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

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| 3<br>⊿   | 1  | Diagnostic utility of diagnostic investigations to identify neuropathic pain in low back   |
| 5        | 2  | related leg pain: protocol for a systematic review   |
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| 50       | 30 |  |
| 51<br>52 | 31 | Neuropathic pain, leg pain, diagnostic utility, diagnostic investigations  |
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|----------|----|---|
| 3<br>4   | 37 | ABSTRACT  |
| 5        | 38 |   |
| 6<br>7   | 39 | Introduction  |
| 8        | 40 | Neuropathic pain (NP) in low back-related leg pain (LBLP) has gained increasing interest in       |
| 9<br>10  | 41 | contemporary research. Identification of NP in LBLP is essential to inform precision              |
| 11<br>12 | 42 | management. Diagnostic investigations are commonly used to identify NP in LBLP; yet the           |
| 13       | 43 | diagnostic utility of these investigations is unknown. The aim of this systematic review will     |
| 14<br>15 | 44 | therefore be to investigate the diagnostic utility of diagnostic investigations to identify NP in |
| 16       | 45 | LBLP.   |
| 17<br>18 | 46 | Methods and analysis  |
| 19       | 47 | This protocol has been designed and is reported in accordance with the Cochrane                   |
| 20<br>21 | 48 | Handbook for Diagnostic Test Accuracy studies, Centre for Reviews and Dissemination               |
| 22       | 49 | (CRD, 2009) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-           |
| 23<br>24 | 50 | Protocols (PRISMA-P) checklist respectively. The search strategy will involve two                 |
| 25<br>26 | 51 | independent reviewers searching electronic databases (CINAHL, EMBASE, MEDLINE, Web                |
| 20<br>27 | 52 | of Science, Cochrane Library, AMED and Pedro), key journals and grey literature to identify       |
| 28<br>20 | 53 | studies that meet the eligibility criteria. Studies evaluating the diagnostic accuracy of         |
| 30       | 54 | diagnostic investigation to identify NP in patients with LBLP will be eligible. The reviewers     |
| 31<br>32 | 55 | will extract the data from included studies, assess risk of bias (Quality Assessment of           |
| 33       | 56 | Diagnostic Accuracy Studies 2) and determine confidence in findings (Grading of                   |
| 34<br>35 | 57 | Recommendations, Assessment, Development and Evaluation guidelines). Methodological               |
| 36<br>27 | 58 | heterogeneity will be assessed to determine if a meta-analysis is possible. If pooling of data    |
| 38       | 59 | is not possible then a narrative synthesis will be conducted.                                     |
| 39<br>40 | 60 | Ethics and dissemination  |
| 41       | 61 | Ethical approval is not required. Findings will be published in a peer reviewed journal,          |
| 42<br>43 | 62 | presented at relevant conferences and shared with the Spinal Pain Patient Partner Advisor         |
| 44       | 63 | Group at Western University, Canada.  |
| 45<br>46 | 64 |   |
| 47<br>49 | 65 | PROSPERO registration number: CRD42023438222  |
| 48<br>49 | 66 |   |
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| 2        | 74 | ARTICLE SUMMARY  |
| 4<br>5   | 75 |  |
| 6<br>7   | 76 | Strengths and Limitations of this study  |
| 8        | 77 |  |
| 9<br>10  | 78 | • This review will add to the growing body of literature investigating the identification of |
| 11       | 79 | NP in LBLP.  |
| 12<br>13 | 80 | The protocol is reported in line with the Cochrane Handbook for Diagnostic Test              |
| 14<br>15 | 81 | Accuracy studies and the Preferred Reporting Items for Systematic Reviews and                |
| 15<br>16 | 82 | Meta-Analysis-Protocols (PRISMA-P) checklist.  |
| 17<br>18 | 83 | Two independent reviewers will be involved at each stage: screening of eligible              |
| 19       | 84 | studies, data extraction, assessment of risk of bias and overall quality of evidence.        |
| 20<br>21 | 85 | Known heterogeneity identified from the scoping review suggests pooling of data will         |
| 22       | 86 | not be possible.   |
| 23<br>24 | 87 | English language bias may occur due to the exclusion of non-English articles                 |
| 25<br>26 | 88 | resulting in reduced generalisability of findings.   |
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#### 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  $\geq 25$  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

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| 3<br>4   | 127 | require further support for diagnostic utility of these indicators. Therefore, an reference      |
| 5        | 128 | standard is needed, against which the clinical indicators can be tested. The International       |
| 6<br>7   | 129 | Association for the Study of Pain (IASP) Special Interest Group on Neuropathic Pain              |
| 8        | 130 | (NeuPSIG) proposed a grading system, (revised in 2016), to guide decisions based on the          |
| 9<br>10  | 131 | level of certainty (possible, probable, and definite) with which NP can be determined in an      |
| 11       | 132 | individual. In order to satisfy the 'definite' criteria, diagnostic investigation/s confirming a |
| 12<br>13 | 133 | lesion or disease of the somatosensory nervous system are required, alongside history and        |
| 14<br>15 | 134 | examination findings (18). However, it is unclear what diagnostic investigations or              |
| 15<br>16 | 135 | combination of such should be used in the case of diagnosis of NP for LBLP.                      |
| 17<br>18 | 136 |  |
| 19       | 137 | Aim  |
| 20<br>21 | 138 |  |
| 22       | 139 | To synthesise evidence investigating the diagnostic utility of diagnostic investigations to      |
| 23<br>24 | 140 | identify NP in LBLP.   |
| 25<br>26 | 141 |  |
| 20<br>27 | 142 | МЕТНОД   |
| 28<br>29 | 143 | This systematic review protocol has been designed and reported in line with The Cochrane         |
| 30       | 144 | Handbook for Diagnostic Test Accuracy studies, Centre for Reviews and Dissemination              |
| 31<br>32 | 145 | (CRD, 2009) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis-          |
| 33<br>34 | 146 | Protocols (PRISMA-P) checklist. A previous systematic review, conducted by the same              |
| 34<br>35 | 147 | research team, has informed the methods of this protocol (15).                                   |
| 36<br>37 | 148 |  |
| 38       | 149 | Patient and public involvement   |
| 39<br>40 | 150 | Patients and the public have informed the conception of this review as part of an existing       |
| 41<br>42 | 151 | programme of research related to lumbar spinal surgery for low back related leg pain.            |
| 42<br>43 | 152 |  |
| 44<br>45 | 153 | Eligibility criteria   |
| 46       | 154 | Eligibility criteria are reported in line with the Sample, Phenomenon of Interest, Design,       |
| 47<br>48 | 155 | Evaluation and Research type (SPIDER) tool (19).   |
| 49<br>50 | 156 | <ul> <li>Sample: adult patients (age &gt;18 years) with LBLP.</li> </ul>                         |
| 50<br>51 | 157 | Phenomenon of Interest: NP in LBLP.  |
| 52<br>53 | 158 | Design: any study design using primary diagnostic accuracy data (specificity,                    |
| 55<br>54 | 159 | sensitivity, likelihood ratios (LRs) and predictive values (PVs)).                               |
| 55<br>56 | 160 | Evaluation: studies evaluating diagnostic accuracy of diagnostic investigations to               |
| 57       | 161 | identify NP in LBLP. Diagnostic investigations will be defined as any instrumented-              |
| 58<br>59 | 162 | based diagnostic test intended to identify a lesion or disease of the somatosensory              |
| 60       |     |  |

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| 1<br>2   |     |   |
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| 3        | 163 | nervous system (imaging, laboratory test, biopsies and neurophysiology (18))                          |
| 4<br>5   | 164 | Diagnostic investigations do not include physical examination tests such as the                       |
| 6<br>7   | 165 | straight leg raise or slump test.   |
| 8        | 166 | Research type: quantitative.  |
| 9<br>10  | 167 | Studies not written in English will be excluded.  |
| 11       | 168 | -   |
| 12<br>13 | 169 | Information sources   |
| 14<br>15 | 170 | Each electronic database (CINAHL, EMBASE, MEDLINE, Web of Science, Cochrane                           |
| 16       | 171 | Library, AMED and Pedro) will be searched from inception to 31 <sup>st</sup> July 2023 using database |
| 17<br>18 | 172 | specific search strategies. There will be no geographical restriction. A manual search of key         |
| 19       | 173 | journals, conducted to compliment the search strategy, will include: `Spine, The Clinical             |
| 20<br>21 | 174 | Journal of Pain, PAIN, European Journal of Pain, The Journal of Pain and Musculoskeletal              |
| 22<br>23 | 175 | Science and Practice. Reference lists of included studies and the Cochrane Back Review                |
| 23       | 176 | Group will be reviewed to identify additional eligible studies. Finally, grey literature will be      |
| 25<br>26 | 177 | reviewed, using key sources including British National Bibliography for report literature,            |
| 27       | 178 | OpenGrey and EThOS.   |
| 28<br>29 | 179 |   |
| 30<br>31 | 180 | Search strategy   |
| 32       | 181 | The search strategy was developed by the lead author (JM) and reviewed by a specialist                |
| 33<br>34 | 182 | librarian at Western University and co-authors to ensure quality. The search strategy has             |
| 35       | 183 | been informed by a previous published review by Mistry et al (15) with previously used key            |
| 36<br>37 | 184 | terms patient history, clinical examination and screening tools replaced with diagnostic              |
| 38<br>30 | 185 | investigations (imaging, laboratory test, biopsies and neurophysiology). See example search           |
| 40       | 186 | strategy in box 1.  |
| 41<br>42 | 187 |   |
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| 2<br>3         |            |  |
| 4              |            |  |
| 5              |            | Box 1: Example of MEDLINE OvidSP search strategy 1948 – Feb 2023   |
| 0<br>7<br>8    |            | <ol> <li>diagnostic accuracy.mp. or "Sensitivity and Specificity"/</li> <li>diagnostic utility mp</li> </ol>       |
| 9              |            | 3. exp "Reproducibility of Results"/ or diagnostic reliability.mp.   |
| 10             |            | 4. 1 or 2 or 3   |
| 11<br>12       |            | 5. diagnostic investigations.mp.   |
| 12             |            | 6. diagnostic imaging.mp. or exp Diagnostic Imaging/   |
| 14             |            | <ol> <li>exp Magnetic Resonance Imaging/ or exp Diffusion Magnetic<br/>Resonance Imaging/ or imaging mp</li> </ol> |
| 15             |            | 8 exp Neurophysiology/ or neurophysiology mp   |
| 16             |            | 9. nerve conduction test.mp. or exp Neural Conduction/   |
| 1/<br>10       |            | 10. exp Biopsy/ or skin biopsy.mp.   |
| 10<br>19       |            | 11. exp Genetic Testing/ or genetic test.mp.   |
| 20             |            | 12. exp Tomography, X-Ray Computed/  |
| 21             |            | 13. laboratory test* mp. or exp Clinical Laboratory Techniques/  |
| 22             |            | 14. Electrophysiology/ or electrophysiology.mp.  |
| 23             |            | 15. 5 01 0 01 7 01 0 01 9 01 10 01 11 01 12 01 13 01 14  |
| 24<br>25       |            | 17 neuropathic pain mp_or exp_Neuralgia/   |
| 26             |            | 18. radicular.mp. or exp Radiculopathy/ or exp Intervertebral Disc   |
| 27             |            | Displacement/  |
| 28             |            | <ol><li>exp Spinal Nerve Roots/ or nerve root*.mp.</li></ol>   |
| 29             |            | 20. radicular pain.mp.   |
| 31             |            | 21. 17 or 18 or 19 or 20   |
| 32             |            | 22. To and 21<br>23. Jow back pain mp, or exp Back Pain/ or exp Low Back Pain/                                     |
| 33             |            | 24 exp Sciatica/ or low back related led pain mp   |
| 34             |            | 25. LBP.mp.  |
| 35             |            | 26. LBLP.mp.   |
| 37             |            | 27. 23 or 24 or 35 or 26   |
| 38             | 100        | 28. 22 and 27  |
| 39             | 188        |  |
| 40             | 189        |  |
| 41<br>42       | 190        | Study records  |
| 43<br>44       | 191        |  |
| 45             | 192        | Data management  |
| 46<br>47       | 193        | Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne,                             |
| 48<br>40       | 194        | Australia, <u>www.covidence.org</u> ) will be used to manage citations, identify and remove                        |
| 49<br>50       | 195<br>106 | duplicates and to store abstracts and full texts.  |
| 57<br>52       | 190        |  |
| 53             | 197        | Selection process  |
| 54             | 198        | The selection of relevant articles will commence with independent screening by the two                             |
| 55<br>56       | 199        | review authors (JM, BB). Initially, titles and abstracts will be screened against the eligibility                  |
| 57             | 200        | criteria. Studies will be categorised into included, excluded (clearly irrelevant) and unsure                      |
| 58<br>59<br>60 | 201        | groups (20). Full texts will be retrieved for studies that may meet the eligibility criteria and                   |
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| 3        | 202 | independently reviewed                           | by the two review authors. Included studies must be agreed by both       |  |
|----------|-----|--|--|--|
| 4<br>5   | 203 | review authors, and any                          | vunresolved disagreements will be brought to a third author for          |  |
| 6        | 204 | decision (AR). Agreeme                           | ent between review authors will be analysed using the kappa statistic    |  |
| 7<br>8   | 205 | at title/abstract screenin                       | ig stage and full-text screening stage (21).                             |  |
| 9<br>10  | 206 |  |  |  |
| 11       | 207 | Data collection process                          |  |  |
| 12<br>13 | 208 | Data will be extracted ir                        | dependently by the two reviewers. A customised data extraction           |  |
| 14       | 209 | form, piloted and emplo                          | yed in our previous systematic review (15), will be used. The third      |  |
| 15<br>16 | 210 | reviewer (AR) will media                         | ate any disagreement in data extraction between the two review           |  |
| 17       | 211 | authors.   |  |  |
| 18<br>19 | 212 |  |  |  |
| 20<br>21 | 213 | Data items                                       |  |  |
| 22       | 214 | Data items to be extract                         | ted from the included studies are summarised in Table 1. If data         |  |
| 23<br>24 | 215 | items are not available,                         | study authors will be contacted via email (22). An initial email will be |  |
| 25       | 216 | sent to study authors to                         | request for missing information if no response is received after 2       |  |
| 26<br>27 | 217 | weeks a second reminder email will be sent (22). |  |  |
| 28       | 218 |  |  |  |
| 29<br>30 | 219 |  |  |  |
| 31<br>32 |     | Table 1 Summary of data items to be extracted    |  |  |
| 33       |     | Content  | Data items   |  |
| 34<br>35 |     | Study details                                    | Study title author publication date study design                         |  |
| 36       |     | Participant                                      | Age gender co-morbidities  |  |
| 37<br>38 |     | characteristics                                  | Age, gender, co-morbidities  |  |
| 39       |     | Index test                                       | Diagnostic investigations (investigations (imaging Jahoratory test       |  |
| 40<br>41 |     | Index lest                                       | biopsics and neuronbygiology)  |  |
| 42       |     |  | biopsies and field oprivsiology)   |  |
| 43<br>44 |     | Deference standard                               | Comparator toot against the diagnostic investigations                    |  |
| 45<br>46 |     |  |  |  |
| 47       |     | Diagnostic accuracy                              | Sensitivity, specificity, predictive values (PVs) and likelihood         |  |
| 48<br>49 |     | data   | ratios (LRS). Diagnostic accuracy data will be entered into 2×2          |  |
| 50       |     |  | contingency tables (23).   |  |
| 51<br>52 |     |  |  |  |
| 53       | 220 |  |  |  |
| 54<br>55 | 220 |  |  |  |
| 56<br>57 | 221 | RISK OF DIAS IN INDIVID                          | ual studies  |  |
| 58       | 222 | The QUADAS-2 tool wil                            | I be applied independently (JM, BB) to assess risk of bias in the        |  |
| 59<br>60 | 223 | included studies. The Q                          | UADAS-2 tool was developed as a tool to assess risk of blas in           |  |

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| 3<br>4   | 224 | diagnostic accuracy studies. The QUADAS-2 tool consists of four domains: patient selection,        |
| 5        | 225 | index test, reference standard, and flow and timing (24). The tool assesses risk of bias           |
| 6<br>7   | 226 | (relating to bias within the study that distorts the primary diagnostic data) and applicability    |
| 8        | 227 | (relating to the extent to which the research study in question is applicable to the systematic    |
| 9<br>10  | 228 | review question). Each domain is assessed for risk of bias. Patient selection, index test,         |
| 11<br>12 | 229 | reference standard domains are assessed for applicability concerns. Both risk of bias and          |
| 12       | 230 | applicability concerns are used to construct an overall summary judgement of each study,           |
| 14<br>15 | 231 | either 'at risk' or 'low risk' (24). Any disagreements between the two reviewers will be           |
| 16       | 232 | discussed initially, and if the disagreement persists it will be brought to the third reviewer for |
| 17<br>18 | 233 | decision (AR).   |
| 19       | 234 |  |
| 20<br>21 | 235 | Summary measures   |
| 22       | 236 | Primary diagnostic data (sensitivity, specificity, PVs and LRs) will be presented as summary       |
| 23<br>24 | 237 | measures. A formula will be used to calculate primary diagnostic data in cases where only          |
| 25<br>26 | 238 | raw data are available (25). Summary tables will describe primary diagnostic data in relation      |
| 27       | 239 | to the index test:   |
| 28<br>29 | 240 | - Level of accuracy  |
| 30       | 241 | - Discriminatory properties  |
| 31<br>32 | 242 | - Strength of agreement  |
| 33<br>24 | 243 |  |
| 34<br>35 | 244 | Level of accuracy  |
| 36<br>37 | 245 | To date, there is no clear accepted taxonomy for characterising level of accuracy for              |
| 38       | 246 | sensitivity and specificity (26). Therefore, previous research has informed how levels of          |
| 39<br>40 | 247 | accuracy for sensitivity and specificity are described in this study; low (<50%), low/moderate     |
| 41       | 248 | (51-64%), moderate (65-74%), moderate/high (75-84%) and high (>85%) (15, 26, 27).                  |
| 42<br>43 | 249 |  |
| 44<br>45 | 250 | Discriminatory properties  |
| 45<br>46 | 251 | Positive and negative likelihood ratios (+LR & -LR) will be used in order to describe the          |
| 47<br>48 | 252 | discriminatory properties of the index test: conclusive (+LR >10 and -LR <0.1), strong (+LR        |
| 49       | 253 | 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)           |
| 50<br>51 | 254 | (15, 27, 28).  |
| 52       | 255 |  |
| 53<br>54 | 256 | Strength of agreement  |
| 55<br>56 | 257 | Landis and Koch (1997) developed a grading system using a kappa-type statistic to describe         |
| 57       | 258 | strength of agreement in reliability, which will be adopted in this review: 0: poor, 0-0.21:       |
| 58<br>59 | 259 | slight, 0.21-0.40: fair, 0.41-0.60: moderate, 0.61-0.80: substantial and 0.81-1.00: almost         |
| 60       | 260 | perfect (15, 27, 29).  |
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| 2<br>3                     | 261 |   |
| 4<br>5                     | 262 | Data synthesis  |
| 6                          | 263 | Data synthesis will follow the same process as our previous review (15). Initially,             |
| /<br>8                     | 264 | heterogeneity will be explored in study designs, population, comparable diagnostic data, and    |
| 9<br>10                    | 265 | reference standard to inform the data synthesis approach. If pooling of data is not possible,   |
| 10<br>11<br>12<br>13       | 266 | which is likely based on initial scoping searches, then a narrative synthesis will be           |
|                            | 267 | conducted.  |
| 14                         | 268 |   |
| 15<br>16                   | 269 | A narrative synthesis framework, specific to systematic reviews, will be adopted (30). The      |
| 17<br>18                   | 270 | framework will be modified for the purpose of this study by removing the initial stage of       |
| 19                         | 271 | synthesis pertaining to developing a theoretical model of how interventions work, as it is not  |
| 20<br>21                   | 272 | relevant to diagnostic accuracy studies. The narrative synthesis will consist of the 3          |
| 22                         | 273 | remaining stages: developing a preliminary synthesis of findings of included studies,           |
| 23<br>24                   | 274 | exploring relationships in the data and assessing the robustness of the synthesis (30).         |
| 25<br>26                   | 275 |   |
| 27                         | 276 | Confidence in cumulative evidence   |
| 28<br>29                   | 277 | Grading of Recommendations, Assessment, Development and Evaluations (GRADE) will be             |
| 30                         | 278 | used to assess the level of evidence (31). GRADE has been adapted for it use in diagnostic      |
| 32                         | 279 | accuracy research (31). The two reviewers will independently assess each study and assign       |
| 33<br>34                   | 280 | a level of evidence (high, moderate, low or very low). Six factors will downgrade the level of  |
| 35                         | 281 | evidence; study design, risk of bias (informed by QUADAS-2), inconsistency of evidence,         |
| 36<br>37                   | 282 | indirectness of evidence, imprecision of results and publication bias. Factors resulting in the |
| 38<br>30                   | 283 | level of evidence being upgraded include; dose effect, large estimates of accuracy and          |
| 40                         | 284 | residual plausible confounding (31).  |
| 41<br>42                   | 285 |   |
| 43                         | 286 | CLINICAL IMPLICATIONS   |
| 44<br>45                   | 287 | Uncertainty amongst researchers and clinicians exists when selecting the best diagnostic        |
| 46<br>47<br>48<br>49<br>50 | 288 | investigation to identify NP in LBLP. Imprecision in the identification of NP in LBLP can lead  |
|                            | 289 | to inappropriate and untimely intervention and therefore poses a great risk to patient care.    |
|                            | 290 | This review aims to address the uncertainty by investigating the diagnostic utility of          |
| 51                         | 291 | diagnostic investigations for LBLP. Knowledge of the most appropriate diagnostic                |
| 52<br>53                   | 292 | investigation will help to inform a clinician's decision-making when identifying NP in LBLP,    |
| 54                         | 293 | which will lead to precision management and thus better patient care. However, as identified    |
| 55<br>56                   | 294 | from the scoping search, heterogeneity is likely in this body of evidence and therefore         |
| 57<br>58                   | 295 | clinical recommendations may not be possible. If recommendations are not possible based         |
| 59                         | 296 | on this synthesis, further research recommendations will be made.                               |
| 60                         | 297 |   |

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|----------|-----|--|
| 2<br>3   | 298 |  |
| 4<br>5   | 299 | ETHICS AND DISSEMINATION   |
| 6        | 300 | Ethical approval is not required for this systematic review. Findings will add to the growing  |
| 7<br>8   | 301 | body of literature investigating the identification of NP in LBLP. The findings of this review |
| 9        | 302 | will be published in a peer reviewed journal and presented at pertinent conferences. Finally.  |
| 10       | 303 | the results of this study will be shared with the Spinal Pain Patient Partner Advisor Group at |
| 12<br>13 | 304 | Western University.  |
| 14       | 305 |  |
| 15<br>16 | 306 | Author contributions   |
| 17       | 307 | JM is a PhD student, lead author and first reviewer. AR is the lead supervisor, DW, NH and     |
| 18<br>19 | 308 | TN are co supervisors. BB is the second reviewer. AR is the guarantor of the review. JM led    |
| 20<br>21 | 309 | on manuscript development. All the authors contributed to the final manuscript. Data           |
| 21       | 310 | collection be will be conducted by JM, BB and AR. Draft manuscripts will be reviewed by AR,    |
| 23<br>24 | 311 | DW, NH and TN. All authors will contribute to the dissemination of the protocol.               |
| 25       | 312 |  |
| 26<br>27 | 313 | Funding  |
| 28       | 314 | None.  |
| 29<br>30 | 315 |  |
| 31<br>32 | 316 | Competing interests  |
| 33       | 317 | None.  |
| 34<br>35 | 318 |  |
| 36       | 319 | Data sharing statement   |
| 37<br>38 | 320 | No further data are available.   |
| 39<br>40 | 321 |  |
| 41       | 322 | Acknowledgements   |
| 42<br>43 | 323 | None.  |
| 44       | 324 |  |
| 45<br>46 | 325 |  |
| 47<br>48 | 326 |  |
| 48<br>49 | 327 |  |
| 50<br>51 | 328 |  |
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| 58<br>59 | 333 |  |
| 60       | 334 |  |

| 3              | 335 | Refere | ences  |
|----------------|-----|--------|--|
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 BMJ Open

 PRISMA-P 2015 Checklist
 BMJ Open

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

| Section/topic             | #      | Checklist item   | 202<br>Jner<br>late  | Information reported Line |              |                                 |
|---------------------------|--------|--|--|---------------------------|--------------|---------------------------------|
|                           | #      |  | 1. D<br>d to   | Yes                       | No           | number(s)                       |
| ADMINISTRATIVE IN         | FORMAT | TION   | ow<br>It S   |                           |              |                                 |
| Title                     |        |  | nlog<br>upe  |                           |              | _                               |
| Identification            | 1a     | Identify the report as a protocol of a systematic review   | adeo<br>rieu<br>nd o   | $\square$                 |              | 1-2                             |
| Update                    | 1b     | If the protocol is for an update of a previous systematic review, identify as such   | l fro<br>r (A<br>lata  |                           | $\boxtimes$  |                                 |
| Registration              | 2      | If registered, provide the name of the registry (e.g., PROSPERO) and registration number Abstract  | nne<br>BEES)<br>Innin  |                           |              | 65                              |
| Authors                   |        |  | •://t  |                           |              |                                 |
| Contact                   | 3а     | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide p<br>mailing address of corresponding author  | tair of the second seco | $\square$                 |              | 5-24                            |
| Contributions             | 3b     | Describe contributions of protocol authors and identify the guarantor of the review  | <mark>en.b</mark><br>Ning  | $\square$                 |              | 302-307                         |
| Amendments                | 4      | If the protocol represents an amendment of a previously completed or published protocol as such and list changes; otherwise, state plan for documenting important protocol amend | aidentify  |                           | $\square$    |                                 |
| Support                   |        |  | n/<br>sim  |                           |              |                                 |
| Sources                   | 5a     | Indicate sources of financial or other support for the review  | on J<br>ilar   | $\square$                 |              | 309-310                         |
| Sponsor                   | 5b     | Provide name for the review funder and/or sponsor  | une<br>:ech  |                           | $\boxtimes$  |                                 |
| Role of<br>sponsor/funder | 5c     | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the prote  | 14, 20<br>nogog  |                           | $\boxtimes$  |                                 |
| INTRODUCTION              |        |  | 25<br>ies.   |                           |              |                                 |
| Rationale                 | 6      | Describe the rationale for the review in the context of what is already known  | at A   | $\square$                 |              | 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)                         | gence Bibli  |                           |              | 137-140                         |
| METHODS                   |        |  | ogr  |                           |              |                                 |
|                           |        | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtm   | aphique de   | (                         | Bio<br>The O | Med Centr<br>pen Access Publish |

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|------------------------------|---|---|--|------------------|--------------------|------------------|-------------------|
| Chec                         | ic # Checklist item   |   | t, incluc                                    | 0.68.302         | Information<br>Yes | n reported<br>No | Line<br>number(s) |
| Specif<br>charac<br>eligibil | teria Specify the study characteristics (e.g., PICO, s<br>characteristics (e.g., years considered, languaç<br>eligibility for the review  | y design, setting, time frame) and report<br>publication status) to be used as criteria | ling for u                                   | 100 no           |                    |                  | 149-163           |
| Descri<br>trial re           | sources 9 Describe all intended information sources (e.g. trial registers, or other grey literature sources)  | ectronic databases, contact with study an elanned dates of coverage                     | seig<br>reig                                 | rs,              |                    |                  | 165-174           |
| Prese<br>limits,             | egy 10 Present draft of search strategy to be used for a limits, such that it could be repeated   | east one electronic database, including   | afted t                                      | ded              |                    |                  | 183-184           |
|                              | ORDS  |   | 5 1 0<br>8 1 0                               |                  |                    |                  |                   |
| Descri                       | nagement 11a Describe the mechanism(s) that will be used to   | anage records and data throughout the   | <u>ře</u>                                    | <u>₹</u> √       |                    |                  | 188-191           |
| State t<br>each p            | n process 11b State the process that will be used for selecting each phase of the review (i.e., screening, eligit   | udies (e.g., two independent reviewers)<br>y, and inclusion in meta-analysis)           | nd da  | ugh              |                    |                  | 193-201           |
| Descri<br>in dup             | ection 11c Describe planned method of extracting data fro<br>in duplicate), any processes for obtaining and o   | reports (e.g., piloting forms, done indep<br>firming data from investigators            | (ABES  | htly,            | $\square$          |                  | 203-207           |
| List ar<br>pre-pla           | List and define all variables for which data will l<br>pre-planned data assumptions and simplificatic   | sought (e.g., PICO items, funding source  | jes),  | any              | $\square$          |                  | 209-216           |
| List ar<br>additic           | 13 List and define all outcomes for which data will additional outcomes, with rationale   | sought, including prioritization of main  | and s  |                  | $\square$          |                  | 209-216           |
| Descri<br>will be<br>synthe  | in<br>udies 14 Describe anticipated methods for assessing ris<br>will be done at the outcome or study level, or b<br>synthesis  | f bias of individual studies, including wh<br>; state how this information will be used | in d   | this<br>ta       |                    |                  | 217-229           |
|                              |   |   | sin  | Į                |                    |                  | 1                 |
| Descri                       | 15a Describe criteria under which study data will be  | uantitatively synthesized   | ilar   | 2                |                    |                  | 258-270           |
| If data<br>of han<br>of con  | If data are appropriate for quantitative synthesis<br>of handling data, and methods of combining da<br>of consistency (e.g., <i>I</i> <sup>2</sup> , Kendall's tau)   | describe planned summary measures, r<br>from studies, including any planned exp         |  | ds<br>Ion        |                    |                  | 258-270           |
| Descri<br>regres             | 15c Describe any proposed additional analyses (e.e.   | sensitivity or subgroup analyses, meta-   | gies.  | 20.22 a          | $\square$          |                  | 258-270           |
| If quar                      | 15d If quantitative synthesis is not appropriate, des   | be the type of summary planned  | L<br>L                                       | ¥<br>P           |                    |                  | 258-270           |
| Specif<br>reporti            | .) 16 Specify any planned assessment of meta-bias(  | ) (e.g., publication bias across studies, s   | seled  | ive              |                    | $\square$        |                   |
| Descri                       | n Describe how the strength of the body of evide  | e will be assessed (e.g., GRADE)  |  | Riblio           |                    |                  | 272-280           |
| Descri                       | 16     Specify any planted assessment of meta-blas(<br>reporting within studies)       n     17       vidence     17       Describe how the strength of the body of evide   For peer review only - http://b | e will be assess  | ed (e.g., GRADE)<br>te/about/guidelines.xhtm | ed (e.g., GRADE) | ed (e.g., GRADE)   | ed (e.g., GRADE) | ed (e.g., GRADE)  |



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

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| Secondary Subject Heading:           | Research methods, Rehabilitation medicine, Radiology and imaging  |
| Keywords:                            | Diagnostic Imaging, Back pain < ORTHOPAEDIC & TRAUMA SURGERY,<br>Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Spine<br>< ORTHOPAEDIC & TRAUMA SURGERY  |
|                                      |   |

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

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#### Key words

Neuropathic pain, leg pain, diagnostic utility, diagnostic investigations

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#### 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 31<sup>st</sup> 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.

review only

• English language bias may occur due to the exclusion of non-English articles resulting in reduced generalisability of findings.

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#### 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

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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

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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

| Electron | nic searches   |
|----------|--|
| Each ele | ectronic database (CINAHL, EMBASE, MEDLINE, Web of Science, Cochrane                         |
| Library. | AMED and Pedro) will be searched from database inception to 31 <sup>st</sup> July 2023 usin  |
| databas  | a specific search strategies. There will be no geographical restriction. The search          |
| ualabas  | e 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              |
| Westerr  | າ University and co-authors to ensure quality. The search strategy has been inforr           |
| by a pre | evious published review by Mistry et al (15) with previously used key terms patient          |
| history, | clinical examination and screening tools replaced with diagnostic investigations             |
| (imaging | g, laboratory test, biopsies and neurophysiology). See example search strategy in            |
| box 1.   |  |
|          |  |
| Box 1.   | Example of MEDLINE OvidSP search strategy 1048 31st July 2023                                |
| DUX 1.   | Example of MEDEINE ONUSP search strategy 1946 – 514 50ly 2025                                |
| 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 Imagin<br>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   |
|          | 22 and 27  |

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#### 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         | Sensitivity, specificity, predictive values (PVs) and likelihood                                   |
| data                        | 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

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 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.

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 PRISMA-P 2015 Checklist
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 This checklist has been adapted for use with protocol submissions to Systematic Reviews from Table \$ in Moher D et al: Preferred reporting

 items for protocol submissions to Systematic Reviews from Table \$ in Moher D et al: Preferred reporting

 items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Review 2015 4:1

|                           | ш      | Checklist item  | 202  | Information reported Line |              |                                     |
|---------------------------|--------|---|--|---------------------------|--------------|-------------------------------------|
| Section/topic             | #      |   | 4. D   | Yes                       | No           | number(s)                           |
| ADMINISTRATIVE IN         | FORMAT | TION to the second s   | t S  |                           |              |                                     |
| Title                     |        |   |  |                           |              | _                                   |
| Identification            | 1a     | Identify the report as a protocol of a systematic review  | adeo   |                           |              | 1-2                                 |
| Update                    | 1b     | If the protocol is for an update of a previous systematic review, identify as such  | l fro<br>r (A                                  |                           | $\square$    |                                     |
| Registration              | 2      | If registered, provide the name of the registry (e.g., PROSPERO) and registration number and Abstract   | Bine<br>S)                                     | $\square$                 |              | 69                                  |
| Authors                   |        |   | o://   |                           |              | _                                   |
| Contact                   | 3а     | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide pay mailing address of corresponding author  | /sizal   |                           |              | 5-24                                |
| Contributions             | 3b     | Describe contributions of protocol authors and identify the guarantor of the review   | en.b   |                           |              | 434-439                             |
| Amendments                | 4      | If the protocol represents an amendment of a previously completed or published protocol, as such and list changes; otherwise, state plan for documenting important protocol amender | le <mark>e</mark> tify<br>ne <mark>6</mark> ts |                           | $\boxtimes$  |                                     |
| Support                   |        | sim   | n,   |                           |              | •                                   |
| Sources                   | 5a     | Indicate sources of financial or other support for the review   | r uc   |                           |              | 441-442                             |
| Sponsor                   | 5b     | Provide name for the review funder and/or sponsor   | une  |                           | $\boxtimes$  |                                     |
| Role of<br>sponsor/funder | 5c     | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protect   | 14, 20   |                           | $\boxtimes$  |                                     |
| INTRODUCTION              |        | ies.  | 25   |                           |              |                                     |
| Rationale                 | 6      | Describe the rationale for the review in the context of what is already known   | at A   |                           |              | 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)                            | gence Bibli                                    |                           |              | 153-156                             |
| METHODS                   |        |   | ogr  |                           |              |                                     |
|                           |        | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml   | aphique de                                     | (                         | Bio<br>The O | Med Central<br>pen Access Publisher |



| Section/topic                         | #   | Checklist item   | 70202      | Information<br>Yes | reported<br>No | Line<br>number(s) |
|---------------------------------------|-----|--|------------|--------------------|----------------|-------------------|
| ligibility criteria                   | 8   | Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report<br>characteristics (e.g., years considered, language, publication status) to be used as criteriation<br>eligibility for the review                          | 200        |                    |                | 175-202           |
| nformation sources                    | 9   | Describe all intended information sources (e.g., electronic databases, contact with study and trial registers, or other grey literature sources) with planned dates of coverage  | rs,        |                    |                | 222-231           |
| earch strategy                        | 10  | Present draft of search strategy to be used for at least one electronic database, including limits, such that it could be repeated   | ded        |                    |                | 248-257           |
| TUDY RECORDS                          |     |  |            |                    |                | 1                 |
| Data management                       | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the to a   | ₩          |                    |                | 259-297           |
| Selection process                     | 11b | State the process that will be used for selecting studies (e.g., two independent reviewers) and each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)  | ygh        | $\square$          |                | 249-257           |
| Data collection rocess                | 11c | Describe planned method of extracting data from reports (e.g., piloting forms, done independent in duplicate), any processes for obtaining and confirming data from investigators  | ntly,      | $\square$          |                | 247-297           |
| ata items                             | 12  | List and define all variables for which data will be sought (e.g., PICO items, funding sources), pre-planned data assumptions and simplifications  | iny        |                    |                | 270-296           |
| utcomes and<br>rioritization          | 13  | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale   |            |                    |                | 270-296           |
| tisk of bias in<br>Individual studies | 14  | Describe anticipated methods for assessing risk of bias of individual studies, including whether will be done at the outcome or study level, or both; state how this information will be used in described by the synthesis                              | this<br>ta |                    |                | 299-312           |
| ΑΤΑ                                   |     | Sin  |            |                    |                | •                 |
|                                       | 15a | Describe criteria under which study data will be quantitatively synthesized  | 2          | $\square$          |                | 345-350           |
| ynthesis                              | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, net the of handling data, and methods of combining data from studies, including any planned experies of consistency (e.g., <i>I</i> <sup>2</sup> , Kendall's tau) | ds<br>on   |                    |                | 338-343           |
| -                                     | 15c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-   | 20.25      | $\square$          |                | 338-343           |
|                                       | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned   | *          |                    |                | 345-350           |
| eta-bias(es)                          | 16  | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selection preparing within studies)  | ive        |                    | $\boxtimes$    |                   |
| onfidence in<br>umulative evidence    | 17  | Describe how the strength of the body of evidence will be assessed (e.g., GRADE)   |            |                    |                | 314-335           |



**BMJ** Open

# **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<br>Author:     | 12-Dec-2023   |
| Complete List of Authors:            | Mistry, Jai; Western University; St Georges Hospital NHS Foundation<br>Trust<br>Walton, David; Western University, School of Physical Therapy<br>Noblet, Tim; St Georges Hospital NHS Foundation Trust, Physiotherapy<br>Bowling, Benjamin; St Georges Hospital NHS Foundation Trust<br>Heneghan, Nicola; University of Birmingham, School of Sport, Exercise<br>and Rehabilitation Sciences<br>Rushton, Alison; Western University Faculty of Health Sciences, School of<br>Physical Therapy |
| <b>Primary Subject<br/>Heading</b> : | Diagnostics   |
| Secondary Subject Heading:           | Research methods, Rehabilitation medicine, Radiology and imaging  |
| Keywords:                            | Diagnostic Imaging, Back pain < ORTHOPAEDIC & TRAUMA SURGERY,<br>Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Spine<br>< ORTHOPAEDIC & TRAUMA SURGERY  |
|                                      | -   |

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| 2        |    |  |
|----------|----|--|
| 3        | 1  | Diagnostic utility of diagnostic investigations to identify neuropathic pain in low back   |
| 4<br>5   | 2  | related leg pain: protocol for a systematic review   |
| 6<br>7   | 3  |  |
| 8        | 4  | Authors  |
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| 34<br>35 | 20 |  |
| 36<br>37 | 21 | Word count: 3108   |
| 38       | 22 |  |
| 39<br>40 | 23 | Keywords   |
| 41       | 24 | Neuropathic pain, leg pain, diagnostic utility, diagnostic investigations  |
| 42<br>43 | 25 |  |
| 44<br>45 | 26 |  |
| 45<br>46 | 27 | ABSTRACT   |
| 47<br>48 | 28 | Introduction   |
| 49       | 29 | Neuropathic pain in low back-related leg pain has gained increasing interest in contemporary   |
| 50<br>51 | 30 | research. Identification of neuropathic pain in low back-related leg pain is essential to inform   |
| 52       | 31 | precision management. Diagnostic investigations are commonly used to identify neuropathic  |
| 53<br>54 | 32 | pain in low back-related leg pain; yet the diagnostic utility of these investigations is unknown.  |
| 55<br>56 | 33 | The aim of this systematic review is to investigate the diagnostic utility of diagnostic   |
| 50<br>57 | 34 | investigations to identify neuropathic pain in low back-related leg pain.  |
| 58<br>59 | 35 | Methods and analysis   |
| 60       |    |  |

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| 2        |    |  |
|----------|----|--|
| 3<br>4   | 36 | This protocol has been designed and reported in accordance with the Cochrane Handbook                  |
| 5        | 37 | for Diagnostic Test Accuracy studies, Centre for Reviews and Dissemination and the                     |
| 6<br>7   | 38 | Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols checklist,                |
| 8        | 39 | respectively. The search strategy will involve two independent reviewers searching                     |
| 9<br>10  | 40 | electronic databases (CINAHL, EMBASE, MEDLINE, Web of Science, Cochrane Library,                       |
| 11       | 41 | AMED, Pedro), key journals (Spine, The Clinical Journal of Pain, PAIN, European Journal of             |
| 12       | 42 | Pain, The Journal of Pain, Musculoskeletal Science and Practice) and grey literature (British          |
| 14<br>15 | 43 | National Bibliography for report literature, OpenGrey, EThOS) from inception to 31 <sup>st</sup> July  |
| 16       | 44 | 2023 to identify studies. Studies evaluating the diagnostic accuracy of diagnostic                     |
| 17<br>18 | 45 | investigation to identify neuropathic pain in patients with low back-related leg pain will be          |
| 19       | 46 | eligible, studies not written in English will be excluded. The reviewers will extract the data         |
| 20<br>21 | 47 | from included studies, assess risk of bias (Quality Assessment of Diagnostic Accuracy                  |
| 22       | 48 | Studies 2) and determine confidence in findings (Grading of Recommendations,                           |
| 23<br>24 | 49 | Assessment, Development and Evaluation guidelines). Methodological heterogeneity will be               |
| 25<br>26 | 50 | assessed to determine if a meta-analysis is possible. If pooling of data is not possible then a        |
| 20       | 51 | narrative synthesis will be done.  |
| 28<br>29 | 52 | Ethics and dissemination   |
| 30       | 53 | Ethical approval is not required. Findings will be published in a peer reviewed journal,               |
| 31<br>32 | 54 | presented at relevant conferences and shared with the Patient Partner Advisor Group at                 |
| 33       | 55 | Western University, Canada.  |
| 34<br>35 | 56 | Study registration   |
| 36<br>37 | 57 | PROSPERO, CRD42023438222.  |
| 38       | 58 |  |
| 39<br>40 | 59 | Strengths and limitations of this study  |
| 41       | 60 | This review will add to the growing body of literature investigating the identification of             |
| 42<br>43 | 61 | neuropathic pain in low back-related leg pain.   |
| 44<br>45 | 62 | The protocol is reported in line with the Cochrane Handbook for Diagnostic Test                        |
| 45<br>46 | 63 | Accuracy studies and the Preferred Reporting Items for Systematic Reviews and                          |
| 47<br>48 | 64 | Meta-Analysis Protocols checklist.   |
| 49       | 65 | Two independent reviewers will be involved at each stage: screening of eligible                        |
| 50<br>51 | 66 | studies, data extraction, assessment of risk of bias and overall quality of evidence.                  |
| 52       | 67 | Known heterogeneity identified from scoping searches suggests that pooling of data                     |
| 53<br>54 | 68 | may not be possible.   |
| 55<br>56 | 69 | <ul> <li>Language bias may occur due to the exclusion of non-English articles, resulting in</li> </ul> |
| 57       | 70 | reduced generalisability of findings.  |
| 58<br>59 |    |  |
| 60       |    |  |

#### 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  $\geq 25$  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

| 2              |     |  |
|----------------|-----|--|
| 3<br>4         | 109 | proposed to increase the index of suspicion for the presence of neuropathic pain in LBLP           |
| 5              | 110 | (17). Stronger recommendations would require further support for diagnostic utility of these       |
| 6<br>7         | 111 | indicators. Therefore, a reference standard is needed, against which the clinical indicators       |
| 8              | 112 | can be tested. The International Association for the Study of Pain (IASP) Special Interest         |
| 9<br>10        | 113 | Group on Neuropathic Pain (NeuPSIG) proposed a grading system, (revised in 2016), to               |
| 11<br>12       | 114 | guide decisions based on the level of certainty (possible, probable, and definite) with which      |
| 12             | 115 | neuropathic pain can be determined in an individual. In order to satisfy the 'definite' criteria,  |
| 14<br>15       | 116 | diagnostic investigation/s confirming a lesion or disease of the somatosensory nervous             |
| 16             | 117 | system are required, alongside history and examination findings (18). Diagnostic                   |
| 17<br>18       | 118 | investigations have been defined by IASP as any instrumented-based diagnostic test                 |
| 19             | 119 | intended to identify a lesion or disease of the somatosensory nervous system (imaging,             |
| 20<br>21       | 120 | laboratory test, biopsies and neurophysiology) (18). However, it is unclear what diagnostic        |
| 22             | 121 | investigations or combination of such should be used in the case of diagnosis of neuropathic       |
| 23<br>24       | 122 | pain for LBLP. The aforementioned diagnostic investigations when placed in a clinical              |
| 25<br>26       | 123 | pathway are usually placed at the end following history taking and physical examination. The       |
| 20             | 124 | results of these investigations can increase the clinicians index of suspicion that neuropathic    |
| 28<br>29       | 125 | pain is present and therefore aid the decision making regarding onward management.                 |
| 30             | 126 |  |
| 31<br>32       | 127 | This systematic review will investigate the diagnostic utility of diagnostic investigations in the |
| 33             | 128 | identification of neuropathic pain in LBLP. Diagnostic investigations will be the index test and   |
| 34<br>35       | 129 | compared against a reference standard (including surgery, expert opinion, assessment               |
| 36<br>37       | 130 | findings and diagnostic investigations).   |
| 38             | 131 |  |
| 39<br>40       | 132 | Aim  |
| 41             | 133 |  |
| 42<br>43       | 134 | To synthesise evidence investigating the diagnostic utility of diagnostic investigations to        |
| 44<br>45       | 135 | identify neuropathic pain in LBLP.   |
| 45<br>46       | 136 |  |
| 47<br>48       | 137 | METHOD AND ANALYSIS  |
| 49             | 138 | This systematic review protocol has been designed and reported in line with The Cochrane           |
| 50<br>51       | 139 | Handbook for Diagnostic Test Accuracy studies, Centre for Reviews and Dissemination                |
| 52             | 140 | (CRD, 2009) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis             |
| 53<br>54       | 141 | Protocols (PRISMA-P) checklist. A previous systematic review, conducted by the same                |
| 55<br>56       | 142 | research team, has informed the methods of this protocol (15).                                     |
| 50<br>57       | 143 |  |
| 58<br>59<br>60 | 144 | Patient and public involvement   |
|                |     |  |

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| 2        |     |   |
|----------|-----|---|
| 3<br>4   | 145 | Patients and the public have informed the conception of this review as part of an existing        |
| 5        | 146 | programme of research related to lumbar spinal surgery for low back related leg pain. The         |
| 6<br>7   | 147 | study was proposed to the spinal pain research Patient Partner Advisory Group in the              |
| 8        | 148 | School of Physical Therapy at Western University, Canada. Following completion of the             |
| 9<br>10  | 149 | systematic review the results will be presented back to the same group to discuss the             |
| 11       | 150 | findings and to compare them to their own experiences. These discussions may lead to the          |
| 12<br>13 | 151 | to the development of future research projects.   |
| 14<br>15 | 152 |   |
| 16       | 153 | Eligibility criteria  |
| 17<br>18 | 154 |   |
| 19       | 155 | Types of studies  |
| 20<br>21 | 156 | Any study design will be considered for inclusion if evaluating diagnostic accuracy of            |
| 22       | 157 | diagnostic investigations to identify neuropathic pain in LBLP. Studies must include              |
| 23<br>24 | 158 | diagnostic accuracy data (specificity, sensitivity, likelihood ratios (LRs) and predictive values |
| 25<br>26 | 159 | (PVs)). Diagnostic investigations do not include physical examination tests such as the           |
| 27       | 160 | straight leg raise or slump test.   |
| 28<br>29 | 161 |   |
| 30       | 162 | Participants  |
| 31<br>32 | 163 | Studies evaluating diagnostic accuracy of diagnostic investigations in adult patients (age >18    |
| 33<br>24 | 164 | years) with LBLP.   |
| 34<br>35 | 165 |   |
| 36<br>37 | 166 | Index test  |
| 38       | 167 | The index test investigation consisted of diagnostic investigations. Diagnostic investigations    |
| 39<br>40 | 168 | will be defined as any instrumented-based diagnostic test intended to identify a lesion or        |
| 41       | 169 | disease of the somatosensory nervous system (imaging, laboratory test, biopsies and               |
| 42<br>43 | 170 | neurophysiology (18).   |
| 44<br>45 | 171 |   |
| 46       | 172 | Target condition  |
| 47<br>48 | 173 | Diagnostic studies were included if the aim of the diagnostic test was to identify neuropathic    |
| 49       | 174 | pain in LBLP.   |
| 50<br>51 | 175 |   |
| 52       | 176 | Reference standards   |
| 53<br>54 | 177 | We included studies where the diagnostic investigation was compared to a reference                |
| 55<br>56 | 178 | standard including: 1) Surgery, 2) Diagnostic investigations, 3) Expert opinion, 4)               |
| 57       | 179 | Subjective/Objective examination items.   |
| 58<br>59 | 180 |   |
| 60       | 181 | Studies not written in English will be excluded.  |
|          |     |   |

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| 102 | Search methods for identification of studies   |
|-----|--|
| 183 | Electronic searches  |
| 184 | Each electronic database (CINAHL, EMBASE, MEDLINE, Web of Science, Cochrane  |
| 185 | Library, AMED and Pedro) will be searched from database inception to 31 <sup>st</sup> July 2023 using                        |
| 186 | database specific search strategies. There will be no geographical restriction. The search                                   |
| 187 | strategy was developed by the lead author (JM) and reviewed by a specialist librarian at                                     |
| 188 | Western University and co-authors to ensure quality. The search strategy has been informed                                   |
| 189 | by a previous published review by Mistry et al (15) with previously used key terms patient                                   |
| 190 | history, clinical examination and screening tools replaced with diagnostic investigations                                    |
| 191 | (imaging Jaboratory test biopsies and neurophysiology) See MEDLINE search strategy in  |
| 192 | box 1 search strategy was adapted for other databases and resources (supplementary file                                      |
| 193 |  |
| 10/ |  |
| 174 | Day 1: MEDLINE OvidED approb attrategy 1049 21st July 2022   |
|     | BOX 1. MEDEINE OVIUSP search strategy 1946 – 514 July 2025   |
|     | <ol> <li>diagnostic accuracy.mp. or "Sensitivity and Specificity"/</li> </ol>  |
|     | <ol> <li>aliagnostic utility.mp.</li> <li>exp "Reproducibility of Results"/ or diagnostic reliability.mp.</li> </ol>         |
|     | 4. 1 or 2 or 3   |
|     | 5. diagnostic investigations.mp.   |
|     | 7. exp Magnetic Resonance Imaging/ or exp Diffusion Magnetic Resonance Imaging/  |
|     | or imaging.mp.   |
|     | <ol> <li>exp Neurophysiology/ or neurophysiology.mp.</li> <li>nerve conduction test.mp. or exp Neural Conduction/</li> </ol> |
|     | 10. exp Biopsy/ or skin biopsy.mp.   |
|     | 11. exp Genetic Testing/ or genetic test.mp.   |
|     | 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<br>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.   |
|     | 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. LDLP.IIIP.<br>27. 23 or 24 or 35 or 26   |
|     | 28. 22 and 27  |
|     |  |
| 195 |  |
|     |  |

| 1<br>ว   |     |   |
|----------|-----|---|
| 3        | 197 |   |
| 4<br>5   | 198 |   |
| 6        | 199 | Searching other resources   |
| 7<br>8   | 200 | A manual search of key journals, conducted to compliment the search strategy, will                |
| 9        | 201 | include: `Spine. The Clinical Journal of Pain. PAIN. European Journal of Pain. The Journal        |
| 10<br>11 | 202 | of Pain and Musculoskeletal Science and Practice. Reference lists of included studies and         |
| 12<br>13 | 203 | the Cochrane Back Review Group will be reviewed to identify additional eligible studies.          |
| 14       | 204 | Finally, grey literature will be reviewed, using key sources including British National           |
| 15<br>16 | 205 | Bibliography for report literature, OpenGrey and EThOS.   |
| 17       | 206 |   |
| 18<br>19 | 207 | Data collection and analysis  |
| 20<br>21 | 208 |   |
| 22       | 209 | Selection of studies  |
| 23<br>24 | 210 | The selection of relevant articles will commence with independent screening by the two            |
| 25       | 211 | review authors (JM, BB). Initially, titles and abstracts will be screened against the eligibility |
| 26<br>27 | 212 | criteria. Studies will be categorised into included, excluded (clearly irrelevant) and unsure     |
| 28<br>29 | 213 | groups (19). Full texts will be retrieved for studies that may meet the eligibility criteria and  |
| 30       | 214 | independently reviewed by the two review authors. Included studies must be agreed by both         |
| 31<br>32 | 215 | review authors, and any unresolved disagreements will be brought to a third author for            |
| 33<br>34 | 216 | decision (AR). Agreement between review authors will be analysed using the kappa statistic        |
| 35       | 217 | at title/abstract screening stage and full-text screening stage (20).                             |
| 36<br>37 | 218 |   |
| 38       | 219 | Data extraction and management  |
| 39<br>40 | 220 | Data will be extracted independently by the two reviewers. A customised data extraction           |
| 41<br>42 | 221 | form, piloted and employed in our previous systematic review (15), will be used. The third        |
| 42<br>43 | 222 | reviewer (AR) will mediate any disagreement in data extraction between the two review             |
| 44<br>45 | 223 | authors. Data items to be extracted from the included studies are summarised in Table 1. If       |
| 46       | 224 | data items are not available, study authors will be contacted via email (21). An initial email    |
| 47<br>48 | 225 | will be sent to study authors to request for missing information if no response is received       |
| 49<br>50 | 226 | after 2 weeks a second reminder email will be sent (21). Covidence (Covidence systematic          |
| 51       | 227 | review software, Veritas Health Innovation, Melbourne, Australia, <u>www.covidence.org</u> ) will |
| 52<br>53 | 228 | be used to manage citations, identify and remove duplicates and to store abstracts and full       |
| 54       | 229 | texts.  |
| 55<br>56 | 230 |   |
| 57<br>58 |     | Table 1 Summary of data items to be extracted   |
| 58<br>59 |     | Content Data items  |
| 60       |     |   |

| Study details              | Study title, author, publication date, study design                    |
|----------------------------|--|
| Participant                | Age, gender, co-morbidities  |
| characteristics            |  |
| Index test                 | Diagnostic investigations (investigations (imaging, laboratory test,   |
|                            | biopsies and neurophysiology)  |
|                            |  |
| Reference standard         | Comparator test against the diagnostic investigations                  |
| Diagnostic accuracy        | Sensitivity, specificity, predictive values (PVs) and likelihood       |
| data                       | ratios (LRs). Diagnostic accuracy data will be entered into 2×2        |
|                            | contingency tables (22).   |
|                            |  |
|                            |  |
|                            | 6  |
|                            |  |
| Assessment of metho        | dological quality  |
| Risk of bias in individua  | I studies  |
| The Quality Assessmer      | It 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 too     | I to assess risk of bias in diagnostic accuracy studies. The QUADAS-   |
| 2 tool consists of four d  | omains: patient selection, index test, reference standard, and flow    |
| and timing (23). The too   | assesses risk of bias (relating to bias within the study that distorts |
| the primary diagnostic of  | lata) and applicability (relating to the extent to which the research  |
| study in question is app   | licable to the systematic review question). Each domain is assessed    |
| for risk of blas. Patient  | selection, index test, reference standard domains are assessed for     |
| applicability concerns. E  | 30th risk of bias and applicability concerns are used to construct an  |
| overall summary judger     | nent of each study, either 'at risk' or 'low risk' (23). Any           |
|                            | the two reviewers will be discussed initially, and if the disagreement |
| persists it will be brough | It to the third reviewer for decision (AR).                            |
| Dete conthe size           |  |
| Data synthesis             |  |
| bata synthesis will tollo  | w the same process as our previous review (15). Initially,             |
| reference standard to in   | ploted in study designs, population, comparable diagnostic data, and   |
| which is likely based on   | inorm the data synthesis approach. If pooling of data is not possible, |
|                            | initial scoping searches, then a harrative synthesis will be           |
| conducted.                 |  |
|                            |  |
|                            |  |

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| 3       255       A narrative synthesis framework, specific to systematic reviews, will be adopted (24). The         5       256       framework will be modified for the purpose of this study by removing the initial stage of         5       57       synthesis pertaining to developing a theoretical model of how interventions work, as it is not         7       257       remaining stages: developing a preliminary synthesis of findings of included studies,         8       reparation to diagnostic accuracy studies. The narrative synthesis will consist of the 3         9       remaining stages: developing a preliminary synthesis of findings of included studies,         9       exploring relationships in the data and assessing the robustness of the synthesis (24).         12       261         14       262       Summary measures         15       263       Primary diagnostic data (sensitivity, specificity, PVs and LRs) will be presented as summary         16       reasures. A formula will be used to calculate primary diagnostic data in cases where only         17       raw data are available (25). Summary tables will describe primary diagnostic data in relation         18       to the index test: level of accuracy, discriminatory properties and strength of agreement.         19       264       tevel of accuracy         265       raw data are esplicitly (26). Therefore, previous research has informed how levels of  | 2  |     |  |
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| <ul> <li>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)</li> <li>278 (15, 27, 28).</li> <li>279</li> <li>280 Strength of agreement</li> <li>Landis and Koch (1997) developed a grading system using a kappa-type statistic to describe</li> <li>strength of agreement in reliability, which will be adopted in this review: 0: poor, 0-0.21:</li> <li>slight, 0.21-0.40: fair, 0.41-0.60: moderate, 0.61-0.80: substantial and 0.81-1.00: almost</li> <li>284 perfect (15, 27, 29).</li> </ul>   |  | 276 | discriminatory properties of the index test: conclusive (+LR >10 and -LR <0.1), strong (+LR    |
| <ul> <li>278 (15, 27, 28).</li> <li>279</li> <li>280 Strength of agreement</li> <li>281 Landis and Koch (1997) developed a grading system using a kappa-type statistic to describe</li> <li>282 strength of agreement in reliability, which will be adopted in this review: 0: poor, 0-0.21:</li> <li>283 slight, 0.21-0.40: fair, 0.41-0.60: moderate, 0.61-0.80: substantial and 0.81-1.00: almost</li> <li>284 perfect (15, 27, 29).</li> </ul>   |  | 277 | 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)       |
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| <ul> <li>Strength of agreement</li> <li>Landis and Koch (1997) developed a grading system using a kappa-type statistic to describe</li> <li>strength of agreement in reliability, which will be adopted in this review: 0: poor, 0-0.21:</li> <li>slight, 0.21-0.40: fair, 0.41-0.60: moderate, 0.61-0.80: substantial and 0.81-1.00: almost</li> <li>perfect (15, 27, 29).</li> </ul>   |  | 279 |  |
| <ul> <li>Landis and Koch (1997) developed a grading system using a kappa-type statistic to describe</li> <li>strength of agreement in reliability, which will be adopted in this review: 0: poor, 0-0.21:</li> <li>slight, 0.21-0.40: fair, 0.41-0.60: moderate, 0.61-0.80: substantial and 0.81-1.00: almost</li> <li>perfect (15, 27, 29).</li> </ul>  |  | 280 | Strength of agreement  |
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| <ul> <li>47</li> <li>48</li> <li>48</li> <li>49</li> <li>284</li> <li>49</li> <li>284</li> <li>285</li> <li>285</li> <li>285</li> <li>319</li> <li>310</li> <li>3</li></ul> | 45<br>46<br>47<br>48<br>49                               | 282 | strength of agreement in reliability, which will be adopted in this review: 0: poor, 0-0.21:   |
| <sup>40</sup> 284 perfect (15, 27, 29).  |  | 283 | slight, 0.21-0.40: fair, 0.41-0.60: moderate, 0.61-0.80: substantial and 0.81-1.00: almost     |
| 50 285   |  | 284 | perfect (15, 27, 29).  |
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| <sup>52</sup> 286 Confidence in cumulative evidence  | 52   | 286 | Confidence in cumulative evidence  |
| 53<br>54 287 Grading of Recommendations, Assessment, Development and Evaluations (GRADE) will be   | 53<br>54   | 287 | Grading of Recommendations, Assessment, Development and Evaluations (GRADE) will be            |
| <sup>55</sup> 288 used to assess the level of evidence (30). GRADE has been adapted for it use in diagnostic   | 55   | 288 | used to assess the level of evidence (30). GRADE has been adapted for it use in diagnostic     |
| 57 289 accuracy research (30). The two reviewers will independently assess each study and assign   | 56<br>57   | 289 | accuracy research (30). The two reviewers will independently assess each study and assign      |
| $\frac{58}{50}$ 290 a level of evidence (high, moderate, low or very low). Six factors will downgrade the level of   | 58<br>59<br>60   | 290 | a level of evidence (high, moderate, low or very low). Six factors will downgrade the level of |
| <sup>60</sup> 291 evidence; study design (cross sectional/longitudinal studies will not be analysed separately   |  | 291 | evidence; study design (cross sectional/longitudinal studies will not be analysed separately   |

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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. 

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| 2<br>3   | 320 |   |
| 4<br>5   | 321 | Contributors  |
| 6        | 322 | JM is a PhD student, lead author and first reviewer, AR is the lead supervisor, DW, NH and  |
| 7<br>8   | 323 | TN are co supervisors. BB is the second reviewer. AR is the guarantor of the review. JM led |
| 9        | 324 | on manuscript development. All the authors contributed to the final manuscript. Data        |
| 10       | 325 | collection be will be conducted by JM, BB and AR. Draft manuscripts will be reviewed by AR, |
| 12<br>13 | 326 | DW, NH and TN. All authors will contribute to the dissemination of the protocol.            |
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| 23<br>24 | 333 |   |
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## MEDLINE OvidSP search strategy 1948 – 31<sup>st</sup> 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/
- 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

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- 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+")
- (MH "Magnetic Resonance Imaging+") OR "magnetic resonance imaging or mri or mri scan"

| 1        |   |
|----------|---|
| 2        |   |
| 4        | 8. (MH Neurophysiology) OR neurophysiology  |
| 5        | 9. (MH "Nerve Conduction Studies") OR (MH "Neural Conduction") OR "nerve                  |
| 6<br>7   | conduction study or nerve conduction velocity or nerve conduction test"                   |
| 8        | 10. (MH "Biopsy+") OR "skin biopsy"   |
| 9        | 11. (MH "Genetic Screening+") OR (MH "Genetics. Medical+") OR "genetic testing"           |
| 10       | 12 (MH "Tomography, X-Ray Computed+") OR (MH "Tomography, X-Ray+") OR (MH                 |
| 12       |   |
| 13       | "X-Ray Film") OR "X-ray"  |
| 14       | 13. "ct scan or computed tomography or cat scan"  |
| 16       | 14. (MH "Diagnosis, Laboratory+") OR "laboratory tests or laboratory diagnostic or        |
| 17<br>18 | clinical laboratory"  |
| 19       | 15. "electrophysiologic testing"  |
| 20       | 16 (MH "Electrophysiology+") OR "electrophysiology"                                       |
| 21<br>22 | 17.5  or  6  or  7  or  9  or  10  or  11  or  12  or  14  or  15  or  16                 |
| 23       |   |
| 24<br>25 | 18. 4 and 17  |
| 25       | 19. "neuropathic pain"  |
| 27       | 20. "radicular pain"  |
| 28<br>29 | 21. (MH "Intervertebral Disk Displacement") OR (MH "Intervertebral Disk+") OR             |
| 30       | "radiculopathy or sciatica or disc"   |
| 31       | 22 (MH "Spinal Nerve Roots+") OR "nerve root*"  |
| 32<br>33 | 22.10  or  20  or  21  or  22   |
| 34       |   |
| 35<br>36 | 24. 18 and 23   |
| 37       | 25. (MH "Back Pain+") OR "low back pain or lumbar pain or lumbar spine pain or non        |
| 38       | specific low back pain"   |
| 39<br>40 | 26. (MH "Sciatic Nerve+") OR (MH "Sciatica") OR "sciatica or sciatic neuralgia or sciatic |
| 41       | neuropathy or lumbar radiculopathy"   |
| 42<br>42 | 27 "low back related leg pain"  |
| 43<br>44 | 28 "I BD"   |
| 45       |   |
| 46<br>47 | 29. "LBLP"  |
| 48       | 30. 25 or 26 or 27 or 28 or 29  |
| 49<br>50 | 31. 24 and 30   |
| 50<br>51 |   |
| 52       | Web of Science  |
| 53<br>54 | 1 TS=(diagnostic accuracy)  |
| 55       | 2 TS = (diagnostic utility)   |
| 56       |   |
| 57<br>58 | 3. 1 or 2   |
| 59       | <ol><li>TS=(diagnostic investigation*)</li></ol>  |
| 60       | 5. TS=(diagnostic imaging)  |
|          |   |

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- 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

 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

 ("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"). Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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

 (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)

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#### Cochrane Back Review Group

#### Search text contents

 (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

 (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

 (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**

 (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)

 

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 BMJ Open

 PRISMA-P 2015 Checklist
 BMJ Open

 This checklist has been adapted for use with protocol submissions to Systematic Reviews from Table \$ in Moher D et al: Preferred reporting

 items for protocol submissions to Systematic Reviews from Table \$ in Moher D et al: Preferred reporting

 items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Review 2015 4:1

| Section/topic          | #      | Checklist item   | 202<br>Jnei<br>Jate                            | Information reported Line |              |           |  |
|------------------------|--------|--|--|---------------------------|--------------|-----------|--|
|                        | #      |  | 4. D   | Yes                       | No           | number(s) |  |
| ADMINISTRATIVE IN      | FORMAT | rion ซี  | ow<br>It S                                     |                           |              |           |  |
| Title                  |        |  |  |                           |              |           |  |
| Identification         | 1a     | Identify the report as a protocol of a systematic review   | adeo   |                           |              | 1-2       |  |
| Update                 | 1b     | If the protocol is for an update of a previous systematic review, identify as such   | l fro<br>Ir (A                                 |                           | $\boxtimes$  |           |  |
| Registration           | 2      | If registered, provide the name of the registry (e.g., PROSPERO) and registration number Abstract  |  |                           |              | 69        |  |
| Authors                |        | 9,   | o://t  |                           |              |           |  |
| Contact                | 3а     | Provide name, institutional affiliation, and e-mail address of all protocol authors; provide prailing address of corresponding author  | ys <mark>is</mark> al                          |                           |              | 5-24      |  |
| Contributions          | 3b     | Describe contributions of protocol authors and identify the guarantor of the review  | en.b   |                           |              | 434-439   |  |
| Amendments             | 4      | If the protocol represents an amendment of a previously completed or published protocol, is as such and list changes; otherwise, state plan for documenting important protocol amender | de <mark>e</mark> tify<br>ne <mark>6</mark> ts |                           | $\square$    |           |  |
| Support                | -      |  | n/   |                           |              |           |  |
| Sources                | 5a     | Indicate sources of financial or other support for the review  | r uc   |                           |              | 441-442   |  |
| Sponsor                | 5b     | Provide name for the review funder and/or sponsor  | une  |                           | $\boxtimes$  |           |  |
| Role of sponsor/funder | 5c     | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protection   | 14, 20   |                           | $\square$    |           |  |
| INTRODUCTION           |        | la l   | 25   |                           |              |           |  |
| Rationale              | 6      | Describe the rationale for the review in the context of what is already known  | at A   | $\square$                 |              | 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)                               | gence Bibli                                    |                           |              | 153-156   |  |
| METHODS                | 1      |  | ogr  | · · · · ·                 |              |           |  |
|                        |        | For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml  | raphique de                                    | (                         | Bio<br>The O | Med Cent  |  |



|  |    | pyright  |            |             |      |                      |
|--|----|--|------------|-------------|------|----------------------|
| Section/topic #                        | ŧ  | Checklist item   | 7839       | Informatior | Line |                      |
| Eligibility criteria 8                 | 3  | 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 criteriation eligibility for the review  |            | Yes         | No   | number(s)<br>175-202 |
| nformation sources 9                   | )  | Describe all intended information sources (e.g., electronic databases, contact with study and trial registers, or other grey literature sources) with planned dates of coverage  | S,         | $\square$   |      | 222-231              |
| Search strategy 1                      | 0  | Present draft of search strategy to be used for at least one electronic database, including line in the second sec | ed         | $\square$   |      | 248-257              |
| STUDY RECORDS                          |    |  |            |             |      |                      |
| Data management 1                      | 1a | Describe the mechanism(s) that will be used to manage records and data throughout the test   | v          | $\square$   |      | 259-297              |
| Selection process 1                    | 1b | State the process that will be used for selecting studies (e.g., two independent reviewers) and each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)  | gh         | $\square$   |      | 249-257              |
| Data collection 1<br>process           | 1c | Describe planned method of extracting data from reports (e.g., piloting forms, done independent in duplicate), any processes for obtaining and confirming data from investigators  | ntly,      |             |      | 247-297              |
| Data items                             | 2  | List and define all variables for which data will be sought (e.g., PICO items, funding sources), a pre-planned data assumptions and simplifications  | ny         | $\square$   |      | 270-296              |
| Dutcomes and 1<br>prioritization       | 3  | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale   |            | $\square$   |      | 270-296              |
| Risk of bias in<br>ndividual studies   | 4  | Describe anticipated methods for assessing risk of bias of individual studies, including whether will be done at the outcome or study level, or both; state how this information will be used in dates of a synthesis  | this<br>ta | $\boxtimes$ |      | 299-312              |
| DATA                                   |    | sin ž  |            |             |      | <u>.</u>             |
| 1                                      | 5a | Describe criteria under which study data will be quantitatively synthesized  |            | $\square$   |      | 345-350              |
| 1<br>Synthesis                         | 5b | If data are appropriate for quantitative synthesis, describe planned summary measures, net the of handling data, and methods of combining data from studies, including any planned exporting of consistency (e.g., 1 <sup>2</sup> , Kendall's tau)   | ds<br>on   |             |      | 338-343              |
| 1                                      | 5c | Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta- 🦉 🤅 🤅 regression)   |            | $\square$   |      | 338-343              |
| 1                                      | 5d | If quantitative synthesis is not appropriate, describe the type of summary planned   |            | $\square$   |      | 345-350              |
| Meta-bias(es)                          | 6  | Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, seled reporting within studies)  | ve         |             |      |                      |
| Confidence in 1<br>cumulative evidence | 7  | Describe how the strength of the body of evidence will be assessed (e.g., GRADE)   |            | $\square$   |      | 314-335              |

