al. [24]:

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(i) up-to-date information is important for decision making: For informed, shared decision making how to proceed with the result of a prostate MRI examination, accurate estimates of diagnostic accuracy of PI-RADS and cancer detection rates of the categories are crucial. Furthermore, management recommendations are planned to be linked to assessment categories in future versions of PI-RADS [14]. Before recommending biopsy, for example, there need to be an established expected cancer rate for a certain assessment category.

- (ii) Certainty in the existing evidence is low: At the moment, we have limited evidence (meta-analyses do exist for diagnostic accuracy and cancer detection rates of PI-RADSv2.1, however they include relatively few patients [9,11]). Furthermore, we see a need to systematically review the performance of subcategories in PI-RADS categories 3 and 4.
- (iii) There will be new research evidence: The publication field of prostate MRI and PI-RADS is highly dynamic, the number of relevant papers is increasing at a fast rate. We expect new accumulating evidence especially for subcategories (different lesion entities in categories 3 and 4). Furthermore, new evidence will be generated given a new iteration of PI-RADS is published. A timely evidence synthesis is warranted in this case.
- 47
 48 313 Our search strategy and data used for analyses will be published as supplement to the
 49
 50 314 systematic review and meta-analysis.
- 54 315 Ethics and dissemination

No original data is collected in this systematic review and meta-analysis, ethical review board
 approval therefore is not required. Results are published in peer reviewed, open-access

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8 scientific journals. We make the collected data accessible as supplemental material to 9 guarantee transparency of results.

320 Discussion

With the recently put forward strong recommendations for prostate MRI prior to biopsy in various national (e.g. [15,25]) and international guidelines [2,3], a rapidly increasing volume of prostate MRI examinations can be expected in the next years. The increasing number of examinations performed requires a standardized, evidence-based diagnostic workflow to streamline patient management.

PI-RADS, having been established in 2012, offers this standardization. PI-RADS provides a universally understood reporting language on the descriptor level and works well as a risk stratification tool for clinically significant prostate cancer [8]. For version 2.0, a systematic review and meta-analysis of inter-reader agreement reported an overall moderate to substantial agreement for PI-RADS category assignment [26]. The diagnostic accuracy of PI-RADS has been subject of a multitude of studies – initial estimates for sensitivity, specificity and the cancer detection rates are available for version 2.1 [9,11]. Park et al. report a pooled sensitivity/specificity of 81%/82% when PI-RADS ≥ 4 is used as a diagnostic threshold, compared to a sensitivity/specificity of 94%/56% when PI-RADS ≥ 3 is used [9]. Reported 95% confidence intervals in this analysis are relatively large, especially for specificity: for the 56% astermate, it ranges from 35 to 97% [9].

As evidence about the diagnostic performance of PI-RADS accrues, these estimates will become more precise. Or, given considerable heterogeneity of estimates between studies, the identification of covariates that affect diagnostic accuracy and cancer detection rates becomes possible. This knowledge could ultimately be included into PI-RADS itself or future guidelines.

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At the moment, assessment categories 3 and 4 are assigned to a heterogeneous group of lesions each. For example, in the transition zone assessment category 3 comprises lesions with different appearance in T2 weighted images (atypical nodules and heterogenous lesions with obscured margins). Costa et al. report a cancer rate of 6% and 11% for these two lesion types, although this difference is not statistically significant in their study [27]. If there are systematic differences of cancer rate between lesion subtypes in the same PI-RADS assessment category, this might influence the planned linking of management recommendations to assessment categories [14]. Our living systematic review framework establishes an evidence base for precise estimates of diagnostic accuracy of the current PI-RADS (with different thresholds considered positive), the cancer detection rates of assessment categories and subcategories, and inter-reader

353 making after prostate MRI and help in the development of PI-RADS itself and future guidelines.

agreement. The results can be employed by urologists, radiologists and patients for decision

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involved in protocol drafting.

359 Competing interests statement

360 Ivo Schoots is a full panel member of the PI-RADS steering committee (ASR/ESR). Fabian
361 Bamberg has received unrestricted research grants and speaker bureau fees from Bayer
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365 Rottapharm, STEBA Biotech. Otherwise, we do not have a competing interest to declare.

⁷ 366 **Supplementary Material**

367 PRISMA-P checklist

368 Authors' contributions

- 369 concept and design: Oerther, Schmucker, Schwarzer, Schoots, Benndorf
- drafting and revising the manuscript: Oerther, Schmucker, Schwarzer, Schoots, Sigle, Gratzke,
- 9 371 Bamberg, Benndorf
- 372 statistical planning: Schwarzer, Benndorf
- 4 373 guarantor of the review: Benndorf
- 374 Data statement
- 375 No data was collected for this protocol.

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BMJ Open PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol* for "Living systematic review and meta-analysis of the prostate MRI diagnostic test with PI-RADS (Prostate Imaging Reporting and Data System) assessment for the detection of prestate cancer: Study protocol"

Section and topic	Item No	Checklist item	Realized, line number
ADMINISTRATIV	E INF(
Title:		: an	
Identification	1a	Identify the report as a protocol of a systematic review	1-3
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 (such as PROSPERO) and registration number	Will be registered after peer review of the protocol
Authors:			1
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mathing address of correspondiauthor	ng 5-25
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	368-372
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as an arch and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:		ar te	
Sources	5a	Indicate sources of financial or other support for the review	355-357
Sponsor	5b	Provide name for the review funder and/or sponsor	355-357
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	355-357
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	91-99
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, the review of the comparators, and outcomes (PICO)	103-107
METHODS		grap	
		For peer review only - http://bmiopen.bmi.com/site/about/guidelines.xhtml	

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Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	103-10 117-12
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	181-18
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned such that it could be repeated	189-19
Study records:		late	
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	197-20
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through the phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	201, 207, 22
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independent in duplicate), any processes for obtaining and confirming data from investigators	207-21
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources)	211-21
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	216-21
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether the state of the outcome or study level, or both; state how this information will be used in data synthesis	221-22
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	231-23
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods and methods	238-244
	15 .	of combining data from studies, including any planned exploration of consistency (such as 1 ⁻ , Kendaliss t)	261-26
	15C	If quantitative synthesis is not appropriate, describe the type of support planned	255-25
Meta-bias(es)	150	Specify any planned assessment of meta-bias(es) (such as publication bias across studies selective reporting within studies)	200-20
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	271-24

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Living systematic review and meta-analysis of the prostate MRI diagnostic test with PI-RADS (Prostate Imaging Reporting and Data System) assessment for the detection of prostate cancer: Study protocol

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Date Submitted by the Author:	08-Sep-2022
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Primary Subject Heading :	Radiology and imaging
Secondary Subject Heading:	Urology
Keywords:	Urological tumours < UROLOGY, Genitourinary imaging < RADIOLOGY & IMAGING, RADIOLOGY & IMAGING



2		
3	1	Living systematic review and meta-analysis of the prostate MRI diagnostic test with
4	2	PI-RADS (Prostate Imaging Reporting and Data System) assessment for the detection of
5 6 7	3	prostate cancer: Study protocol
, 8 9	4	
10 11	5	Benedict Oerther ^a , Dr. sc. hum. Christine Schmucker ^b , Dr. rer. nat. Guido Schwarzer ^c , Prof.
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53	29	Word count abstract: 235
54 55 56	30	Word count manuscript: 3124
50 57	31	Keywords: Prostate MRI; Prostate Cancer; PI-RADS; Prostate Imaging Reporting and Data
58	32	System; Systematic Review
59 60	33	

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Abstract

Introduction: The Prostate Imaging Reporting and Data System (PI-RADS) standardizes reporting of prostate MRI for the detection of clinically significant prostate cancer. We provide the protocol of a planned living systematic review and meta-analysis for (i) diagnostic accuracy (sensitivity and specificity), (ii) cancer detection rates of assessment categories and (iii) inter-reader agreement.

Methods and analysis: Retrospective and prospective studies reporting on at least one of the outcomes of interest are included. Each step that requires literature evaluation and data extraction is performed by two independent reviewers. Since PI-RADS is intended as a living document itself, a 12-month update cycle of the systematic review and meta-analysis planned.

This protocol is in accordance with the PRISMA-P statement. The search strategy including databases, study eligibility criteria, index and reference test definitions, outcome definitions and data analysis processes are detailed. A full list of extracted data items is provided.

Summary estimates of sensitivity and specificity (for PI-RADS \geq 3 and PI-RADS \geq 4 considered positive) are derived with bivariate binomial models. Summary estimates of cancer detection rates are calculated with random intercept logistic regression models for single proportions. Summary estimates of inter-reader agreement are derived with random effects models.

Ethics and dissemination: No original patient data is collected, ethical review board approval therefore is not necessary. Results are published in peer reviewed, open-access scientific journals. We make the collected data accessible as supplemental material to guarantee transparency of results.

1 2		
2 3 4	57	Strengths and limitations of this study
5 6	58	- We establish an evidence-base for the diagnostic performance (diagnostic accuracy,
7 8 9	59	cancer detection rates, inter-reader agreement) of PI-RADS that is continuously
10 11	60	updated.
12 13 14	61	- Since PI-RADS is itself intended as a living document, our data synthesis will adapt
15 16	62	accordingly if a new version of PI-RADS is released.
17 18 19	63	- The growing body of evidence will allow subgroup analyses for PI-RADS
20 21	64	subcategories.
22 23	65	- We expect the majority of included studies to be retrospective cohort studies. This
24 25 26	66	will affect the certainty of evidence that is generated by our project.
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68 Introduction

Prostate MRI (magnetic resonance imaging) has emerged as a fundamental tool in the diagnostic pathway for prostate cancer [1]. Recently, it has been strongly recommended by international guidelines for diagnosis in various clinical settings [2,3] – including biopsy naïve patients and patients with prior negative biopsy and persistent suspicion of prostate cancer. Because of these strong recommendations, the number of prostate MRI examinations performed will substantially increase throughout the next years.

The interpretation of prostate MRI is standardized with a formal lexicon: the PI-RADS (Prostate Imaging Reporting and Data System). PI-RADS was introduced in 2012 [4], has been updated to version 2.0 (v2.0) in 2015 [5] and moved to version 2.1 (v2.1) in 2019 [6]. Analysis of T2-weighted, diffusion-weighted (DWI) and contrast enhanced images lead to assessment categories 1 to 5, for single lesions and the entire prostate. The higher the assessment category, the higher the probability of clinically significant cancer. The interpretation lexicon has been updated in each iteration of PI-RADS, meaning changes in MRI descriptor definition and influence of the single imaging sequences on final assessment categories have taken place. The PI-RADS lexicon is explicitly designed as a living document [7], meaning that the interpretation lexicon is adapted as evidence about the diagnostic performance is generated.

Currently, there is still more evidence regarding the v2.0 lexicon as compared to v2.1 lexicon.
Regarding diagnostic accuracy, in 2017 Woo et al. performed a meta-analysis of 21 studies
(3857 patients) using PI-RADv2.0 and reported a pooled sensitivity of 89% and a pooled
specificity of 73% [8]. For PI-RADSv2.1, Park et al. performed a similar analysis in 2021 and
reported a pooled sensitivity of 87% and specificity of 74% [9]. This initial analysis includes
data from 10 studies and 1240 patients. The cancer detection rates of PI-RADSv2.0 have

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been estimated with 8% for PI-RADS 2, 13% for PI-RADS 3, 40% for PI-RADS 4 and 69% for PI-RADS 5 [10]. For v2.1 an initial systematic review and meta-analysis reported cancer detection rates of 2% for PI-RADS 1, 4% for PI-RADS 2, 20% for PI-RADS 3, 52% for PI-RADS 4 and 89% for PI-RADS 5 (lesion level analysis) [11]. The PI-RADS lexicon does, in the current edition, not give numeric definitions of the expected cancer rates in the assessment categories. Furthermore, no management recommendations are linked to the assessment categories.

To account for the continuously generated evidence of the diagnostic performance of PI-RADS and expected future iterations of the lexicon (with changes in descriptor definitions and assessment category definitions, and therefore expected changes in diagnostic performance), we want to establish a living systematic review and meta-analysis. This living review will estimate the diagnostic accuracy of the current PI-RADS (sensitivity and specificity), the cancer detection rates (CDR) of the assessment categories and inter-reader agreement of category assignment. We plan to perform update searches and analyses in 12-month cycles.

Our objective is the implementation of a living systematic review and meta-analysis of the diagnostic performance of prostate MRI with PI-RADS assessment (intervention, v2.1 and upcoming versions considered) for the detection of prostate cancer (outcome) in patients with suspicion for prostate cancer (participants). Diagnostic performance of prostate MRI will not be compared to another diagnostic test (comparator), reference standard is histopathology. **BMJ** Open

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Methods and analysis

Study design and registration

This is a systematic review protocol, it follows the PRISMA-P (preferred reporting items for systematic reviews and meta-analyses - protocols) guidelines and format [12]. The systematic review has been registered in PROSPERO (CRD42022343931). The PRISMA-P checklist for our protocol is enclosed as a supplement.

Study eligibility criteria

We include prospective and retrospective studies reporting on the diagnostic accuracy, and/or cancer detection rates of PI-RADS and/or inter-reader agreement of PI-RADS rating, starting with PI-RADSv2.1. Studies that use older versions of the lexicon are not considered. Studies reporting on a subset of PI-RADS categories are eligible. We consider studies published as full text in English. Date restriction is applied, considered studies need to be conducted in 2019 or later, that is after the release of the current PI-RADSv2.1. Studies are still considered as eligible if included patients were examined prior to this date but have been re-interpreted by blinded readers according to the current PI-RADS.

Study population

Our target populations are men with suspicion for prostate cancer, either biopsy naïve or with a prior negative biopsy. Biopsy naïve patients have a higher pretest probability for clinically significant cancer [13]. Biopsy status will be considered as a covariate in our analysis. Patients with known malignancy at the date of prostate MRI or with prior treatment of the prostate are not considered eligible.

Index test

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Prostate MRI read according to the current PI-RADS (version 2.1 at the time of writing this protocol) is the diagnostic test of interest. We record MRI parameters of single studies to account for deviations from the proposed imaging protocol [14]. Experience of the involved radiologist(s) is recorded. We document whether MRI reading is performed without knowledge of the histopathological result. We investigate diagnostic performance on lesion level (up to four lesions per patient are possible) and patient level (equals highest assigned lesion category compared to overall histopathological result).

Comparators

Diagnostic accuracy and cancer detection rates of PI-RADS will not be compared to anotherdiagnostic test.

Reference Test

Histopathological verification of suspicious lesions and the prostate can be performed in several ways. The type of targeted lesion biopsy is recorded (cognitive fusion, transrectal ultrasound MRI fusion, transperineal MRI ultrasound fusion, in-bore). A systematic biopsy and additional MRI-directed perilesional biopsies may also be performed. We record the type and result of targeted biopsy, type of systematic biopsy (if any) and type of perilesional biopsies (if any). Histopathological upgrade of targeted biopsies given the information from systematic biopsy is recorded. Furthermore, analysis of prostatectomy specimen is eligible as reference standard.

1 156 **Outcomes**

157Primary outcome is the detection (sensitivity and specificity, cancer detection rates) of5455158clinically significant cancer. The most widely adapted procedure in the literature regarding56158PI-RADS is to consider any occurrence of a histopathological Gleason pattern \geq 3+4 as59160clinically significant [10,11]. The PI-RADS lexicon offers a more elaborate definition, which is

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more challenging to establish in clinical routine: "Gleason score \geq 7, including 3+4 with prominent but not predominant Gleason 4 component, and/or volume > 0.5cc, and/or extraprostatic extension" [14]. Especially the last point is, given that histopathological verification is performed by targeted lesion biopsy ± systematic biopsy (this is the case in the majority of individual cases and studies), often not possible to establish prior to surgery. Type of definition of clinically significant cancer will be considered as a covariate. Analysis is performed on lesion level (each lesion observed in the MRI examination, up to four lesions per patient, targeted biopsy as reference standard; studies reporting only the results of targeted biopsies without additional systematic biopsy are eligible for the lesion level analysis only) and patient level (highest PI-RADS category as index test, lesion and systematic biopsy and (if performed) perilesional biopsy or prostatectomy as reference standard). Secondary outcomes are the detection (sensitivity and specificity, cancer detection rates) of

insignificant cancer, any cancer, Gleason \geq 4+3 (if reported) and \geq 3+4 with cribriform growth pattern (if reported). Although the PI-RADS lexicon explicitly does not aim at the detection of clinically insignificant cancer [14], knowledge about occurrence of these cancers is still important from a public health perspective. Patients with a diagnosis of clinically insignificant cancer will be closely monitored with active surveillance, including serial PSA testing, MRI and biopsies [15]. For primary outcome and secondary outcomes, we investigate the scenarios PI-RADS \geq 3 and \geq 4 considered positive for the estimation of sensitivity and specificity.

181 Inter-reader agreement of lesion and patient classification with PI-RADS (Cohen's kappa182 values) is defined as a secondary outcome.

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1 2		
2 3 4	184	Information sources and search strategy
5 6	185	We search the following databases for published studies, ongoing studies or completed
7 8	186	studies not (yet) published: MEDLINE, Embase, Cochrane Library, ISRCTN, ClinicalTrials.gov,
9 10 11	187	ICTRP and Deutsches Register Klinischer Studien (DRKS). Time restriction will be applied. We
12 13	188	consider all studies conducted from 03/2019 onwards – PI-RADSv2.1 has been published at
14 15	189	03/2019. Bibliographies of included articles will be manually checked for further eligible
16 17 18	190	studies. The search strategy will be re-used for the planned update cycles in the living
19 20	191	systematic review framework.
21 22		
22 23 24	192	Our MEDLINE search is structured as follows: ((PIRADS) OR ("PI-RADS") OR ("prostate
25 26	193	imaging reporting and data system")) AND ("2019/03/01" [Date - Publication]: "3000/12/12"
27 28 29	194	[Date - Publication]). Searches of the other databases are adapted accordingly. Full search
30 31	195	strategies of all databases are provided as a supplement to this protocol.
32 33	400	
34	196	Data management
35 36 27	197	Search results from the different databases are combined in a dedicated software
37 38 39	198	environment (e.g. Rayyan, https://www.rayyan.ai/), duplicates will be removed. Backup
40 41 42	199	copies are generated after the single database searches.
43 44	200	Selection process
45 46	201	Two independent reviewers evaluate eligibility of search results. First, selection is performed
47 48 49	202	on title and abstract basis. Studies considered relevant (or potentially relevant) based on
50 51	203	title and abstract screening are further considered based on their full text (full text
52 53	204	screening). In each step, discrepancies will be resolved by discussion and by consultation of a
54 55 56	205	third reviewer, if needed. The reason for exclusion is recorded in each selection step.
57 58 59 60	206	Data collection process

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Two independent reviewers extract data from the included studies in duplicate spreadsheets with predefined data items. We define a core set of data items (compare for table 1 and 2). If any items of this set are missing, authors of primary studies are contacted (at least twice) to obtain this missing data.

211 Risk of bias assessment

For the evaluation of risk of bias and applicability of results (study level analysis each) the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) framework is used [16]. Two independent reviewers evaluate risk of bias and applicability of results in the domains patient selection, index test, reference standard and flow and timing (the latter not for applicability evaluation). Discrepancies are resolved by discussion and by consultation of a third reviewer, if needed. From the results of the QUADAS-2 analysis, we will infer the overall risk of bias for obtained results. Studies are not excluded from data synthesis based on the QUADAS-2 evaluation alone.

220 Data synthesis and statistical analysis

Data describing patient populations of the included studies (e.g. mean age, mean PSA value, mean prostate volume, prior biopsy status) is presented in table format. Data synthesis of outcomes (diagnostic accuracy in terms of sensitivity and specificity, cancer detection rates, inter-reader agreement in terms of Cohen's kappa values) is performed given a set of homogeneous studies is identified. The required minimum set of homogeneous study characteristics is: (i) reading of prostate MRI is performed without knowledge of the histopathological results (ii) MRI is performed according to PI-RADS recommendations, (iii) for inter-reader agreement, comparable metrics are reported.

We derive pooled estimates of sensitivity and specificity with bivariate binomial models [17].
 A summary ROC curve with a 95% confidence region is derived for graphical representation.

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We examine the scenarios with PI-RADS \geq 3 and PI-RADS \geq 4 considered as a positive test on lesion level and patient level (overall, four scenarios). Possible publication bias is visually assessed with funnel plots, Deek's test will be used to test for asymmetry [18]. Coupled forest plots of sensitivity and specificity and correlation between sensitivity and 1-specificity are analyzed for assessment of heterogeneity of results [19].

We expect cancer rates in the assessment categories to vary across studies; partly because of different local reading standards, partly because of local differences/thresholds for referral to prostate MRI and targeted biopsy, partly because of different pretest probabilities and thus differences in the patient cohorts examined. In other words, we assume a certain degree of clinical and methodological heterogeneity between studies and do not expect results to vary because of random sampling error alone. For this reason we employ random intercept logistic regression models for meta-analysis of single proportions to derive summary estimates for cancer detection rates of the PI-RADS categories [20] and subcategories of PI-RADS 3 and 4. Heterogeneity of reported cancer detection rates is assessed with Higgins' I² statistic, with I²>50% denoting substantial heterogeneity [19].

Meta-regression with the following covariates (if data is sufficient) is performed to examine possible causes of heterogeneity (diagnostic accuracy and cancer detection rates): type of study population (prior biopsy status), magnetic field strength, multiparametric vs biparametric MRI, definition of clinically significant cancer, type of lesion verification, lesion localization (peripheral zone vs transition zone), reader experience, pretest probability and mean/median PSA in the study population. Subgroup analyses of covariates are performed for univariate analyses.

253 The summary measure for inter-reader agreement (Cohen's kappa values) will be derived 254 with a random effects model. This approach follows the method proposed by Sun [21]. We Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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examine the role of reader experience as a covariate – two highly experienced readers can
be expected to agree more often compared to two relatively unexperienced readers or two
readers with different levels of experience.

258 If quantitative data synthesis is not considered appropriate for one or more defined 259 outcomes, a synopsis of findings is given table format. Order of presentation is stratified by 260 risk of bias and definition of clinically significant cancer used.

261 All statistical analyses are conducted using R (<u>https://www.R-project.org/</u>) [22].

262 GRADE assessment

Quality of evidence per outcome is analyzed according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) System [23], results from the QUADAS-2 analysis are used for risk of bias assessment in this context. Certainty of evidence is rated as high, moderate, low or very low. Results are made available in a summary of findings table.

268 Patient and public involvement

In the development phase of the project the Bundesverband Prostatakrebs Selbsthilfe e.V.
(https://prostatakrebs-bps.de/) was involved in defining relevant research questions. The
Bundesverband Prostatakrebs Selbsthilfe e.V. agreed to disseminate results in their network
of support groups.

1 273

274 Living review framework

We plan to implement a 12-month cycle to update our literature search, study selection and
 data analysis. This is because an accumulation of evidence about the diagnostic performance
 of PI-RADS can be expected, especially for subcategories in categories 3 and 4. Furthermore,

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[7] – that is, new iterations can be
er adapted, changes in diagnostic
is released, our literature search
orting of results will pertain to the
table for our project, because the
ed in the initial discussion of living
ion making: For informed, shared
ult of a prostate MRI examination,
I-RADS and cancer detection rates
anagement recommendations are
in future versions of PI-RADS [14].
there need to be an established
category.
t the moment, we have limited
tic accuracy and cancer detection
e relatively few patients [9,11]).
cally review the performance of

PI-RADS is itself intended as a living diagnostic algorithm expected. Given that the diagnostic algorithm is further dapted, changes in diagnostic eleased, our literature search accuracy can be expected. If a new version of PI-RADS strategy will remain unchanged. Data collection and repo g of results will pertain to the current version of PI-RADS. We consider the living systematic review framework suit e for our project, because the scope and needs address the three demands as expresse systematic reviews by Elliott et al. [24]: (i) up-to-date information is important for decisi making: For informed, shared decision making how to proceed with the resu of a prostate MRI examination, accurate estimates of diagnostic accuracy of Pl DS and cancer detection rates of the categories are crucial. Furthermore, ma gement recommendations are planned to be linked to assessment categories uture versions of PI-RADS [14]. Before recommending biopsy, for example, e need to be an established expected cancer rate for a certain assessment c gory. (ii) Certainty in the existing evidence is low: A e moment, we have limited evidence (meta-analyses do exist for diagnost ccuracy and cancer detection rates of PI-RADSv2.1, however they include elatively few patients [9,11]). Furthermore, we see a need to systematic subcategories in PI-RADS categories 3 and 4. There will be new research evidence: The publication field of prostate MRI and PI-(iii) RADS is highly dynamic, the number of relevant papers is increasing at a fast rate. We expect new accumulating evidence especially for subcategories (different lesion entities in categories 3 and 4). Furthermore, new evidence will be

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302 generated given a new iteration of PI-RADS is published. A timely evidence
303 synthesis is warranted in this case.

304 Our search strategy and data used for analyses will be published as supplement to the 305 systematic review and meta-analysis.

306 Ethics and dissemination

No original data is collected in this systematic review and meta-analysis, ethical review board approval therefore is not required. Results are published in peer reviewed, openaccess scientific journals. We make the collected data accessible as supplemental material to guarantee transparency of results.

311 Discussion

With the recently put forward strong recommendations for prostate MRI prior to biopsy in various national (e.g. [15,25]) and international guidelines [2,3], a rapidly increasing volume of prostate MRI examinations can be expected in the next years. The increasing number of examinations performed requires a standardized, evidence-based diagnostic workflow to streamline patient management.

PI-RADS, having been established in 2012, offers this standardization. PI-RADS provides a universally understood reporting language on the descriptor level and works well as a risk stratification tool for clinically significant prostate cancer [8]. For version 2.0, a systematic review and meta-analysis of inter-reader agreement reported an overall moderate to substantial agreement for PI-RADS category assignment [26]. The diagnostic accuracy of PI-RADS has been subject of a multitude of studies – initial estimates for sensitivity, specificity and the cancer detection rates are available for version 2.1 [9,11]. Park et al. report a pooled sensitivity/specificity of 81%/82% when PI-RADS ≥ 4 is used as a diagnostic threshold, compared to a sensitivity/specificity of 94%/56% when PI-RADS \geq 3 is used [9]. Reported

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95% confidence intervals in this analysis are relatively large, especially for specificity: for the
56% estimate, it ranges from 35 to 97% [9].

As evidence about the diagnostic performance of PI-RADS accrues, these estimates will become more precise. Or, given considerable heterogeneity of estimates between studies, the identification of covariates that affect diagnostic accuracy and cancer detection rates becomes possible. This knowledge could ultimately be included into PI-RADS itself or future guidelines.

At the moment, assessment categories 3 and 4 are assigned to a heterogeneous group of lesions each. For example, in the transition zone assessment category 3 comprises lesions with different appearance in T2 weighted images (atypical nodules and heterogenous lesions with obscured margins). Costa et al. report a cancer rate of 6% and 11% for these two lesion types, although this difference is not statistically significant in their study [27]. If there are systematic differences of cancer rate between lesion subtypes in the same PI-RADS assessment category, this might influence the planned linking of management recommendations to assessment categories [14].

Our living systematic review framework establishes an evidence base for precise estimates of diagnostic accuracy of the current PI-RADS (with different thresholds considered positive), the cancer detection rates of assessment categories and subcategories, and inter-reader agreement. The results can be employed by urologists, radiologists and patients for decision making after prostate MRI and help in the development of PI-RADS itself and future guidelines.

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348 Funding statement

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352 Competing interests statement

Ivo Schoots is a full panel member of the PI-RADS steering committee (ASR/ESR). Fabian Bamberg has received unrestricted research grants and speaker bureau fees from Bayer Healthcare and Siemens Healthineers. Christian Gratzke has received grants/research support from Astellas Pharma, Bayer, GSK, MSD and Recordati and honoraria/consultation fees from Amgen, Astellas Pharma, Bayer, GSK, Ipsen, Janssen, Lilly Pharma, Recordati, Pfizer, Rottapharm, STEBA Biotech. Otherwise, we do not have a competing interest to declare.

[°]9 360 **Supplementary Material**

1 361 PRISMA-P checklist

4 362 Search strategies

⁵ 363 Authors' contributions

⁹ 364 concept and design: Oerther, Schmucker, Schwarzer, Schoots, Benndorf

365 drafting and revising the manuscript: Oerther, Schmucker, Schwarzer, Schoots, Sigle,

- ³ 366 Gratzke, Bamberg, Benndorf
- 6 367 statistical planning: Schwarzer, Benndorf
- ¹⁸ 368 guarantor of the review: Benndorf

1 369 Data statement

5354 370 No data was collected for this protocol.

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 Evaluating Diagnostic Test Accuracy: A Practical Review for Clinical Researchers-Part II. Statistical Methods of Meta-Analysis. <i>Korean J Radiol.</i> 2015;16(6):1188-1196. doi:10.3348/kjr.2015.16.6.1188 Schwarzer G, Chemaitelly H, Abu-Raddad LJ, Rücker G. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions. <i>Res Synth Methods.</i> 2019;10(3):476-483. doi:10.1002/jrsm.1348 Sun S. Meta-analysis of Cohen's kappa. <i>Health Serv Outcomes Res Method.</i> 2011;11(3):145-163. doi:10.1007/s10742-011-0077-3 R <i>Core Team (2022). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.</i> Https://Www.R-Project.Org/). Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. <i>J Clin Epidemiol.</i> 2011;64(4):383-394. doi:10.1016/j.jclinepi.2010.04.026 Elliott JH, Synnot A, Turner T, et al. Living systematic review: 1. Introduction - the why, what, when, and how. <i>J Clin Epidemiol.</i> 2017;91:23-30. doi:10.1016/j.jclinepi.2017.08.010 Recommendations Prostate cancer: diagnosis and management Guidance NICE. Accessed April 25, 2022. https://www.nice.org.uk/guidance/ng131/chapter/recommendations Park KJ, Choi SH, Lee JS, Kim JK, Kim MH. Interreader Agreement with Prostate Imaging Reporting and Data System Version 2 for Prostate Cancer Detection: A Systematic Review and Meta-Analysis. <i>J Urol.</i> 2020;204(4):661-670. doi:10.10197/JU.0000000000001200 Costa DN, Jia L, Subramanian N, et al. Prospectively-Reported PI-RADS Version 2.1 Atypical Benign Prostatic Hyperplasia Nodules with Marked Restricted Diffusion ("2+1" Transition Zone Lesions): Clinically Significant Prostate Cancer Detection Rates on Multiparametric MRI. <i>AJR Am J Roentgenol.</i> Published online September 2, 2020. doi:10.2214/AJR.20.24370 	19	420	19.	Lee J. Kim KW. Choi SH. Huh J. Park SH. Systematic Review and Meta-Analysis of Studies
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 426 Res Synth Methods. 2019;10(3):476-483. doi:10.1002/jrsm.1348 427 21. Sun S. Meta-analysis of Cohen's kappa. Health Serv Outcomes Res Method. 2011;11(3):145-163. doi:10.1007/s10742-011-0077-3 429 22. R Core Team (2022). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. Https://Www.R-Project.Org/). 431 23. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-394. doi:10.1016/j.jclinepi.2010.04.026 434 24. Elliott JH, Synnot A, Turner T, et al. Living systematic review: 1. Introduction - the why, what, when, and how. J Clin Epidemiol. 2017;91:23-30. doi:10.1016/j.jclinepi.2017.08.010 436 25. Recommendations Prostate cancer: diagnosis and management Guidance NICE. Accessed April 25, 2022. https://www.nice.org.uk/guidance/ng131/chapter/recommendations 439 Reporting and Data System Version 2 for Prostate Cancer Detection: A Systematic Review and Meta-Analysis. J Urol. 2020;204(4):661-670. doi:10.1097/JU.0000000000001200 441 27. Costa DN, Jia L, Subramanian N, et al. Prospectively-Reported PI-RADS Version 2.1 Atypical Benign Prostatic Hyperplasia Nodules with Marked Restricted Diffusion ("2+1" Transition Zone Lesions): Clinically Significant Prostate Cancer Detection Rates on Multiparametric MRI. AJR Am J Roentgenol. Published online September 2, 2020. doi:10.2214/AJR.20.24370 	26	425		inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions.
 21. Sun S. Meta-analysis of Cohen's kappa. <i>Health Serv Outcomes Res Method</i>. 2011;11(3):145-163. doi:10.1007/s10742-011-0077-3 22. <i>R Core Team (2022). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. Https://Www.R-Project.Org/).</i> 23. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. <i>J Clin Epidemiol.</i> 2011;64(4):383-394. doi:10.1016/j.jclinepi.2010.04.026 24. Elliott JH, Synnot A, Turner T, et al. Living systematic review: 1. Introduction - the why, what, when, and how. <i>J Clin Epidemiol.</i> 2017;91:23-30. doi:10.1016/j.jclinepi.2017.08.010 25. Recommendations Prostate cancer: diagnosis and management Guidance NICE. Accessed April 25, 2022. https://www.nice.org.uk/guidance/ng131/chapter/recommendations 26. Park KJ, Choi SH, Lee JS, Kim JK, Kim MH. Interreader Agreement with Prostate Imaging Reporting and Data System Version 2 for Prostate Cancer Detection: A Systematic Review and Meta-Analysis. <i>J Urol.</i> 2020;204(4):661-670. doi:10.1097/JU.00000000001200 27. Costa DN, Jia L, Subramanian N, et al. Prospectively-Reported PI-RADS Version 2.1 Atypical Benign Prostatic Hyperplasia Nodules with Marked Restricted Diffusion ("2+1" Transition Zone Lesions): Clinically Significant Prostate Cancer Detection Rates on Multiparametric MRI. <i>AIR Am J Roentgenol.</i> Published online September 2, 2020. doi:10.2214/AJR.20.24370 	27	426		Res Synth Methods. 2019;10(3):476-483. doi:10.1002/jrsm.1348
 427 11. Sun S. Meta-analysis of Cohen S kappa. <i>Hedith Serv Outcomes Res Method</i>. 2011;11(3):145-163. doi:10.1007/s10742-011-0077-3 428 429 22. <i>R Core Team (2022). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. Https://Www.R-Project.Org/).</i> 431 23. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. <i>J Clin Epidemiol.</i> 2011;64(4):383-394. doi:10.1016/j.jclinepi.2010.04.026 434 24. Elliott JH, Synnot A, Turner T, et al. Living systematic review: 1. Introduction - the why, what, when, and how. <i>J Clin Epidemiol.</i> 2017;91:23-30. doi:10.1016/j.jclinepi.2017.08.010 436 25. Recommendations Prostate cancer: diagnosis and management Guidance NICE. Accessed April 25, 2022. https://www.nice.org.uk/guidance/ng131/chapter/recommendations 438 26. Park KJ, Choi SH, Lee JS, Kim JK, Kim MH. Interreader Agreement with Prostate Imaging Reporting and Data System Version 2 for Prostate Cancer Detection: A Systematic Review and Meta-Analysis. <i>J Urol.</i> 2020;204(4):661-670. doi:10.1097/JU.000000000001200 441 27. Costa DN, Jia L, Subramanian N, et al. Prospectively-Reported PI-RADS Version 2.1 Atypical Benign Prostatic Hyperplasia Nodules with Marked Restricted Diffusion ("2+1" Transition Zone Lesions): Clinically Significant Prostate Cancer Detection Rates on Multiparametric MRI. <i>AJR Am J Roentgenol.</i> Published online September 2, 2020. doi:10.2214/AJR.20.24370 	20 29	407	24	Curr C. Mata analysis of Calenda lyange Uselth Care Outcomes Des Mathed 2011.11/2):115-162
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 431 23. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. <i>J Clin Epidemiol</i>. 2011;64(4):383-394. 433 doi:10.1016/j.jclinepi.2010.04.026 434 24. Elliott JH, Synnot A, Turner T, et al. Living systematic review: 1. Introduction - the why, what, when, and how. <i>J Clin Epidemiol</i>. 2017;91:23-30. doi:10.1016/j.jclinepi.2017.08.010 436 25. Recommendations Prostate cancer: diagnosis and management Guidance NICE. Accessed April 25, 2022. https://www.nice.org.uk/guidance/ng131/chapter/recommendations 438 26. Park KJ, Choi SH, Lee JS, Kim JK, Kim MH. Interreader Agreement with Prostate Imaging Reporting and Data System Version 2 for Prostate Cancer Detection: A Systematic Review and Meta-Analysis. <i>J Urol</i>. 2020;204(4):661-670. doi:10.1097/JU.0000000000001200 441 27. Costa DN, Jia L, Subramanian N, et al. Prospectively-Reported PI-RADS Version 2.1 Atypical Benign Prostatic Hyperplasia Nodules with Marked Restricted Diffusion ("2+1" Transition Zone Lesions): Clinically Significant Prostate Cancer Detection Rates on Multiparametric MRI. <i>AJR Am</i> <i>J Roentgenol</i>. Published online September 2, 2020. doi:10.2214/AJR.20.24370 	35			
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57 445 58	56			
86	57	445		
59 446	58 59	116		
60	60			

48					
149	Table 1: Extracted data items – meta-data, MRI technique, reference test and patient				
450	characteristics				
	Data item(s)	levels	explanation		
	Meta-data of study+		journal / year / volume / authors		
	Study type†	prospective or retrospective			
		observational or			
		interventional			
	MRI technique, index test				
	vendor		manufacturer, magnet product type		
	field strength†	3 Tesla, 1.5 Tesla, other			
	sequence parameters		sequence type, slice thickness, gap,		
	T2w		planes obtained		
	sequence parameters		sequence type, slice thickness, gap, b-		
	DWI		values used		
	sequence parameters		sequence type, slice thickness, gap,		
	DCE		temporal resolution		
	endorectal coil used	categorical			
	spasmolytic agent used	categorical			
	number of radiologists	numerical			
	involved		1		
	experience of radiologists	numerical (in years)	most experienced radiologist considered		
	involved		for diagnostic accuracy estimation		
	Reference test				
	target lesion biopsy	cognitive ultrasound fusion,	additionally: mean/median number of		
	technique†	MRI US fusion transrectal,	biopsy cores per lesion		
		MRI US fusion			
		transperineal, in-bore			
	systematic biopsy	not performed, standard 8-	additionally: mean/median number of		
	technique†	12 cores, extended	systematic biopsy cores taken per		
		systematic biopsy (e.g.	patient		
		Ginsburg scheme),			
		template biopsy,			
		prostatectomy specimen			
		used			
	MRI-directed perilesional	categorical	if available, mean/median number of		
	biopsies		perilesional biopsies per lesion is		
			recorded		

	Patient characteristics		
	number of patients and/or	numerical	if information for lesion localization
	number of lesions†		(peripheral zone and transition zone) i
			reported separately, this information is
			recorded
	mean/median age†	numerical	
	mean/median PSA†	numerical	
	mean/median prostate	numerical	
	volume		
451 452	PSA: prostate specific antigen, M	RI: magnetic resonance in thors of the primary stud	naging, US: ultrasound. ies are contacted twice to obtain the missing data
452			
453			
454			

	Data item(s)	levels	explanation
	Outcome data		
	definition of csCA used	PI-RADS Lexicon definition,	exact definition is recorded
		other definition	
	number of lesions and	numerical	
	patients with csCA†		
	number of lesions and	numerical	
	patients with ncsCA		
	number of lesions and	numerical	
	patients with Gleason		
	score ≥ 4+3		
	number of lesions and	numerical	
	patients with Gleason		
	score ≥ 3+4 and		
	cribriform growth pattern		
	sensitivity and specificity†	numerical	 reported in paper or reconstructed from presented data, 2x2
			contingency tables from paper or
			reconstructed are recorded
			Scenarios PI-RADS ≥ 3 and PI-
			RADS ≥ 4 considered positive are examined
			-Zdata is extracted on lesion level an
			patient level, for all extracted
			definitions of prostate cancer
			(csCA, ncsCA, Gleason score ≥
			4+3 and ≥ 3+4 with cribriform growth pattern)
	cancer detection rates†	numerical	- number of malignant cases in each
			reported PI-RADS category divide
			by all cases in each PI-RADS
			category
			- data is extracted on lesion level ar
			patient level, for all extracted
			definitions of prostate cancer
			(csCA, ncsCA, Gleason score ≥
			4+3 and ≥ 3+4 with cribriform growth pattern)
			- subcategories in PI-RADS 3 and 4

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			are recorded separately, if
			information is available
			- for low PI-RADS categories, the
			information will also be expressed
			as negative predictive value
	reader agreement†	type of obtained inter-	
		reader agreement metric,	
		numerical value of metric	
456 457 458	csCA: clinically significant can †: core data items (reporting contacted twice to obtain th	ncer, ncsCA: clinically non-significant/in g of at least one defined outcome is reque e missing data.	significant cancer uired). If missing, authors of the primary studies are
459			
160			
460			

Living systematic review and meta-analysis of the prostate MRI diagnostic test with PI-RADS (Prostate Imaging Reporting and Data System) assessment for the detection of prostate cancer: Study protocol

Search strategies

database	url	search
MEDLINE	https://pubmed.ncbi.nlm.ni	((PIRADS) OR ("PI-RADS") OR ("prostate
	<u>h.gov/</u>	imaging reporting and data system")) AND
		("2019/03/01" [Date - Publication]:
		"3000/12/12" [Date - Publication])
Embase	https://www.embase.com/l	(PIRADS OR "PI-RADS" OR "prostate imaging
	anding?status=grey	reporting and data system") AND [2019-
		2022]/ру
		All article types considered but conference
		abstracts.
Cochrane	https://www.cochranelibrar	PIRADS OR "PI-RADS" OR "prostate imaging
Library	<u>y.com/advanced-search</u>	reporting and data system"
		date limit: with Cochrane Library publication
		date from Mar 2019 to date of search (search
		limit)
ISRCTN	https://www.isrctn.com/edi	PIRADS OR "PI-RADS" OR "prostate imaging
	tAdvancedSearch	reporting and data system";
		search in "text search" field.
		date limit: filter from 03/2019 to date of
		search
ClinicalTrials.	https://clinicaltrials.gov/ct2	PIRADS OR "PI-RADS" (synonym "prostate
gov	<u>/search/advanced</u>	imaging reporting and data system is
		automatically included", doublecheck is
		performed);
		search in "other terms" field.
		date limit: study start from 03/2019 to date of
	https://twiclessuch.uks.int/	
ICIRP	<u>nttps://thaisearcn.who.int/</u>	PIRADS OR PI-RADS OR prostate imaging
	Default.aspx	reporting and data system ;
		search in standard search .
		date limit: date of registration from 03/2019
		to date of search
Deutsches	https://www.drks.de/drks	PIRADS OR "PI-RADS" OR "prostate imaging
Register	<u>web/</u>	reporting and data system"
Klinischer		
Studien		date limit: date of registration from 03/2019
		to date of search

BMJ Open PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol* for "Living systematic review and meta-analysis of the prostate MRI diagnostic test with PI-RADS (Prostate Imaging Reporting and Data System) assessment for the detection of prestate cancer: Study protocol"

Section and topic	Item No	Checklist item	Realized, line number
ADMINISTRATIVI	E INFO		
Title:		an	
Identification	1a	Identify the report as a protocol of a systematic review	1-3
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 (such as PROSPERO) and registration number	118
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	5-25
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	364-368
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
Support:			
Sources	5a	Indicate sources of financial or other support for the review	349-351
Sponsor	5b	Provide name for the review funder and/or sponsor	349-351
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	349-351
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	86-98
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants interventions, comparators, and outcomes (PICO)	107-112
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	107-112, 121-128
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		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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		pyright, i	
Information source	s 9	Describe all intended information sources (such as electronic databases, contact with study authors, tigal registers or other grey literature sources) with planned dates of coverage	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned that it could be repeated	1
Study records: Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	1
Selection	11b	State the process that will be used for selecting studies (such as two independent reviewers) through the phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	2
Data collection process	n 11c	Describe planned method of extracting data from reports (such as piloting forms, done independ by an duplicate), any processes for obtaining and confirming data from investigators	2
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources) to be a superior of the source	2
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	2
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether the swill be done at the outcome or study level, or both; state how this information will be used in data synthesis	2
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	2
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods a_{μ} handling data and methods of combining data from studies, including any planned exploration of consistency (such as I ² , Kadalbs τ)	2
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression	2
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned <u><u>u</u> <u><u>u</u></u></u>	2
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	2
Confidence in cumulative evidence	17 ce	Describe how the strength of the body of evidence will be assessed (such as GRADE)	2
* It is strongly rec clarification on th PRISMA-P Group From: Shamseer L, meta-analysis prote	ommeno e items. p and is Moher pcols (Pl	Ied that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (ffte when available) for imp Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by distributed under a Creative Commons Attribution Licence 4.0. D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred referred	ortant y the review
		3ibliographique	