BMJ Open

Diagnostic utility of diagnostic investigations to identify neuropathic pain in low back related leg pain: protocol for a systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-078392
Article Type:	Protocol
Date Submitted by the Author:	31-Jul-2023
Complete List of Authors:	Mistry, Jai; Western University; St Georges Hospital NHS Foundation Trust Bowling, Benjamin; St Georges Hospital NHS Foundation Trust Walton, David; Western University, School of Physical Therapy Noblet, Tim; St Georges Hospital NHS Foundation Trust, Physiotherapy Heneghan, Nicola; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences Rushton, Alison; Western University Faculty of Health Sciences, School of Physical Therapy
Keywords:	Diagnostic Imaging, Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Spine < ORTHOPAEDIC & TRAUMA SURGERY

Diagnostic utility of diagnostic investigations to identify neuropathic pain in low back related leg pain: protocol for a systematic review

Authors

Jai Mistry[1,2], David M Walton[1], Tim Noblet[1,2], Benjamin Bowling[2], Nicola R Heneghan[3], Alison Rushton[1]

Affiliations

[1] School of Physical Therapy, Faculty of Health Sciences, Western University, London, ON, Canada

[2] St Georges Hospital NHS Foundation Trust
London, UK

[3] School of Sport, Exercise and Rehabilitation Sciences
College of Life and Environmental Sciences,
University of Birmingham
Birmingham, UK

Corresponding author

Jai Mistry
jmistr22@uwo.ca

Word count: 2544

Key words

Neuropathic pain, leg pain, diagnostic utility, diagnostic investigations

ABSTRACT

Introduction

Neuropathic pain (NP) in low back-related leg pain (LBLP) has gained increasing interest in contemporary research. Identification of NP in LBLP is essential to inform precision management. Diagnostic investigations are commonly used to identify NP in LBLP; yet the diagnostic utility of these investigations is unknown. The aim of this systematic review will therefore be to investigate the diagnostic utility of diagnostic investigations to identify NP in LBLP.

Methods and analysis

This protocol has been designed and is reported in accordance with the Cochrane Handbook for Diagnostic Test Accuracy studies, Centre for Reviews and Dissemination (CRD, 2009) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-Protocols (PRISMA-P) checklist respectively. The search strategy will involve two independent reviewers searching electronic databases (CINAHL, EMBASE, MEDLINE, Web of Science, Cochrane Library, AMED and Pedro), key journals and grey literature to identify studies that meet the eligibility criteria. Studies evaluating the diagnostic accuracy of diagnostic investigation to identify NP in patients with LBLP will be eligible. The reviewers will extract the data from included studies, assess risk of bias (Quality Assessment of Diagnostic Accuracy Studies 2) and determine confidence in findings (Grading of Recommendations, Assessment, Development and Evaluation guidelines). Methodological heterogeneity will be assessed to determine if a meta-analysis is possible. If pooling of data is not possible then a narrative synthesis will be conducted.

Ethics and dissemination

Ethical approval is not required. Findings will be published in a peer reviewed journal, presented at relevant conferences and shared with the Spinal Pain Patient Partner Advisor Group at Western University, Canada.

PROSPERO registration number: CRD42023438222

ARTICLE SUMMARY

Strengths and Limitations of this study

- This review will add to the growing body of literature investigating the identification of NP in LBLP.
- The protocol is reported in line with the Cochrane Handbook for Diagnostic Test Accuracy studies and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-Protocols (PRISMA-P) checklist.
- Two independent reviewers will be involved at each stage: screening of eligible studies, data extraction, assessment of risk of bias and overall quality of evidence.
- Known heterogeneity identified from the scoping review suggests pooling of data will not be possible.
- English language bias may occur due to the exclusion of non-English articles resulting in reduced generalisability of findings.

INTRODUCTION

Low Back Pain (LBP) is the leading cause of years lived with disability worldwide (1). Individuals with LBP commonly present with associated concomitant leg pain (2). Increased reliance on healthcare resources and poorer health related outcomes have been found in those with low back-related leg pain (LBLP) when compared to those with LBP alone (3). Neuropathic pain (NP) in LBLP has gained increasing interest in contemporary research due to the burden it places on the individual and wider society (4). NP is commonly reported in patients with LBLP with prevalence estimates ranging between 48-74% (5). Identification of NP in LBLP is essential as international treatment recommendations (pharmacological, invasive procedures) differ for those with LBLP and NP (sciatica) compared to those with LBLP alone (6-9). The primary issue concerning the identification of NP in LBLP is the absence of a gold standard (e.g., test, battery of tests, investigations etc) and an accepted reference standard to inform diagnosis.

Various methods have been employed to identify NP in LBLP including self-report screening tools (10,11), clusters of patient history and physical testing items (12,13) and diagnostic investigations (e.g imaging) (14). A recent systematic review investigated the diagnostic utility of clinical investigations (patient history, clinical examination and screening tool data) to identify NP in LBLP (15). The diagnostic utility of diagnostic investigations, defined as any instrumented-based diagnostic test (e.g. imaging, laboratory test, biopsies and neurophysiology) was not included in this review. Low to moderate level evidence was identified in support of the Standardised Evaluation of Pain (StEP) tool and a cluster of eight assessment items (age: 16-40 years, duration of disease <15 days, presence of paroxysmal pain, pain worse in leg than back, typical dermatomal distribution, worse on coughing/sneezing/straining, finger to floor distance ≥25 cm and presence of paresis) (15). Indirectness, in the included studies was identified due to the large variation in terminology used to define NP in LBLP. Furthermore, heterogeneity of reference standards was evident (including expert opinion, imaging and surgery), therefore the primary diagnostic data must be interpreted with caution.

Consensus studies have been conducted in response to the uncertainty highlighted in contemporary research. An expert derived list of clinical indicators was initially developed by Smart *et al* (16) to identify NP mechanisms in musculoskeletal pain, and this list was developed further following an updated study focusing on the identification of NP in LBLP (17). Findings revealed a list of eight clinical indicators that are proposed to increase the index of suspicion for the presence of NP in LBLP (17). Stronger recommendations would

require further support for diagnostic utility of these indicators. Therefore, an reference standard is needed, against which the clinical indicators can be tested. The International Association for the Study of Pain (IASP) Special Interest Group on Neuropathic Pain (NeuPSIG) proposed a grading system, (revised in 2016), to guide decisions based on the level of certainty (possible, probable, and definite) with which NP can be determined in an individual. In order to satisfy the 'definite' criteria, diagnostic investigation/s confirming a lesion or disease of the somatosensory nervous system are required, alongside history and examination findings (18). However, it is unclear what diagnostic investigations or combination of such should be used in the case of diagnosis of NP for LBLP.

Aim

To synthesise evidence investigating the diagnostic utility of diagnostic investigations to identify NP in LBLP.

METHOD

This systematic review protocol has been designed and reported in line with The Cochrane Handbook for Diagnostic Test Accuracy studies, Centre for Reviews and Dissemination (CRD, 2009) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-Protocols (PRISMA-P) checklist. A previous systematic review, conducted by the same research team, has informed the methods of this protocol (15).

Patient and public involvement

Patients and the public have informed the conception of this review as part of an existing programme of research related to lumbar spinal surgery for low back related leg pain.

Eligibility criteria

Eligibility criteria are reported in line with the Sample, Phenomenon of Interest, Design, Evaluation and Research type (SPIDER) tool (19).

- Sample: adult patients (age >18 years) with LBLP.
- Phenomenon of Interest: NP in LBLP.
- Design: any study design using primary diagnostic accuracy data (specificity, sensitivity, likelihood ratios (LRs) and predictive values (PVs)).
- Evaluation: studies evaluating diagnostic accuracy of diagnostic investigations to identify NP in LBLP. Diagnostic investigations will be defined as any instrumented-based diagnostic test intended to identify a lesion or disease of the somatosensory

nervous system (imaging, laboratory test, biopsies and neurophysiology (18)) Diagnostic investigations do not include physical examination tests such as the straight leg raise or slump test.

- Research type: quantitative.
- Studies not written in English will be excluded.

Information sources

Each electronic database (CINAHL, EMBASE, MEDLINE, Web of Science, Cochrane Library, AMED and Pedro) will be searched from inception to 31st July 2023 using database specific search strategies. There will be no geographical restriction. A manual search of key journals, conducted to compliment the search strategy, will include: `*Spine, The Clinical Journal of Pain*, *PAIN*, *European Journal of Pain*, *The Journal of Pain* and *Musculoskeletal Science and Practice*. Reference lists of included studies and the Cochrane Back Review Group will be reviewed to identify additional eligible studies. Finally, grey literature will be reviewed, using key sources including British National Bibliography for report literature, OpenGrey and EThOS.

Search strategy

The search strategy was developed by the lead author (JM) and reviewed by a specialist librarian at Western University and co-authors to ensure quality. The search strategy has been informed by a previous published review by Mistry et al (15) with previously used key terms patient history, clinical examination and screening tools replaced with diagnostic investigations (imaging, laboratory test, biopsies and neurophysiology). See example search strategy in box 1.

Box 1: Example of MEDLINE OvidSP search strategy 1948 – Feb 2023

1. diagnostic accuracy.mp. or "Sensitivity and Specificity"/
2. diagnostic utility.mp.
3. exp "Reproducibility of Results"/ or diagnostic reliability.mp.
4. 1 or 2 or 3
5. diagnostic investigations.mp.
6. diagnostic imaging.mp. or exp Diagnostic Imaging/
7. exp Magnetic Resonance Imaging/ or exp Diffusion Magnetic Resonance Imaging/ or imaging.mp.
8. exp Neurophysiology/ or neurophysiology.mp.
9. nerve conduction test.mp. or exp Neural Conduction/
10. exp Biopsy/ or skin biopsy.mp.
11. exp Genetic Testing/ or genetic test.mp.
12. exp Tomography, X-Ray Computed/
13. laboratory test*.mp. or exp Clinical Laboratory Techniques/
14. Electrophysiology/ or electrophysiology.mp.
15. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 4 and 15
17. neuropathic pain.mp. or exp Neuralgia/
18. radicular.mp. or exp Radiculopathy/ or exp Intervertebral Disc Displacement/
19. exp Spinal Nerve Roots/ or nerve root*.mp.
20. radicular pain.mp.
21. 17 or 18 or 19 or 20
22. 16 and 21
23. low back pain.mp. or exp Back Pain/ or exp Low Back Pain/
24. exp Sciatica/ or low back related leg pain.mp.
25. LBP.mp.
26. LBLP.mp.
27. 23 or 24 or 35 or 26
28. 22 and 27

Study records

Data management

Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia, www.covidence.org) will be used to manage citations, identify and remove duplicates and to store abstracts and full texts.

Selection process

The selection of relevant articles will commence with independent screening by the two review authors (JM, BB). Initially, titles and abstracts will be screened against the eligibility criteria. Studies will be categorised into included, excluded (clearly irrelevant) and unsure groups (20). Full texts will be retrieved for studies that may meet the eligibility criteria and

independently reviewed by the two review authors. Included studies must be agreed by both review authors, and any unresolved disagreements will be brought to a third author for decision (AR). Agreement between review authors will be analysed using the kappa statistic at title/abstract screening stage and full-text screening stage (21).

Data collection process

Data will be extracted independently by the two reviewers. A customised data extraction form, piloted and employed in our previous systematic review (15), will be used. The third reviewer (AR) will mediate any disagreement in data extraction between the two review authors.

Data items

Data items to be extracted from the included studies are summarised in Table 1. If data items are not available, study authors will be contacted via email (22). An initial email will be sent to study authors to request for missing information if no response is received after 2 weeks a second reminder email will be sent (22).

Table 1 Summary of data items to be extracted

Content	Data items
Study details	Study title, author, publication date, study design
Participant characteristics	Age, gender, co-morbidities
Index test	Diagnostic investigations (investigations (imaging, laboratory test, biopsies and neurophysiology)
Reference standard	Comparator test against the diagnostic investigations
Diagnostic accuracy data	Sensitivity, specificity, predictive values (PVs) and likelihood ratios (LRs). Diagnostic accuracy data will be entered into 2×2 contingency tables (23).

Risk of bias in individual studies

The QUADAS-2 tool will be applied independently (JM, BB) to assess risk of bias in the included studies. The QUADAS-2 tool was developed as a tool to assess risk of bias in

diagnostic accuracy studies. The QUADAS-2 tool consists of four domains: patient selection, index test, reference standard, and flow and timing (24). The tool assesses risk of bias (relating to bias within the study that distorts the primary diagnostic data) and applicability (relating to the extent to which the research study in question is applicable to the systematic review question). Each domain is assessed for risk of bias. Patient selection, index test, reference standard domains are assessed for applicability concerns. Both risk of bias and applicability concerns are used to construct an overall summary judgement of each study, either 'at risk' or 'low risk' (24). Any disagreements between the two reviewers will be discussed initially, and if the disagreement persists it will be brought to the third reviewer for decision (AR).

Summary measures

Primary diagnostic data (sensitivity, specificity, PVs and LRs) will be presented as summary measures. A formula will be used to calculate primary diagnostic data in cases where only raw data are available (25). Summary tables will describe primary diagnostic data in relation to the index test:

- Level of accuracy
- Discriminatory properties
- Strength of agreement

Level of accuracy

To date, there is no clear accepted taxonomy for characterising level of accuracy for sensitivity and specificity (26). Therefore, previous research has informed how levels of accuracy for sensitivity and specificity are described in this study; low (<50%), low/moderate (51-64%), moderate (65-74%), moderate/high (75-84%) and high (>85%) (15, 26, 27).

Discriminatory properties

Positive and negative likelihood ratios (+LR & -LR) will be used in order to describe the discriminatory properties of the index test: conclusive (+LR >10 and -LR <0.1), strong (+LR 5-10 and -LR 0.1-0.2), weak (+LR 2-5 and -LR 0.2-0.5, negligible (+LR 1-2 and -LR 0.5-1) (15, 27, 28).

Strength of agreement

Landis and Koch (1997) developed a grading system using a kappa-type statistic to describe strength of agreement in reliability, which will be adopted in this review: 0: poor, 0-0.21: slight, 0.21-0.40: fair, 0.41-0.60: moderate, 0.61-0.80: substantial and 0.81-1.00: almost perfect (15, 27, 29).

Data synthesis

Data synthesis will follow the same process as our previous review (15). Initially, heterogeneity will be explored in study designs, population, comparable diagnostic data, and reference standard to inform the data synthesis approach. If pooling of data is not possible, which is likely based on initial scoping searches, then a narrative synthesis will be conducted.

A narrative synthesis framework, specific to systematic reviews, will be adopted (30). The framework will be modified for the purpose of this study by removing the initial stage of synthesis pertaining to developing a theoretical model of how interventions work, as it is not relevant to diagnostic accuracy studies. The narrative synthesis will consist of the 3 remaining stages: developing a preliminary synthesis of findings of included studies, exploring relationships in the data and assessing the robustness of the synthesis (30).

Confidence in cumulative evidence

Grading of Recommendations, Assessment, Development and Evaluations (GRADE) will be used to assess the level of evidence (31). GRADE has been adapted for it use in diagnostic accuracy research (31). The two reviewers will independently assess each study and assign a level of evidence (high, moderate, low or very low). Six factors will downgrade the level of evidence; study design, risk of bias (informed by QUADAS-2), inconsistency of evidence, indirectness of evidence, imprecision of results and publication bias. Factors resulting in the level of evidence being upgraded include; dose effect, large estimates of accuracy and residual plausible confounding (31).

CLINICAL IMPLICATIONS

Uncertainty amongst researchers and clinicians exists when selecting the best diagnostic investigation to identify NP in LBLP. Imprecision in the identification of NP in LBLP can lead to inappropriate and untimely intervention and therefore poses a great risk to patient care. This review aims to address the uncertainty by investigating the diagnostic utility of diagnostic investigations for LBLP. Knowledge of the most appropriate diagnostic investigation will help to inform a clinician's decision-making when identifying NP in LBLP, which will lead to precision management and thus better patient care. However, as identified from the scoping search, heterogeneity is likely in this body of evidence and therefore clinical recommendations may not be possible. If recommendations are not possible based on this synthesis, further research recommendations will be made.

ETHICS AND DISSEMINATION

Ethical approval is not required for this systematic review. Findings will add to the growing body of literature investigating the identification of NP in LBLP. The findings of this review will be published in a peer reviewed journal and presented at pertinent conferences. Finally, the results of this study will be shared with the Spinal Pain Patient Partner Advisor Group at Western University.

Author contributions

JM is a PhD student, lead author and first reviewer, AR is the lead supervisor, DW, NH and TN are co supervisors. BB is the second reviewer. AR is the guarantor of the review. JM led on manuscript development. All the authors contributed to the final manuscript. Data collection be will be conducted by JM, BB and AR. Draft manuscripts will be reviewed by AR, DW, NH and TN. All authors will contribute to the dissemination of the protocol.

Funding

None.

Competing interests

None.

Data sharing statement

No further data are available.

Acknowledgements

None.

References

1. Hartvigsen J, Hancock MJ, Kongsted A, *et al*. What low back pain is and why we need to pay attention. Lancet2018;**391**:2356–2367.doi:10.1016/S0140-6736(18)30480-X
2. Hill JC, Konstantinou K, Egbewale BE, *et al*. Clinical outcomes among low back pain consulters with referred leg pain in primary care. Spine2011;**36**:2168–75.doi: 10.1097/BRS.0b013e31820712bb
3. Konstantinou K, Hider SL, Jordan JL, *et al*. The impact of low back-related leg pain on outcomes as compared with low back pain alone: a systematic review of the literature. Clin J Pain2013;**29**:644–654.doi:10.1097/AJP.0b013e31826f9a52
4. Liedgens H, Obradovic M, De Courcy J, *et al*. A burden of illness study for NP in Europe. Clin Econ Outcomes Res2016;**8**:113–26.doi: 10.2147/CEOR.S81396
5. Harrison SA, Ogollah R, Dunn KM, *et al*. Prevalence, Characteristics, and Clinical Course of Neuropathic Pain in Primary Care Patients Consulting With Low Back-related Leg Pain. Clin J Pain2020:**36**;813–824.doi:10.1097/AJP.0000000000000879
6. Mouline, DE, Boulanger, A, Clark, AJ, *et al*. Pharmacological Management of Chronic Neuropathic Pain: Revised Consensus Statement from the Canadian Pain Society. Pain Research and Management 2014;**19**:328–35.doi:10.1155/2014/754693.
7. Finnerup NB, Attal, N, Haroutounian, S, *et al*. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet2015;**14**:162–173.doi: 10.1016/S1474-4422(14)70251-0
8. Schlereth, T. Guideline “diagnosis and non interventional therapy of neuropathic pain” of the German Society of Neurology (deutsche Gesellschaft für Neurologie). Neurol Res Pract2020;**16**.doi:10.1186/s42466-020-00063-3
9. National Institute for Health and Care Excellence. Low back pain and sciatica in over 16S: assessment and management (NICE guideline 33),2020. Available: https://www.nice.org.uk/guidance/ng59 [Accessed 8th January 2023].
10. Beith ID, Kemp A, Kenyon J, *et al*. Identifying neuropathic back and leg pain: a cross-sectional study. Pain2011;**152**:1511–6.doi:10.1016/j.pain.2011.02.033
11. Walsh J, Hall T. Classification of low back-related leg pain: do subgroups differ in disability and psychosocial factors?J Man Manip Ther2009;**17**:118–23.doi:10.1179/106698109790824703
12. Verwoerd AJ, Peul WC, Willemsen SP, *et al*. Diagnostic accuracy of history taking to assess lumbosacral nerve root compression. Spine J2014;**14**:2028–37.doi:10.1016/j.spinee.2013.11.049

13. Vroomen P, de Krom MCTFM, Wilmink J, *et al*. Diagnostic value of history and physical examination in patients suspected of lumbosacral nerve root compression. J Neurol Neurosurg Psychiatry2002;**72**:630–4.doi:10.1136/jnnp.72.5.630
14. Freynhagen R, Rolke R, Baron R, *et al*. Pseudoradicular and radicular low-back pain – a disease continuum rather than different entities? answers from quantitative sensory testing. Pain2008;**135**:65–74.doi:10.1016/j.pain.2007.05.004
15. Mistry J, Heneghan NR, Noblet T, *et al*. Diagnostic utility of patient history, clinical examination and screening tool data to identify neuropathic pain in low back related leg pain: a systematic review and narrative synthesis. BMC Musculoskelet Disord 2020a;**21**:532. doi.org/10.1186/s12891-020-03436-6
16. Smart, KM, Blake, C, Staines, A, *et al*. Clinical indicators of 'nociceptive', 'peripheral neuropathic' and 'central' mechanisms of musculoskeletal pain. A Delphi survey of expert clinicians. Manual Therapy2010;**15**:80–87.doi:10.1016/j.math.2009.07.005
17. Mistry J, Falla, D, Noblet, T, *et al.* Clinical indicators to identify neuropathic pain in low back related leg pain: a modified Delphi study. BMC Musculoskelet Disord2020b;**21**:601.doi.org/10.1186/s12891-020-03600-y
18. Finnerup NB, Haroutounian S, Kamerman P, *et al*. Neuropathic pain: an updated grading system for research and clinical practice. Pain2016;**157**:1599–606.doi:10.1097/j.pain.0000000000000492
19. Cooke A, Smith D, Booth A, *et al*. Beyond PICO: the spider tool for qualitative evidence synthesis. Qual Health Res2012;**22**:1435–43.doi:10.1177/1049732312452938
20. van Tulder M, Furlan A, Bombardier C, *et al*. Updated method guidelines for systematic reviews in the Cochrane collaboration back review group. Spine 2003;**28**:1290–9.doi:10.1097/01.BRS.0000065484.95996.AF
21. Higgins J, Green S. *Cochrane Handbook for systematic reviews of interventions*. The Cochrane Collaboration, 2011.
22. Young T, Hopewell S. Methods for obtaining unpublished data. Cochrane Database Syst Rev2011:MR000027.doi:10.1002/14651858.MR000027.pub2
23. Whiting PF, Davenport C, Jameson C, *et al*. How well do health professionals interpret diagnostic information? A systematic review. BMJ Open 2015;**5**:e008155.doi:10.1136/bmjopen-2015-008155
24. Whiting PF, Rutjes AW, Westwood ME, *et al*. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;**155**:529–36.doi:10.7326/0003-4819-155-8-201110180-00009
25. Akobeng AK. Understanding diagnostic tests 1: sensitivity, specificity and predictive values. Acta Paediatr 2007;**96**:338–41.doi:10.1111/j.1651-2227.2006.00180.x

26. Schneiders AG, Sullivan SJ, Hendrick PA, *et al*. The ability of clinical tests to diagnose stress fractures: a systematic review and meta-analysis. J Orthop Sports Phys Ther2012:**42**;760–71.
27. Grødahl LH, Fawcett L, Nazareth M *et al.* Diagnostic utility of patient history and physical examination data to detect spondylolysis and spondylolisthesis in athletes with low back pain: A systematic review. Man Ther2016;**24**:7–17.doi10.1016/j.math.2016.03.011
28. Jaeschke R, Guyatt, G, Sackett, DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. Jama1994;**271**:389–391.doi10.1001/jama.271.5.389
29. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics1977:**33**;159–74. doi:10.2307/2529310
30. Popay J, Roberts H, Sowden A, *et al*. *Guidance on the conduct of narrative synthesis in systematic reviews: a product from the ESRC methods programme*. Lancaster, UK: Lancaster University, 2006.
31. Schünemann HJ, Guyatt G, Oxman A. The GRADE approach for diagnostic tests and strategies. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE working group; 2013.

PRISMA-P 2015 Checklist

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

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	65
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	5-24
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	302-307
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	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	309-310
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	90-135
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	137-140
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	149-163
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	165-174
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	183-184
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	188-191
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	193-201
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	203-207
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	209-216
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	209-216
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	217-229
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	258-270
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	258-270
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	258-270
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	258-270
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☒	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	272-280

BMJ Open

Diagnostic utility of diagnostic investigations to identify neuropathic pain in low back related leg pain: protocol for a systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-078392.R1
Article Type:	Protocol
Date Submitted by the Author:	08-Nov-2023
Complete List of Authors:	Mistry, Jai; Western University; St Georges Hospital NHS Foundation Trust Walton, David; Western University, School of Physical Therapy Noblet, Tim; St Georges Hospital NHS Foundation Trust, Physiotherapy Bowling, Benjamin; St Georges Hospital NHS Foundation Trust Heneghan, Nicola; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences Rushton, Alison; Western University Faculty of Health Sciences, School of Physical Therapy
Primary Subject Heading:	Diagnostics
Secondary Subject Heading:	Research methods, Rehabilitation medicine, Radiology and imaging
Keywords:	Diagnostic Imaging, Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Spine < ORTHOPAEDIC & TRAUMA SURGERY

Diagnostic utility of diagnostic investigations to identify neuropathic pain in low back related leg pain: protocol for a systematic review

Authors

Jai Mistry[1,2], David M Walton[1], Tim Noblet[1,2], Benjamin Bowling[2], Nicola R Heneghan[3], Alison Rushton[1]

Affiliations

[1] School of Physical Therapy, Faculty of Health Sciences, Western University, London, ON, Canada

[2] St Georges Hospital NHS Foundation Trust
London, UK

[3] School of Sport, Exercise and Rehabilitation Sciences
College of Life and Environmental Sciences,
University of Birmingham
Birmingham, UK

Corresponding author

Jai Mistry
jmistr22@uwo.ca

Word count: 2832

Key words

Neuropathic pain, leg pain, diagnostic utility, diagnostic investigations

ABSTRACT

Introduction

Neuropathic pain (NP) in low back-related leg pain (LBLP) has gained increasing interest in contemporary research. Identification of NP in LBLP is essential to inform precision management. Diagnostic investigations are commonly used to identify NP in LBLP; yet the diagnostic utility of these investigations is unknown. The aim of this systematic review will therefore be to investigate the diagnostic utility of diagnostic investigations to identify NP in LBLP.

Methods and analysis

This protocol has been designed and is reported in accordance with the Cochrane Handbook for Diagnostic Test Accuracy studies, Centre for Reviews and Dissemination (CRD, 2009) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-Protocols (PRISMA-P) checklist respectively. The search strategy will involve two independent reviewers searching electronic databases (CINAHL, EMBASE, MEDLINE, Web of Science, Cochrane Library, AMED and Pedro), key journals (*Spine, The Clinical Journal of Pain*, *PAIN*, *European Journal of Pain*, *The Journal of Pain* and *Musculoskeletal Science and Practice*) and grey literature (British National Bibliography for report literature, OpenGrey and EThOS) from inception to 31st July 2023 to identify studies that meet the eligibility criteria. Studies evaluating the diagnostic accuracy of diagnostic investigation to identify NP in patients with LBLP will be eligible, studies not written in English will be excluded. The reviewers will extract the data from included studies, assess risk of bias (Quality Assessment of Diagnostic Accuracy Studies 2) and determine confidence in findings (Grading of Recommendations, Assessment, Development and Evaluation guidelines). Methodological heterogeneity will be assessed to determine if a meta-analysis is possible. If pooling of data is not possible then a narrative synthesis will be conducted.

Ethics and dissemination

Ethical approval is not required. Findings will be published in a peer reviewed journal, presented at relevant conferences and shared with the Patient Partner Advisor Group at Western University, Canada.

PROSPERO registration number: CRD42023438222

ARTICLE SUMMARY

Strengths and Limitations of this study

- This review will add to the growing body of literature investigating the identification of NP in LBLP.
- The protocol is reported in line with the Cochrane Handbook for Diagnostic Test Accuracy studies and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-Protocols (PRISMA-P) checklist.
- Two independent reviewers will be involved at each stage: screening of eligible studies, data extraction, assessment of risk of bias and overall quality of evidence.
- Known heterogeneity identified from the scoping review suggests pooling of data will not be possible.
- English language bias may occur due to the exclusion of non-English articles resulting in reduced generalisability of findings.

INTRODUCTION

Low Back Pain (LBP) is the leading cause of years lived with disability worldwide (1). Individuals with LBP commonly present with associated concomitant leg pain (2). Increased reliance on healthcare resources and poorer health related outcomes have been found in those with low back-related leg pain (LBLP) when compared to those with LBP alone (3). Neuropathic pain (NP) in LBLP has gained increasing interest in contemporary research due to the burden it places on the individual and wider society (4). NP is commonly reported in patients with LBLP with prevalence estimates ranging between 48-74% (5). Identification of NP in LBLP is essential as international treatment recommendations (pharmacological, invasive procedures) differ for those with LBLP and NP (sciatica) compared to those with LBLP alone (6-9). The primary issue concerning the identification of NP in LBLP is the absence of a gold standard (e.g., test, battery of tests, investigations etc) and an accepted reference standard to inform diagnosis.

Various methods have been employed to identify NP in LBLP including self-report screening tools (10,11), clusters of patient history and physical testing items (12,13) and diagnostic investigations (e.g imaging) (14). A recent systematic review investigated the diagnostic utility of clinical investigations (patient history, clinical examination and screening tool data) to identify NP in LBLP (15). The diagnostic utility of diagnostic investigations, defined as any instrumented-based diagnostic test (e.g. imaging, laboratory test, biopsies and neurophysiology) was not included in this review. Low to moderate level evidence was identified in support of the Standardised Evaluation of Pain (StEP) tool and a cluster of eight assessment items (age: 16-40 years, duration of disease <15 days, presence of paroxysmal pain, pain worse in leg than back, typical dermatomal distribution, worse on coughing/sneezing/straining, finger to floor distance ≥25 cm and presence of paresis) (15). Indirectness, in the included studies was identified due to the large variation in terminology used to define NP in LBLP. Furthermore, heterogeneity of reference standards was evident (including expert opinion, imaging and surgery), therefore the primary diagnostic data must be interpreted with caution.

Consensus studies have been conducted in response to the uncertainty highlighted in contemporary research. An expert derived list of clinical indicators was initially developed by Smart *et al* (16) to identify NP mechanisms in musculoskeletal pain, and this list was developed further following an updated study focusing on the identification of NP in LBLP (17). Findings revealed a list of eight clinical indicators that are proposed to increase the index of suspicion for the presence of NP in LBLP (17). Stronger recommendations would

require further support for diagnostic utility of these indicators. Therefore, an reference standard is needed, against which the clinical indicators can be tested. The International Association for the Study of Pain (IASP) Special Interest Group on Neuropathic Pain (NeuPSIG) proposed a grading system, (revised in 2016), to guide decisions based on the level of certainty (possible, probable, and definite) with which NP can be determined in an individual. In order to satisfy the 'definite' criteria, diagnostic investigation/s confirming a lesion or disease of the somatosensory nervous system are required, alongside history and examination findings (18). Diagnostic investigations have been defined by IASP as any instrumented-based diagnostic test intended to identify a lesion or disease of the somatosensory nervous system (imaging, laboratory test, biopsies and neurophysiology) (18). However, it is unclear what diagnostic investigations or combination of such should be used in the case of diagnosis of NP for LBLP. The aforementioned diagnostic investigations when placed in a clinical pathway are usually placed at the end following history taking and physical examination. The results of these investigations can increase the clinicians index of suspicion that NP is present and therefore aid the decision making regarding onward management.

This systematic review will investigate the diagnostic utility of diagnostic investigations in the identification of NP in LBLP. Diagnostic investigations will be the index test and compared against a reference standard (including surgery, expert opinion, assessment findings and diagnostic investigations).

Aim

To synthesise evidence investigating the diagnostic utility of diagnostic investigations to identify NP in LBLP.

METHOD AND ANALYSIS

This systematic review protocol has been designed and reported in line with The Cochrane Handbook for Diagnostic Test Accuracy studies, Centre for Reviews and Dissemination (CRD, 2009) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-Protocols (PRISMA-P) checklist. A previous systematic review, conducted by the same research team, has informed the methods of this protocol (15).

Patient and public involvement

Patients and the public have informed the conception of this review as part of an existing programme of research related to lumbar spinal surgery for low back related leg pain. The

study was proposed to the spinal pain research Patient Partner Advisory Group in the School of Physical Therapy at Western University, Canada. Following completion of the systematic review the results will be presented back to the same group to discuss the findings and to compare them to their own experiences. These discussions may lead to the to the development of future research projects.

Eligibility criteria

Types of studies

Any study design will be considered for inclusion if evaluating diagnostic accuracy of diagnostic investigations to identify NP in LBLP. Studies must include diagnostic accuracy data (specificity, sensitivity, likelihood ratios (LRs) and predictive values (PVs)). Diagnostic investigations do not include physical examination tests such as the straight leg raise or slump test.

Participants

Studies evaluating diagnostic accuracy of diagnostic investigations in adult patients (age >18 years) with LBLP.

Index test

The index test investigation consisted of diagnostic investigations. Diagnostic investigations will be defined as any instrumented-based diagnostic test intended to identify a lesion or disease of the somatosensory nervous system (imaging, laboratory test, biopsies and neurophysiology (18).

Target condition

Diagnostic studies were included if the aim of the diagnostic test was to identify NP in LBLP.

Reference standards

We included studies where the diagnostic investigation was compared to a reference standard including: 1) Surgery, 2) Diagnostic investigations, 3) Expert opinion, 4) Subjective/Objective examination items.

Studies not written in English will be excluded.

Search methods for identification of studies

Electronic searches

Each electronic database (CINAHL, EMBASE, MEDLINE, Web of Science, Cochrane Library, AMED and Pedro) will be searched from database inception to 31st July 2023 using database specific search strategies. There will be no geographical restriction. The search strategy was developed by the lead author (JM) and reviewed by a specialist librarian at Western University and co-authors to ensure quality. The search strategy has been informed by a previous published review by Mistry et al (15) with previously used key terms patient history, clinical examination and screening tools replaced with diagnostic investigations (imaging, laboratory test, biopsies and neurophysiology). See example search strategy in box 1.

Box 1: Example of MEDLINE OvidSP search strategy 1948 – 31st July 2023

1. diagnostic accuracy.mp. or "Sensitivity and Specificity"/
2. diagnostic utility.mp.
3. exp "Reproducibility of Results"/ or diagnostic reliability.mp.
4. 1 or 2 or 3
5. diagnostic investigations.mp.
6. diagnostic imaging.mp. or exp Diagnostic Imaging/
7. exp Magnetic Resonance Imaging/ or exp Diffusion Magnetic Resonance Imaging/ or imaging.mp.
8. exp Neurophysiology/ or neurophysiology.mp.
9. nerve conduction test.mp. or exp Neural Conduction/
10. exp Biopsy/ or skin biopsy.mp.
11. exp Genetic Testing/ or genetic test.mp.
12. exp Tomography, X-Ray Computed/
13. laboratory test*.mp. or exp Clinical Laboratory Techniques/
14. Electrophysiology/ or electrophysiology.mp.
15. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 4 and 15
17. neuropathic pain.mp. or exp Neuralgia/
18. radicular.mp. or exp Radiculopathy/ or exp Intervertebral Disc Displacement/
19. exp Spinal Nerve Roots/ or nerve root*.mp.
20. radicular pain.mp.
21. 17 or 18 or 19 or 20
22. 16 and 21
23. low back pain.mp. or exp Back Pain/ or exp Low Back Pain/
24. exp Sciatica/ or low back related leg pain.mp.
25. LBP.mp.
26. LBLP.mp.
27. 23 or 24 or 35 or 26
28. 22 and 27

Searching other resources

A manual search of key journals, conducted to compliment the search strategy, will include: `*Spine, The Clinical Journal of Pain*, *PAIN*, *European Journal of Pain*, *The Journal of Pain* and *Musculoskeletal Science and Practice*. Reference lists of included studies and the Cochrane Back Review Group will be reviewed to identify additional eligible studies. Finally, grey literature will be reviewed, using key sources including British National Bibliography for report literature, OpenGrey and EThOS.

Data collection and analysis

Selection of studies

The selection of relevant articles will commence with independent screening by the two review authors (JM, BB). Initially, titles and abstracts will be screened against the eligibility criteria. Studies will be categorised into included, excluded (clearly irrelevant) and unsure groups (19). Full texts will be retrieved for studies that may meet the eligibility criteria and independently reviewed by the two review authors. Included studies must be agreed by both review authors, and any unresolved disagreements will be brought to a third author for decision (AR). Agreement between review authors will be analysed using the kappa statistic at title/abstract screening stage and full-text screening stage (20).

Data extraction and management

Data will be extracted independently by the two reviewers. A customised data extraction form, piloted and employed in our previous systematic review (15), will be used. The third reviewer (AR) will mediate any disagreement in data extraction between the two review authors. Data items to be extracted from the included studies are summarised in Table 1. If data items are not available, study authors will be contacted via email (21). An initial email will be sent to study authors to request for missing information if no response is received after 2 weeks a second reminder email will be sent (21). Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia, www.covidence.org) will be used to manage citations, identify and remove duplicates and to store abstracts and full texts.

Table 1 Summary of data items to be extracted	
Content	**Data items**

Study details	Study title, author, publication date, study design
Participant characteristics	Age, gender, co-morbidities
Index test	Diagnostic investigations (investigations (imaging, laboratory test, biopsies and neurophysiology)
Reference standard	Comparator test against the diagnostic investigations
Diagnostic accuracy data	Sensitivity, specificity, predictive values (PVs) and likelihood ratios (LRs). Diagnostic accuracy data will be entered into 2×2 contingency tables (22).

Assessment of methodological quality

Risk of bias in individual studies

The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool will be applied independently (JM, BB) to assess risk of bias in the included studies. The QUADAS-2 tool was developed as a tool to assess risk of bias in diagnostic accuracy studies. The QUADAS-2 tool consists of four domains: patient selection, index test, reference standard, and flow and timing (23). The tool assesses risk of bias (relating to bias within the study that distorts the primary diagnostic data) and applicability (relating to the extent to which the research study in question is applicable to the systematic review question). Each domain is assessed for risk of bias. Patient selection, index test, reference standard domains are assessed for applicability concerns. Both risk of bias and applicability concerns are used to construct an overall summary judgement of each study, either 'at risk' or 'low risk' (23). Any disagreements between the two reviewers will be discussed initially, and if the disagreement persists it will be brought to the third reviewer for decision (AR).

Confidence in cumulative evidence

Grading of Recommendations, Assessment, Development and Evaluations (GRADE) will be used to assess the level of evidence (24). GRADE has been adapted for it use in diagnostic accuracy research (24). The two reviewers will independently assess each study and assign a level of evidence (high, moderate, low or very low). Six factors will downgrade the level of evidence; study design, risk of bias (informed by QUADAS-2), inconsistency of evidence, indirectness of evidence, imprecision of results and publication bias. Factors resulting in the

level of evidence being upgraded include; dose effect, large estimates of accuracy and residual plausible confounding (24).

Data synthesis

Data synthesis will follow the same process as our previous review (15). Initially, heterogeneity will be explored in study designs, population, comparable diagnostic data, and reference standard to inform the data synthesis approach. If pooling of data is not possible, which is likely based on initial scoping searches, then a narrative synthesis will be conducted.

A narrative synthesis framework, specific to systematic reviews, will be adopted (25). The framework will be modified for the purpose of this study by removing the initial stage of synthesis pertaining to developing a theoretical model of how interventions work, as it is not relevant to diagnostic accuracy studies. The narrative synthesis will consist of the 3 remaining stages: developing a preliminary synthesis of findings of included studies, exploring relationships in the data and assessing the robustness of the synthesis (25).

Summary measures

Primary diagnostic data (sensitivity, specificity, PVs and LRs) will be presented as summary measures. A formula will be used to calculate primary diagnostic data in cases where only raw data are available (26). Summary tables will describe primary diagnostic data in relation to the index test: level of accuracy, discriminatory properties and strength of agreement.

Level of accuracy

To date, there is no clear accepted taxonomy for characterising level of accuracy for sensitivity and specificity (27). Therefore, previous research has informed how levels of accuracy for sensitivity and specificity are described in this study; low (<50%), low/moderate (51-64%), moderate (65-74%), moderate/high (75-84%) and high (>85%) (15, 27, 28).

Discriminatory properties

Positive and negative likelihood ratios (+LR & -LR) will be used in order to describe the discriminatory properties of the index test: conclusive (+LR >10 and -LR <0.1), strong (+LR 5-10 and -LR 0.1-0.2), weak (+LR 2-5 and -LR 0.2-0.5, negligible (+LR 1-2 and -LR 0.5-1) (15, 28, 29).

Strength of agreement

Landis and Koch (1997) developed a grading system using a kappa-type statistic to describe strength of agreement in reliability, which will be adopted in this review: 0: poor, 0-0.21: slight, 0.21-0.40: fair, 0.41-0.60: moderate, 0.61-0.80: substantial and 0.81-1.00: almost perfect (15, 28, 30).

ETHICS AND DISSEMINATION

Ethical approval is not required for this systematic review. Findings will add to the growing body of literature investigating the identification of NP in LBLP. The findings of this review will be published in a peer reviewed journal and presented at pertinent conferences. Finally, the results of this study will be shared with the Spinal Pain Patient Partner Advisor Group at Western University.

DISCUSSION

Uncertainty amongst researchers and clinicians exists when selecting the best diagnostic investigation to identify NP in LBLP. Imprecision in the identification of NP in LBLP can lead to inappropriate and untimely intervention and therefore poses a great risk to patient care. This review aims to address the uncertainty by investigating the diagnostic utility of diagnostic investigations for LBLP. Knowledge of the most appropriate diagnostic investigation will help to inform a clinician's decision-making when identifying NP in LBLP, which will lead to precision management and thus better patient care. However, as identified from the scoping search, heterogeneity is likely in this body of evidence and therefore clinical recommendations may not be possible. Furthermore, due to the exclusion of non-English studies generalisability of findings will be reduced. If recommendations are not possible based on this synthesis, further research recommendations will be made.

Author contributions

JM is a PhD student, lead author and first reviewer, AR is the lead supervisor, DW, NH and TN are co supervisors. BB is the second reviewer. AR is the guarantor of the review. JM led on manuscript development. All the authors contributed to the final manuscript. Data collection be will be conducted by JM, BB and AR. Draft manuscripts will be reviewed by AR, DW, NH and TN. All authors will contribute to the dissemination of the protocol.

Funding

None.

Competing interests

None.

References

1. Hartvigsen J, Hancock MJ, Kongsted A, *et al*. What low back pain is and why we need to pay attention. Lancet2018;**391**:2356–2367.doi:10.1016/S0140-6736(18)30480-X
2. Hill JC, Konstantinou K, Egbewale BE, *et al*. Clinical outcomes among low back pain consulters with referred leg pain in primary care. Spine2011;**36**:2168–75.doi: 10.1097/BRS.0b013e31820712bb
3. Konstantinou K, Hider SL, Jordan JL, *et al*. The impact of low back-related leg pain on outcomes as compared with low back pain alone: a systematic review of the literature. Clin J Pain2013;**29**:644–654.doi:10.1097/AJP.0b013e31826f9a52
4. Liedgens H, Obradovic M, De Courcy J, *et al*. A burden of illness study for NP in Europe. Clin Econ Outcomes Res2016;**8**:113–26.doi: 10.2147/CEOR.S81396
5. Harrison SA, Ogollah R, Dunn KM, *et al*. Prevalence, Characteristics, and Clinical Course of Neuropathic Pain in Primary Care Patients Consulting With Low Back-related Leg Pain. Clin J Pain2020:**36**;813–824.doi:10.1097/AJP.0000000000000879
6. Mouline, DE, Boulanger, A, Clark, AJ, *et al*. Pharmacological Management of Chronic Neuropathic Pain: Revised Consensus Statement from the Canadian Pain Society. Pain Research and Management 2014;**19**:328–35.doi:10.1155/2014/754693.
7. Finnerup NB, Attal, N, Haroutounian, S, *et al*. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet2015;**14**:162–173.doi: 10.1016/S1474-4422(14)70251-0
8. Schlereth, T. Guideline “diagnosis and non interventional therapy of neuropathic pain” of the German Society of Neurology (deutsche Gesellschaft für Neurologie). Neurol Res Pract2020;**16**.doi:10.1186/s42466-020-00063-3
9. National Institute for Health and Care Excellence. Low back pain and sciatica in over 16S: assessment and management (NICE guideline 33),2020. Available: https://www.nice.org.uk/guidance/ng59 [Accessed 8th January 2023].
10. Beith ID, Kemp A, Kenyon J, *et al*. Identifying neuropathic back and leg pain: a cross-sectional study. Pain2011;**152**:1511–6.doi:10.1016/j.pain.2011.02.033
11. Walsh J, Hall T. Classification of low back-related leg pain: do subgroups differ in disability and psychosocial factors?J Man Manip Ther2009;**17**:118–23.doi:10.1179/106698109790824703
12. Verwoerd AJ, Peul WC, Willemsen SP, *et al*. Diagnostic accuracy of history taking to assess lumbosacral nerve root compression. Spine J2014;**14**:2028–37.doi:10.1016/j.spinee.2013.11.049

13. Vroomen P, de Krom MCTFM, Wilmink J, *et al*. Diagnostic value of history and physical examination in patients suspected of lumbosacral nerve root compression. J Neurol Neurosurg Psychiatry2002;**72**:630–4.doi:10.1136/jnnp.72.5.630
14. Freynhagen R, Rolke R, Baron R, *et al*. Pseudoradicular and radicular low-back pain – a disease continuum rather than different entities? answers from quantitative sensory testing. Pain2008;**135**:65–74.doi:10.1016/j.pain.2007.05.004
15. Mistry J, Heneghan NR, Noblet T, *et al*. Diagnostic utility of patient history, clinical examination and screening tool data to identify neuropathic pain in low back related leg pain: a systematic review and narrative synthesis. BMC Musculoskelet Disord 2020a;**21**:532. doi.org/10.1186/s12891-020-03436-6
16. Smart, KM, Blake, C, Staines, A, *et al*. Clinical indicators of 'nociceptive', 'peripheral neuropathic' and 'central' mechanisms of musculoskeletal pain. A Delphi survey of expert clinicians. Manual Therapy2010;**15**:80–87.doi:10.1016/j.math.2009.07.005
17. Mistry J, Falla, D, Noblet, T, *et al.* Clinical indicators to identify neuropathic pain in low back related leg pain: a modified Delphi study. BMC Musculoskelet Disord2020b;**21**:601.doi.org/10.1186/s12891-020-03600-y
18. Finnerup NB, Haroutounian S, Kamerman P, *et al*. Neuropathic pain: an updated grading system for research and clinical practice. Pain2016;**157**:1599–606.doi:10.1097/j.pain.0000000000000492
19. van Tulder M, Furlan A, Bombardier C, *et al*. Updated method guidelines for systematic reviews in the Cochrane collaboration back review group. Spine 2003;**28**:1290–9.doi:10.1097/01.BRS.0000065484.95996.AF
20. Higgins J, Green S. *Cochrane Handbook for systematic reviews of interventions*. The Cochrane Collaboration, 2011.
21. Young T, Hopewell S. Methods for obtaining unpublished data. Cochrane Database Syst Rev2011:MR000027.doi:10.1002/14651858.MR000027.pub2
22. Whiting PF, Davenport C, Jameson C, *et al*. How well do health professionals interpret diagnostic information? A systematic review. BMJ Open 2015;**5**:e008155.doi:10.1136/bmjopen-2015-008155
23. Whiting PF, Rutjes AW, Westwood ME, *et al*. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;**155**:529–36.doi:10.7326/0003-4819-155-8-201110180-00009
24. Schünemann HJ, Guyatt G, Oxman A. The GRADE approach for diagnostic tests and strategies. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE working group; 2013.

25. Popay J, Roberts H, Sowden A, *et al*. *Guidance on the conduct of narrative synthesis in systematic reviews: a product from the ESRC methods programme*. Lancaster, UK: Lancaster University, 2006.
26. Akobeng AK. Understanding diagnostic tests 1: sensitivity, specificity and predictive values. Acta Paediatr 2007;**96**:338–41.doi:10.1111/j.1651-2227.2006.00180.x
27. Schneiders AG, Sullivan SJ, Hendrick PA, *et al*. The ability of clinical tests to diagnose stress fractures: a systematic review and meta-analysis. J Orthop Sports Phys Ther2012:**42**;760–71.
28. Grødahl LH, Fawcett L, Nazareth M *et al.* Diagnostic utility of patient history and physical examination data to detect spondylolysis and spondylolisthesis in athletes with low back pain: A systematic review. Man Ther2016;**24**:7–17.doi10.1016/j.math.2016.03.011
29. Jaeschke R, Guyatt, G, Sackett, DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. Jama1994;**271**:389–391.doi10.1001/jama.271.5.389
30. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics1977:**33**;159–74. doi:10.2307/2529310

PRISMA-P 2015 Checklist

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

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	69
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	5-24
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	434-439
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	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	441-442
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	94-151
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	153-156
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	175-202
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	222-231
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	248-257
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	259-297
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	249-257
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	247-297
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	270-296
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	270-296
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	299-312
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	345-350
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	338-343
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	338-343
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	345-350
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☒	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	314-335

BMJ Open

Diagnostic utility of diagnostic investigations to identify neuropathic pain in low back related leg pain: protocol for a systematic review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-078392.R2
Article Type:	Protocol
Date Submitted by the Author:	12-Dec-2023
Complete List of Authors:	Mistry, Jai; Western University; St Georges Hospital NHS Foundation Trust Walton, David; Western University, School of Physical Therapy Noblet, Tim; St Georges Hospital NHS Foundation Trust, Physiotherapy Bowling, Benjamin; St Georges Hospital NHS Foundation Trust Heneghan, Nicola; University of Birmingham, School of Sport, Exercise and Rehabilitation Sciences Rushton, Alison; Western University Faculty of Health Sciences, School of Physical Therapy
Primary Subject Heading:	Diagnostics
Secondary Subject Heading:	Research methods, Rehabilitation medicine, Radiology and imaging
Keywords:	Diagnostic Imaging, Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Spine < ORTHOPAEDIC & TRAUMA SURGERY

Diagnostic utility of diagnostic investigations to identify neuropathic pain in low back related leg pain: protocol for a systematic review

Authors

Jai Mistry[1,2], David M Walton[1], Tim Noblet[1,2], Benjamin Bowling[2], Nicola R Heneghan[3], Alison Rushton[1]

Affiliations

[1] School of Physical Therapy, Faculty of Health Sciences, Western University, London, ON, Canada

[2] St Georges Hospital NHS Foundation Trust, London, UK

[3] School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences, University of Birmingham, Birmingham, UK

Correspondence to:

Jai Mistry

jmistr22@uwo.ca

Word count: 3108

Keywords

Neuropathic pain, leg pain, diagnostic utility, diagnostic investigations

ABSTRACT

Introduction

Neuropathic pain in low back-related leg pain has gained increasing interest in contemporary research. Identification of neuropathic pain in low back-related leg pain is essential to inform precision management. Diagnostic investigations are commonly used to identify neuropathic pain in low back-related leg pain; yet the diagnostic utility of these investigations is unknown. The aim of this systematic review is to investigate the diagnostic utility of diagnostic investigations to identify neuropathic pain in low back-related leg pain.

Methods and analysis

This protocol has been designed and reported in accordance with the Cochrane Handbook for Diagnostic Test Accuracy studies, Centre for Reviews and Dissemination and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols checklist, respectively. The search strategy will involve two independent reviewers searching electronic databases (CINAHL, EMBASE, MEDLINE, Web of Science, Cochrane Library, AMED, Pedro), key journals (*Spine, The Clinical Journal of Pain*, *PAIN*, *European Journal of Pain*, *The Journal of Pain*, *Musculoskeletal Science and Practice*) and grey literature (British National Bibliography for report literature, OpenGrey, EThOS) from inception to 31st July 2023 to identify studies. Studies evaluating the diagnostic accuracy of diagnostic investigation to identify neuropathic pain in patients with low back-related leg pain will be eligible, studies not written in English will be excluded. The reviewers will extract the data from included studies, assess risk of bias (Quality Assessment of Diagnostic Accuracy Studies 2) and determine confidence in findings (Grading of Recommendations, Assessment, Development and Evaluation guidelines). Methodological heterogeneity will be assessed to determine if a meta-analysis is possible. If pooling of data is not possible then a narrative synthesis will be done.

Ethics and dissemination

Ethical approval is not required. Findings will be published in a peer reviewed journal, presented at relevant conferences and shared with the Patient Partner Advisor Group at Western University, Canada.

Study registration

PROSPERO, CRD42023438222.

Strengths and limitations of this study

- This review will add to the growing body of literature investigating the identification of neuropathic pain in low back-related leg pain.
- The protocol is reported in line with the Cochrane Handbook for Diagnostic Test Accuracy studies and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols checklist.
- Two independent reviewers will be involved at each stage: screening of eligible studies, data extraction, assessment of risk of bias and overall quality of evidence.
- Known heterogeneity identified from scoping searches suggests that pooling of data may not be possible.
- Language bias may occur due to the exclusion of non-English articles, resulting in reduced generalisability of findings.

INTRODUCTION

Low Back Pain (LBP) is the leading cause of years lived with disability worldwide (1). Individuals with LBP commonly present with associated concomitant leg pain (2). Increased reliance on healthcare resources and poorer health related outcomes have been found in those with low back-related leg pain (LBLP) when compared to those with LBP alone (3). Neuropathic pain in LBLP has gained increasing interest in contemporary research due to the burden it places on the individual and wider society (4). Neuropathic pain is commonly reported in patients with LBLP with prevalence estimates ranging between 48-74% (5). Identification of neuropathic pain in LBLP is essential as international treatment recommendations (pharmacological, invasive procedures) differ for those with LBLP and neuropathic pain (sciatica) compared to those with LBLP alone (6-9). The primary issue concerning the identification of neuropathic pain in LBLP is the absence of a gold standard (e.g., test, battery of tests, investigations etc) and an accepted reference standard to inform diagnosis.

Various methods have been employed to identify neuropathic pain in LBLP including self-report screening tools (10,11), clusters of patient history and physical testing items (12,13) and diagnostic investigations (e.g imaging) (14). A recent systematic review investigated the diagnostic utility of clinical investigations (patient history, clinical examination and screening tool data) to identify neuropathic pain in LBLP (15). The diagnostic utility of diagnostic investigations, defined as any instrumented-based diagnostic test (e.g. imaging, laboratory test, biopsies and neurophysiology) was not included in this review. Low to moderate level evidence was identified in support of the Standardised Evaluation of Pain (StEP) tool and a cluster of eight assessment items (age: 16-40 years, duration of disease <15 days, presence of paroxysmal pain, pain worse in leg than back, typical dermatomal distribution, worse on coughing/sneezing/straining, finger to floor distance ≥25 cm and presence of paresis) (15). Indirectness, in the included studies was identified due to the large variation in terminology used to define neuropathic pain in LBLP. Furthermore, heterogeneity of reference standards was evident (including expert opinion, imaging and surgery), therefore the primary diagnostic data must be interpreted with caution.

Consensus studies have been conducted in response to the uncertainty highlighted in contemporary research. An expert derived list of clinical indicators was initially developed by Smart *et al* (16) to identify neuropathic pain mechanisms in musculoskeletal pain, and this list was developed further following an updated study focusing on the identification of neuropathic pain in LBLP (17). Findings revealed a list of eight clinical indicators that are

proposed to increase the index of suspicion for the presence of neuropathic pain in LBLP (17). Stronger recommendations would require further support for diagnostic utility of these indicators. Therefore, a reference standard is needed, against which the clinical indicators can be tested. The International Association for the Study of Pain (IASP) Special Interest Group on Neuropathic Pain (NeuPSIG) proposed a grading system, (revised in 2016), to guide decisions based on the level of certainty (possible, probable, and definite) with which neuropathic pain can be determined in an individual. In order to satisfy the 'definite' criteria, diagnostic investigation/s confirming a lesion or disease of the somatosensory nervous system are required, alongside history and examination findings (18). Diagnostic investigations have been defined by IASP as any instrumented-based diagnostic test intended to identify a lesion or disease of the somatosensory nervous system (imaging, laboratory test, biopsies and neurophysiology) (18). However, it is unclear what diagnostic investigations or combination of such should be used in the case of diagnosis of neuropathic pain for LBLP. The aforementioned diagnostic investigations when placed in a clinical pathway are usually placed at the end following history taking and physical examination. The results of these investigations can increase the clinicians index of suspicion that neuropathic pain is present and therefore aid the decision making regarding onward management.

This systematic review will investigate the diagnostic utility of diagnostic investigations in the identification of neuropathic pain in LBLP. Diagnostic investigations will be the index test and compared against a reference standard (including surgery, expert opinion, assessment findings and diagnostic investigations).

Aim

To synthesise evidence investigating the diagnostic utility of diagnostic investigations to identify neuropathic pain in LBLP.

METHOD AND ANALYSIS

This systematic review protocol has been designed and reported in line with The Cochrane Handbook for Diagnostic Test Accuracy studies, Centre for Reviews and Dissemination (CRD, 2009) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) checklist. A previous systematic review, conducted by the same research team, has informed the methods of this protocol (15).

Patient and public involvement

Patients and the public have informed the conception of this review as part of an existing programme of research related to lumbar spinal surgery for low back related leg pain. The study was proposed to the spinal pain research Patient Partner Advisory Group in the School of Physical Therapy at Western University, Canada. Following completion of the systematic review the results will be presented back to the same group to discuss the findings and to compare them to their own experiences. These discussions may lead to the to the development of future research projects.

Eligibility criteria

Types of studies

Any study design will be considered for inclusion if evaluating diagnostic accuracy of diagnostic investigations to identify neuropathic pain in LBLP. Studies must include diagnostic accuracy data (specificity, sensitivity, likelihood ratios (LRs) and predictive values (PVs)). Diagnostic investigations do not include physical examination tests such as the straight leg raise or slump test.

Participants

Studies evaluating diagnostic accuracy of diagnostic investigations in adult patients (age >18 years) with LBLP.

Index test

The index test investigation consisted of diagnostic investigations. Diagnostic investigations will be defined as any instrumented-based diagnostic test intended to identify a lesion or disease of the somatosensory nervous system (imaging, laboratory test, biopsies and neurophysiology (18).

Target condition

Diagnostic studies were included if the aim of the diagnostic test was to identify neuropathic pain in LBLP.

Reference standards

We included studies where the diagnostic investigation was compared to a reference standard including: 1) Surgery, 2) Diagnostic investigations, 3) Expert opinion, 4) Subjective/Objective examination items.

Studies not written in English will be excluded.

Search methods for identification of studies

Electronic searches

Each electronic database (CINAHL, EMBASE, MEDLINE, Web of Science, Cochrane Library, AMED and Pedro) will be searched from database inception to 31st July 2023 using database specific search strategies. There will be no geographical restriction. The search strategy was developed by the lead author (JM) and reviewed by a specialist librarian at Western University and co-authors to ensure quality. The search strategy has been informed by a previous published review by Mistry et al (15) with previously used key terms patient history, clinical examination and screening tools replaced with diagnostic investigations (imaging, laboratory test, biopsies and neurophysiology). See MEDLINE search strategy in box 1, search strategy was adapted for other databases and resources (supplementary file 1).

Box 1: MEDLINE OvidSP search strategy 1948 – 31st July 2023

1. diagnostic accuracy.mp. or "Sensitivity and Specificity"/
2. diagnostic utility.mp.
3. exp "Reproducibility of Results"/ or diagnostic reliability.mp.
4. 1 or 2 or 3
5. diagnostic investigations.mp.
6. diagnostic imaging.mp. or exp Diagnostic Imaging/
7. exp Magnetic Resonance Imaging/ or exp Diffusion Magnetic Resonance Imaging/ or imaging.mp.
8. exp Neurophysiology/ or neurophysiology.mp.
9. nerve conduction test.mp. or exp Neural Conduction/
10. exp Biopsy/ or skin biopsy.mp.
11. exp Genetic Testing/ or genetic test.mp.
12. exp Tomography, X-Ray Computed/
13. laboratory test*.mp. or exp Clinical Laboratory Techniques/
14. Electrophysiology/ or electrophysiology.mp.
15. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 4 and 15
17. neuropathic pain.mp. or exp Neuralgia/
18. radicular.mp. or exp Radiculopathy/ or exp Intervertebral Disc Displacement/
19. exp Spinal Nerve Roots/ or nerve root*.mp.
20. radicular pain.mp.
21. 17 or 18 or 19 or 20
22. 16 and 21
23. low back pain.mp. or exp Back Pain/ or exp Low Back Pain/
24. exp Sciatica/ or low back related leg pain.mp.
25. LBP.mp.
26. LBLP.mp.
27. 23 or 24 or 35 or 26
28. 22 and 27

Searching other resources

A manual search of key journals, conducted to compliment the search strategy, will include: `*Spine, The Clinical Journal of Pain*, *PAIN*, *European Journal of Pain*, *The Journal of Pain* and *Musculoskeletal Science and Practice*. Reference lists of included studies and the Cochrane Back Review Group will be reviewed to identify additional eligible studies. Finally, grey literature will be reviewed, using key sources including British National Bibliography for report literature, OpenGrey and EThOS.

Data collection and analysis

Selection of studies

The selection of relevant articles will commence with independent screening by the two review authors (JM, BB). Initially, titles and abstracts will be screened against the eligibility criteria. Studies will be categorised into included, excluded (clearly irrelevant) and unsure groups (19). Full texts will be retrieved for studies that may meet the eligibility criteria and independently reviewed by the two review authors. Included studies must be agreed by both review authors, and any unresolved disagreements will be brought to a third author for decision (AR). Agreement between review authors will be analysed using the kappa statistic at title/abstract screening stage and full-text screening stage (20).

Data extraction and management

Data will be extracted independently by the two reviewers. A customised data extraction form, piloted and employed in our previous systematic review (15), will be used. The third reviewer (AR) will mediate any disagreement in data extraction between the two review authors. Data items to be extracted from the included studies are summarised in Table 1. If data items are not available, study authors will be contacted via email (21). An initial email will be sent to study authors to request for missing information if no response is received after 2 weeks a second reminder email will be sent (21). Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia, www.covidence.org) will be used to manage citations, identify and remove duplicates and to store abstracts and full texts.

Table 1 Summary of data items to be extracted	
Content	**Data items**

Study details	Study title, author, publication date, study design
Participant characteristics	Age, gender, co-morbidities
Index test	Diagnostic investigations (investigations (imaging, laboratory test, biopsies and neurophysiology)
Reference standard	Comparator test against the diagnostic investigations
Diagnostic accuracy data	Sensitivity, specificity, predictive values (PVs) and likelihood ratios (LRs). Diagnostic accuracy data will be entered into 2×2 contingency tables (22).

Assessment of methodological quality

Risk of bias in individual studies

The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool will be applied independently (JM, BB) to assess risk of bias in the included studies. The QUADAS-2 tool was developed as a tool to assess risk of bias in diagnostic accuracy studies. The QUADAS-2 tool consists of four domains: patient selection, index test, reference standard, and flow and timing (23). The tool assesses risk of bias (relating to bias within the study that distorts the primary diagnostic data) and applicability (relating to the extent to which the research study in question is applicable to the systematic review question). Each domain is assessed for risk of bias. Patient selection, index test, reference standard domains are assessed for applicability concerns. Both risk of bias and applicability concerns are used to construct an overall summary judgement of each study, either 'at risk' or 'low risk' (23). Any disagreements between the two reviewers will be discussed initially, and if the disagreement persists it will be brought to the third reviewer for decision (AR).

Data synthesis

Data synthesis will follow the same process as our previous review (15). Initially, heterogeneity will be explored in study designs, population, comparable diagnostic data, and reference standard to inform the data synthesis approach. If pooling of data is not possible, which is likely based on initial scoping searches, then a narrative synthesis will be conducted.

A narrative synthesis framework, specific to systematic reviews, will be adopted (24). The framework will be modified for the purpose of this study by removing the initial stage of synthesis pertaining to developing a theoretical model of how interventions work, as it is not relevant to diagnostic accuracy studies. The narrative synthesis will consist of the 3 remaining stages: developing a preliminary synthesis of findings of included studies, exploring relationships in the data and assessing the robustness of the synthesis (24).

Summary measures

Primary diagnostic data (sensitivity, specificity, PVs and LRs) will be presented as summary measures. A formula will be used to calculate primary diagnostic data in cases where only raw data are available (25). Summary tables will describe primary diagnostic data in relation to the index test: level of accuracy, discriminatory properties and strength of agreement.

Level of accuracy

To date, there is no clear accepted taxonomy for characterising level of accuracy for sensitivity and specificity (26). Therefore, previous research has informed how levels of accuracy for sensitivity and specificity are described in this study; low (<50%), low/moderate (51-64%), moderate (65-74%), moderate/high (75-84%) and high (>85%) (15, 27, 28).

Discriminatory properties

Positive and negative likelihood ratios (+LR & -LR) will be used in order to describe the discriminatory properties of the index test: conclusive (+LR >10 and -LR <0.1), strong (+LR 5-10 and -LR 0.1-0.2), weak (+LR 2-5 and -LR 0.2-0.5, negligible (+LR 1-2 and -LR 0.5-1) (15, 27, 28).

Strength of agreement

Landis and Koch (1997) developed a grading system using a kappa-type statistic to describe strength of agreement in reliability, which will be adopted in this review: 0: poor, 0-0.21: slight, 0.21-0.40: fair, 0.41-0.60: moderate, 0.61-0.80: substantial and 0.81-1.00: almost perfect (15, 27, 29).

Confidence in cumulative evidence

Grading of Recommendations, Assessment, Development and Evaluations (GRADE) will be used to assess the level of evidence (30). GRADE has been adapted for it use in diagnostic accuracy research (30). The two reviewers will independently assess each study and assign a level of evidence (high, moderate, low or very low). Six factors will downgrade the level of evidence; study design (cross sectional/longitudinal studies will not be analysed separately

to case control studies), risk of bias (informed by QUADAS-2), inconsistency of evidence, indirectness of evidence, imprecision of results and publication bias. Factors resulting in the level of evidence being upgraded include; dose effect, large estimates of accuracy and residual plausible confounding (30).

ETHICS AND DISSEMINATION

Ethical approval is not required for this systematic review. Findings will add to the growing body of literature investigating the identification of neuropathic pain in LBLP. The findings of this review will be published in a peer reviewed journal and presented at pertinent conferences. Finally, the results of this study will be shared with the Spinal Pain Patient Partner Advisor Group at Western University.

DISCUSSION

Uncertainty amongst researchers and clinicians exists when selecting the best diagnostic investigation to identify neuropathic pain in LBLP. Imprecision in the identification of neuropathic pain in LBLP can lead to inappropriate and untimely intervention and therefore poses a great risk to patient care. This review aims to address the uncertainty by investigating the diagnostic utility of diagnostic investigations for LBLP. Knowledge of the most appropriate diagnostic investigation will help to inform a clinician's decision-making when identifying neuropathic pain in LBLP, which will lead to precision management and thus better patient care. However, as identified from the scoping search, heterogeneity is likely in this body of evidence and therefore clinical recommendations may not be possible. Furthermore, due to the exclusion of non-English studies generalisability of findings will be reduced. Case control design studies have been included in this review in order to capture all relevant studies however this design is associated with a higher risk of bias. If recommendations are not possible based on this synthesis, further research recommendations will be made.

Contributors

JM is a PhD student, lead author and first reviewer, AR is the lead supervisor, DW, NH and TN are co supervisors. BB is the second reviewer. AR is the guarantor of the review. JM led on manuscript development. All the authors contributed to the final manuscript. Data collection be will be conducted by JM, BB and AR. Draft manuscripts will be reviewed by AR, DW, NH and TN. All authors will contribute to the dissemination of the protocol.

Funding

None.

Competing interests

None.

References

1. Hartvigsen J, Hancock MJ, Kongsted A, *et al*. What low back pain is and why we need to pay attention. Lancet2018;**391**:2356–2367.doi:10.1016/S0140-6736(18)30480-X
2. Hill JC, Konstantinou K, Egbewale BE, *et al*. Clinical outcomes among low back pain consulters with referred leg pain in primary care. Spine2011;**36**:2168–75.doi: 10.1097/BRS.0b013e31820712bb
3. Konstantinou K, Hider SL, Jordan JL, *et al*. The impact of low back-related leg pain on outcomes as compared with low back pain alone: a systematic review of the literature. Clin J Pain2013;**29**:644–654.doi:10.1097/AJP.0b013e31826f9a52
4. Liedgens H, Obradovic M, De Courcy J, *et al*. A burden of illness study for NP in Europe. Clin Econ Outcomes Res2016;**8**:113–26.doi: 10.2147/CEOR.S81396
5. Harrison SA, Ogollah R, Dunn KM, *et al*. Prevalence, Characteristics, and Clinical Course of Neuropathic Pain in Primary Care Patients Consulting With Low Back-related Leg Pain. Clin J Pain2020:**36**;813–824.doi:10.1097/AJP.0000000000000879
6. Mouline, DE, Boulanger, A, Clark, AJ, *et al*. Pharmacological Management of Chronic Neuropathic Pain: Revised Consensus Statement from the Canadian Pain Society. Pain Research and Management 2014;**19**:328–35.doi:10.1155/2014/754693.
7. Finnerup NB, Attal, N, Haroutounian, S, *et al*. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet2015;**14**:162–173.doi: 10.1016/S1474-4422(14)70251-0
8. Schlereth, T. Guideline “diagnosis and non interventional therapy of neuropathic pain” of the German Society of Neurology (deutsche Gesellschaft für Neurologie). Neurol Res Pract2020;**16**.doi:10.1186/s42466-020-00063-3
9. National Institute for Health and Care Excellence. Low back pain and sciatica in over 16S: assessment and management (NICE guideline 33),2020. Available: https://www.nice.org.uk/guidance/ng59 [Accessed 8th January 2023].
10. Beith ID, Kemp A, Kenyon J, *et al*. Identifying neuropathic back and leg pain: a cross-sectional study. Pain2011;**152**:1511–6.doi:10.1016/j.pain.2011.02.033
11. Walsh J, Hall T. Classification of low back-related leg pain: do subgroups differ in disability and psychosocial factors?J Man Manip Ther2009;**17**:118–23.doi:10.1179/106698109790824703
12. Verwoerd AJ, Peul WC, Willemsen SP, *et al*. Diagnostic accuracy of history taking to assess lumbosacral nerve root compression. Spine J2014;**14**:2028–37.doi:10.1016/j.spinee.2013.11.049

13. Vroomen P, de Krom MCTFM, Wilmink J, *et al*. Diagnostic value of history and physical examination in patients suspected of lumbosacral nerve root compression. J Neurol Neurosurg Psychiatry2002;**72**:630–4.doi:10.1136/jnnp.72.5.630
14. Freynhagen R, Rolke R, Baron R, *et al*. Pseudoradicular and radicular low-back pain – a disease continuum rather than different entities? answers from quantitative sensory testing. Pain2008;**135**:65–74.doi:10.1016/j.pain.2007.05.004
15. Mistry J, Heneghan NR, Noblet T, *et al*. Diagnostic utility of patient history, clinical examination and screening tool data to identify neuropathic pain in low back related leg pain: a systematic review and narrative synthesis. BMC Musculoskelet Disord 2020a;**21**:532. doi.org/10.1186/s12891-020-03436-6
16. Smart, KM, Blake, C, Staines, A, *et al*. Clinical indicators of 'nociceptive', 'peripheral neuropathic' and 'central' mechanisms of musculoskeletal pain. A Delphi survey of expert clinicians. Manual Therapy2010;**15**:80–87.doi:10.1016/j.math.2009.07.005
17. Mistry J, Falla, D, Noblet, T, *et al.* Clinical indicators to identify neuropathic pain in low back related leg pain: a modified Delphi study. BMC Musculoskelet Disord2020b;**21**:601.doi.org/10.1186/s12891-020-03600-y
18. Finnerup NB, Haroutounian S, Kamerman P, *et al*. Neuropathic pain: an updated grading system for research and clinical practice. Pain2016;**157**:1599–606.doi:10.1097/j.pain.0000000000000492
19. van Tulder M, Furlan A, Bombardier C, *et al*. Updated method guidelines for systematic reviews in the Cochrane collaboration back review group. Spine 2003;**28**:1290–9.doi:10.1097/01.BRS.0000065484.95996.AF
20. Higgins J, Green S. *Cochrane Handbook for systematic reviews of interventions*. The Cochrane Collaboration, 2011.
21. Young T, Hopewell S. Methods for obtaining unpublished data. Cochrane Database Syst Rev2011:MR000027.doi:10.1002/14651858.MR000027.pub2
22. Whiting PF, Davenport C, Jameson C, *et al*. How well do health professionals interpret diagnostic information? A systematic review. BMJ Open 2015;**5**:e008155.doi:10.1136/bmjopen-2015-008155
23. Whiting PF, Rutjes AW, Westwood ME, *et al*. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;**155**:529–36.doi:10.7326/0003-4819-155-8-201110180-00009
24. Popay J, Roberts H, Sowden A, *et al*. *Guidance on the conduct of narrative synthesis in systematic reviews: a product from the ESRC methods programme*. Lancaster, UK: Lancaster University, 2006.
25. Akobeng AK. Understanding diagnostic tests 1: sensitivity, specificity and predictive values. Acta Paediatr 2007;**96**:338–41.doi:10.1111/j.1651-2227.2006.00180.x

26. Schneiders AG, Sullivan SJ, Hendrick PA, *et al*. The ability of clinical tests to diagnose stress fractures: a systematic review and meta-analysis. J Orthop Sports Phys Ther2012:**42**;760–71.
27. Grødahl LH, Fawcett L, Nazareth M *et al.* Diagnostic utility of patient history and physical examination data to detect spondylolysis and spondylolisthesis in athletes with low back pain: A systematic review. Man Ther2016;**24**:7–17.doi10.1016/j.math.2016.03.011
28. Jaeschke R, Guyatt, G, Sackett, DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. Jama1994;**271**:389–391.doi10.1001/jama.271.5.389
29. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics1977:**33**;159–74. doi:10.2307/2529310
30. Schünemann HJ, Guyatt G, Oxman A. The GRADE approach for diagnostic tests and strategies. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE working group; 2013.

MEDLINE OvidSP search strategy 1948 – 31st July 2023

1. diagnostic accuracy.mp. or "Sensitivity and Specificity"/
2. diagnostic utility.mp.
3. exp "Reproducibility of Results"/ or diagnostic reliability.mp.
4. 1 or 2 or 3
5. diagnostic investigation*.mp.
6. diagnostic imaging.mp. or exp Diagnostic Imaging/
7. exp Magnetic Resonance Imaging/ or exp Diffusion Magnetic Resonance Imaging/ or imaging.mp.
8. exp Neurophysiology/ or neurophysiology.mp.
9. nerve conduction test.mp. or exp Neural Conduction/
10. exp Biopsy/ or skin biopsy.mp.
11. exp Genetic Testing/ or genetic test.mp.
12. exp Tomography, X-Ray Computed/
13. laboratory test*.mp. or exp Clinical Laboratory Techniques/
14. Electrophysiology/ or electrophysiology.mp.
15. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 4 and 15
17. neuropathic pain.mp. or exp Neuralgia/
18. radicular.mp. or exp Radiculopathy/ or exp Intervertebral Disc Displacement/
19. exp Spinal Nerve Roots/ or nerve root*.mp.
20. radicular pain.mp.
21. 17 or 18 or 19 or 20
22. 16 and 21
23. low back pain.mp. or exp Back Pain/ or exp Low Back Pain/
24. exp Sciatica/ or low back related leg pain.mp.
25. LBP.mp.
26. LBLP.mp.
27. 23 or 24 or 35 or 26
28. 22 and 27

EMBASE

1. diagnostic accuracy.mp. or exp diagnostic accuracy/
2. diagnostic utility.mp. or exp diagnostic value/
3. 1 or 2
4. diagnostic investigation*.mp.
5. diagnostic imaging.mp. or exp diagnostic imaging/

6. magnetic resonance imaging.mp. or exp nuclear magnetic resonance imaging/
7. neurophysiology.mp. or exp neurophysiology/
8. nerve conduction test*.mp.
9. skin biopsy.mp. or exp skin biopsy/
10. exp laboratory test/ or laboratory test*.mp.
11. exp nervous system electrophysiology/ or exp electrophysiology/ or electrophysiology.mp.
12. exp genetic analysis/ or genetic test*.mp.
13. X-ray.mp. or exp X ray/
14. computed tomography.mp. or exp computer assisted tomography/
15. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 3 and 15
17. neuropathic pain.mp. or exp neuropathic pain/
18. exp radicular pain/ or radicular.mp.
19. radiculopathy.mp. or exp radiculopathy/
20. nerve root.mp. or exp "nerve root"/
21. 17 or 18 or 19 or 20
22. 16 and 21
23. low back pain.mp. or exp low back pain/
24. sciatica.mp. or exp sciatica/
25. LBP.mp.
26. LBLP.mp.
27. low back related leg pain.mp.
28. 23 or 24 or 25 or 26 or 27
29. 22 and 28

CINAHL

1. "diagnostic accuracy"
2. "diagnostic utility"
3. "sensitivity and specificity"
4. 1 or 2 or 3
5. (MH "Diagnostic Tests, Routine+") OR "diagnostic investigation*"
6. (MH "Diagnostic Imaging+") OR (MH "Imaging, Three-Dimensional+") OR (MH "Image Processing, Computer Assisted+") OR (MH "Radiographic Image Interpretation, Computer-Assisted+")
7. (MH "Magnetic Resonance Imaging+") OR "magnetic resonance imaging or mri or mri scan"

8. (MH "Neurophysiology") OR "neurophysiology"
9. (MH "Nerve Conduction Studies") OR (MH "Neural Conduction") OR "nerve conduction study or nerve conduction velocity or nerve conduction test"
10. (MH "Biopsy+") OR "skin biopsy"
11. (MH "Genetic Screening+") OR (MH "Genetics, Medical+") OR "genetic testing"
12. (MH "Tomography, X-Ray Computed+") OR (MH "Tomography, X-Ray+") OR (MH "X-Ray Film") OR "x-ray"
13. "ct scan or computed tomography or cat scan"
14. (MH "Diagnosis, Laboratory+") OR "laboratory tests or laboratory diagnostic or clinical laboratory"
15. "electrophysiologic testing"
16. (MH "Electrophysiology+") OR "electrophysiology"
17. 5 or 6 or 7 or 8 or 9 or 19 or 11 or 12 or 13 or 14 or 15 or 16
18. 4 and 17
19. "neuropathic pain"
20. "radicular pain"
21. (MH "Intervertebral Disk Displacement") OR (MH "Intervertebral Disk+") OR "radiculopathy or sciatica or disc"
22. (MH "Spinal Nerve Roots+") OR "nerve root*"
23. 19 or 20 or 21 or 22
24. 18 and 23
25. (MH "Back Pain+") OR "low back pain or lumbar pain or lumbar spine pain or non specific low back pain"
26. (MH "Sciatic Nerve+") OR (MH "Sciatica") OR "sciatica or sciatic neuralgia or sciatic neuropathy or lumbar radiculopathy"
27. "low back related leg pain"
28. "LBP"
29. "LBLP"
30. 25 or 26 or 27 or 28 or 29
31. 24 and 30

Web of Science

1. TS=(diagnostic accuracy)
2. TS=(diagnostic utility)
3. 1 or 2
4. TS=(diagnostic investigation*)
5. TS=(diagnostic imaging)

6. (TS=(Magnetic resonance imaging)) OR TS=(MRI)
7. ((TS=(neurophysiology)) OR TS=(nerve conduction test*)) OR TS=(NCS)
8. TS=(skin biopsy)
9. TS=(genetic test*)
10. TS=(X-ray)
11. (TS=(CT)) OR TS=(computed tomography)
12. TS=(laboratory test*)
13. TS=(electrophysiology)
14. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 3 and 14
16. TS=(neuropathic pain)
17. (TS=(radicular pain)) OR TS=(radiculopathy)
18. TS=(nerve root*)
19. TS=(Intervertebral Disc)
20. 16 or 17 or 18 or 19
21. 15 and 21
22. (TS=(low back pain)) OR TS=(LBP)
23. TS=(sciatica)
24. (TS=(low back related leg pain)) OR TS=(LBLP)
25. 22 or 23 or 24
26. 21 and 25

Cochrane Library

1. Diagnostic accuracy OR diagnostic reliability OR diagnostic utility: ti, ab, kw
2. diagnostic investigation*: ti, ab, kw
3. MeSH descriptor: (diagnostic imaging)
4. MeSH descriptor: (magnetic resonance imaging)
5. MeSH descriptor: (neurophysiology)
6. MeSH descriptor: (nerve conduction test*)
7. MeSH descriptor: (biopsy)
8. MeSH descriptor: (genetic testing)
9. MeSH descriptor: (Computed Tomography Scanner, X-ray)
10. MeSH descriptor: (Laboratory Test, Clinical)
11. MeSH descriptor: (electrophysiology)
12. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. 1 and 12
14. MeSH descriptor: (neuropathic pain)

15. MeSH descriptor: (radiculopathy)
16. Radicular pain: ti, ab, kw
17. MeSH descriptor: (nerve root, spinal)
18. 14 or 15 or 16 or 17
19. 13 and 18
20. MeSH descriptor: (Low back pain)
21. MeSH descriptor: (sciatica)
22. Low back related leg pain OR LBLP: ti, ab, kw
23. 20 or 21 or 22
24. 19 and 23

AMED

1. TX 1. (diagnostic accuracy OR diagnostic utility) AND (diagnostic imaging OR magnetic resonance imaging OR neurophysiology OR nerve conduction test* OR biopsy OR genetic testing OR Computed Tomography* OR X ray OR laboratory test OR electrophysiology) AND (neuropathic pain OR radicular pain OR radiculopathy OR nerve root) AND (low back related leg pain OR LBLP OR LBP OR low back pain OR sciatica)
2.

PEDro

1. ("diagnostic accuracy" or diagnostic utility) AND ("diagnostic imaging" or "magnetic resonance imaging" or "neurophysiology" or "nerve conduction test*" or "biopsy" or "genetic testing" or "Computed Tomography*" or "X-ray" or "laboratory test" or "electrophysiology") AND ("neuropathic pain" or "radicular pain" or "radiculopathy" or "nerve root*") AND ("low back related leg pain" or "LBLP" or "LBP" or "low back pain" or "sciatica").

   Key terms searched separately and collectively

Spine/The Clinical Journal of Pain/PAIN/European Journal of Pain/The Journal of Pain/ Musculoskeletal Science and Practice

1. (diagnostic accuracy OR diagnostic utility) AND (diagnostic imaging OR magnetic resonance imaging OR neurophysiology OR nerve conduction test* OR biopsy OR genetic testing OR Computed Tomography* OR X ray OR laboratory test OR electrophysiology) AND (neuropathic pain OR radicular pain OR radiculopathy OR nerve root) AND (low back related leg pain OR LBLP OR LBP OR low back pain OR sciatica)

Cochrane Back Review Group

Search text contents

1. (diagnostic accuracy OR diagnostic utility) AND (diagnostic imaging OR magnetic resonance imaging OR neurophysiology OR nerve conduction test* OR biopsy OR genetic testing OR Computed Tomography* OR X ray OR laboratory test OR electrophysiology) AND (neuropathic pain OR radicular pain OR radiculopathy OR nerve root) AND (low back related leg pain OR LBLP OR LBP OR low back pain OR sciatica)

British National Bibliography for report literature

1. (diagnostic accuracy OR diagnostic utility) AND (diagnostic imaging OR magnetic resonance imaging OR neurophysiology OR nerve conduction test* OR biopsy OR genetic testing OR Computed Tomography* OR X ray OR laboratory test OR electrophysiology) AND (neuropathic pain OR radicular pain OR radiculopathy OR nerve root) AND (low back related leg pain OR LBLP OR LBP OR low back pain OR sciatica)

OpenGrey

1. (diagnostic accuracy OR diagnostic utility) AND (diagnostic imaging OR magnetic resonance imaging OR neurophysiology OR nerve conduction test* OR biopsy OR genetic testing OR Computed Tomography* OR X ray OR laboratory test OR electrophysiology) AND (neuropathic pain OR radicular pain OR radiculopathy OR nerve root) AND (low back related leg pain OR LBLP OR LBP OR low back pain OR sciatica)

EThOS

1. (diagnostic accuracy OR diagnostic utility) AND (diagnostic imaging OR magnetic resonance imaging OR neurophysiology OR nerve conduction test* OR biopsy OR genetic testing OR Computed Tomography* OR X ray OR laboratory test OR electrophysiology) AND (neuropathic pain OR radicular pain OR radiculopathy OR nerve root) AND (low back related leg pain OR LBLP OR LBP OR low back pain OR sciatica)

PRISMA-P 2015 Checklist

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

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	69
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	5-24
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	434-439
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	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	441-442
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	94-151
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	153-156
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	175-202
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	222-231
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	248-257
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	259-297
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	249-257
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	247-297
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	270-296
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	270-296
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	299-312
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	345-350
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	338-343
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	338-343
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	345-350
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☒	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	314-335