## Appendices Contents

## Appendix S5: Neuropathic pain questionnaires

## **Appendix S1:** Literature Search

The searches conducted and updated on seven databases are detailed in this Appendix.

### *Updated Systematic Review Search Strategy 09/12/2024*

Search undertaken by Pip Divall, Clinical Librarian Service Manager
Please reference this search as Divall, P. Evidence Search: . Leicester: University Hospitals of Leicester NHS Trust Libraries and information services, 09/12/2024. De-duplication done by the clinical librarian (PD) on the results using sr-accelerator and further checked by reviewers.

**Results (date)**

| **Database** | **Provider** | **No. of Results (total)** | **No. results 19/8/21 - 9/12./24 update** |
|---|---|---|---|
| MEDLINE | Ovid | 2469 | 626 |
| Embase | Ovid | 1310 | 289 |
| Emcare | Ovid | 401 | 83 |
| Cochrane CENTRAL | Wiley | 1030 | 162 |
| CINAHL | EBSCOHost | 2355 | 579 |

Limits applied to this search: none

Methodological filters applied to this search: Cochrane Highly Sensitive Search Strategy for RCTS for Ovid MEDLINE and Embase.

Lefebvre C, Glanville J, Briscoe S, Featherstone R, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Paynter R, Rader T, Thomas J, Wieland LS. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6.3 (updated February 2022). Cochrane, 2022. Available from: www.training.cochrane.org/handbook.

## Ovid MEDLINE(R) ALL

<1946 to December 06, 2024>

| | | |
|---|---|---|
| 1 | (knee* adj3 (replace* or arthroplast* or prosthe* or endoprosthe* or implant*)).ti,ab. | 49666 |
| 2 | (tkr or tka).ti,ab. | 21079 |
| 3 | Arthroplasty, Replacement, Knee/ | 34708 |
| 4 | Knee Prosthesis/ | 14427 |
| 5 | exp Arthroplasty/ | 95795 |
| 6 | Joint Prosthesis/ | 10909 |
| 7 | exp "PROSTHESES AND IMPLANTS"/ | 613948 |
| 8 | Knee/ | 16628 |
| 9 | Knee Joint/ | 69054 |
| 10 | or/5-7 | 677509 |
| 11 | 8 or 9 | 80858 |

| | | |
|---|---|---|
| 12 | 10 and 11 | 21134 |
| 13 | 1 or 2 or 3 or 4 or 12 | 63166 |
| 14 | exp Neuralgia/ | 26224 |
| 15 | ((pain* or discomfort*) adj10 (central or complex or myofasci* or nerv* or neuralg* or neuropath*)).ti,ab. | 77716 |
| 16 | ((neur* or nerv*) adj6 (compress* or damag*)).ti,ab. | 85149 |
| 17 | pain, postoperative/ | 51807 |
| 18 | or/14-17 | 217068 |
| 19 | 13 and 18 | 3776 |
| 20 | randomized controlled trial.pt. | 627681 |
| 21 | controlled clinical trial.pt. | 95647 |
| 22 | randomized.ab. | 671390 |
| 23 | placebo.ab. | 254209 |
| 24 | drug therapy.fs. | 2761422 |
| 25 | randomly.ab. | 448246 |
| 26 | trial.ab. | 727611 |
| 27 | groups.ab. | 2775382 |
| 28 | or/20-27 | 6144761 |

29 exp animals/ not humans.sh. 5285177

30 28 not 29 5381834

31 19 and 30 2469

## Embase

<1974 to 2024 December 05>

1 (knee* adj3 (replace* or arthroplast* or prosthe* or endoprosthe* or implant*)).ti,ab. 60708

2 (tkr or tka).ti,ab. 24886

3 exp knee arthroplasty/ 47419

4 exp knee prosthesis/ 14668

5 arthroplasty/ 22642

6 joint prosthesis/ 12059

7 "prostheses and orthoses"/ 13596

8 knee/ 78044

9 5 or 6 or 7 45897

10 8 and 92189

11 1 or 2 or 3 or 4 or 10 76144

12 neuralgia/ 10088

13 ((pain* or discomfort*) adj10 (central or complex or myofasci* or nerv* or neuralg* or neuropath*)).ti,ab. 113257

14 ((neur* or nerv*) adj6 (compress* or damag*)).ti,ab. 112499

15 neuropathic pain/ 46207

16 postoperative pain/ 97452

17 or/12-16 327271

18 Randomized controlled trial/ 857181

19 Controlled clinical study/ 474564

20 random*.ti,ab. 2151665

21 randomization/ 100412

22 intermethod comparison/ 309923

23 placebo.ti,ab. 387140

24 (compare or compared or comparison).ti. 640937

25 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 3045665

26 (open adj label).ti,ab. 121082

27 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 289969

28 double blind procedure/ 226606

29 parallel group*1.ti,ab. 34750

30 (crossover or cross over).ti,ab. 131781

31 ((assign* or match or matched or allocation) adj5 (alternate or group*1 or intervention*1 or patient*1 or subject*1 or participant*1)).ti,ab. 448600

32 (assigned or allocated).ti,ab. 530727

33 (controlled adj7 (study or design or trial)).ti,ab. 491052

34 (volunteer or volunteers).ti,ab. 294577

35 human experiment/ 676648

36 or/20-35 6578792

37 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) 10302

38 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group*1.ti,ab.) 420602

39 (((case adj control*) and random*) not randomi?ed controlled).ti,ab. 23168

40 (Systematic review not (trial or study)).ti. 308536

41 (nonrandom* not random*).ti,ab. 20003

42 "Random field*".ti,ab. 3142

43 (random cluster adj3 sampl*).ti,ab. 1704

44 (review.ab. and review.pt.) not trial.ti. 1254599

45 "we searched".ab. and (review.ti. or review.pt.) 56027

46 update review.ab. 148

47 (databases adj4 searched).ab. 73177

48 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset*1).ti. and animal experiment/ 1278205

49 Animal experiment/ not (human experiment/ or human/) 2690523

50 or/37-49 4698554

51 36 not 50 5763843

52 12 and 17 and 51 1310

## Ovid Emcare

<1995 to 2024 Week 48>

1 (knee* adj3 (replace* or arthroplast* or prosthe* or endoprosthe* or implant*)).ti,ab. 32720

2 (tkr or tka).ti,ab. 13625

| | | |
|---|---|---|
| 3 | exp knee arthroplasty/ | 24502 |
| 4 | exp knee prosthesis/ | 6359 |
| 5 | arthroplasty/ | 12579 |
| 6 | joint prosthesis/ | 5104 |
| 7 | "prostheses and orthoses"/ | 638 |
| 8 | knee/ | 39835 |
| 9 | 5 or 6 or 7 | 17263 |
| 10 | 8 and 9 | 1591 |
| 11 | 1 or 2 or 3 or 4 or 10 | 40191 |
| 12 | neuralgia/ | 2469 |
| 13 | ((pain* or discomfort*) adj10 (central or complex or myofasci* or nerv* or neuralg* or neuropath*)).ti,ab. | 34200 |
| 14 | ((neur* or nerv*) adj6 (compress* or damag*)).ti,ab. | 19635 |
| 15 | neuropathic pain/ | 15284 |
| 16 | postoperative pain/ | 40448 |
| 17 | or/12-16 | 96066 |
| 18 | Randomized controlled trial/ | 285730 |
| 19 | Controlled clinical study/ | 79506 |

20 random*.ti,ab. 661331

21 randomization/ 21750

22 intermethod comparison/ 104754

23 placebo.ti,ab. 94825

24 (compare or compared or comparison).ti. 155633

25 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 729526

26 (open adj label).ti,ab. 22089

27 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 76111

28 double blind procedure/ 66999

29 parallel group*1.ti,ab. 10647

30 (crossover or cross over).ti,ab. 33425

31 ((assign* or match or matched or allocation) adj5 (alternate or group*1 or intervention*1 or patient*1 or subject*1 or participant*1)).ti,ab. 133831

32 (assigned or allocated).ti,ab. 169842

33 (controlled adj7 (study or design or trial)).ti,ab. 177379

34 (volunteer or volunteers).ti,ab. 71001

35 human experiment/ 378591

36 or/20-35 1851672

37 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) 4899

38 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group*1.ti,ab.) 133995

39 (((case adj control*) and random*) not randomi?ed controlled).ti,ab. 6874

40 (Systematic review not (trial or study)).ti. 133889

41 (nonrandom* not random*).ti,ab. 5744

42 "Random field*".ti,ab. 918

43 (random cluster adj3 sampl*).ti,ab. 668

44 (review.ab. and review.pt.) not trial.ti. 354907

45 "we searched".ab. and (review.ti. or review.pt.) 22891

46 update review.ab. 42

47 (databases adj4 searched).ab. 33520

48 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset*1).ti. and animal experiment/ 149228

49 Animal experiment/ not (human experiment/ or human/) 292486

50 or/37-49 883293

51 36 not 50 1620064

52 12 and 17 and 51 401

## CINAHL

Mon, December 9, 2024 3:29:05 PM

| # | Query | Results |
|---|---|---|
| S1 | knee* n3 (replace* or arthroplast* or prosthe* or endoprosthe* or implant*) | 27,390 |
| S2 | tkr or tka | 9,113 |
| S3 | (MH "Arthroplasty, Replacement, Knee") | 20,031 |
| S4 | (MH "Arthroplasty") | 3,766 |
| S5 | (MH "Joint Prosthesis") | 12,345 |
| S6 | (MH "Prostheses and Implants") | 18,908 |
| S7 | (MH "Knee") | 10,572 |

| | | |
|---|---|---|
| S8 | (MH "Knee Joint") | 21,746 |
| S9 | S7 OR S8 | 31,268 |
| S10 | S4 OR S5 OR S6 | 34,396 |
| S11 | S9 AND S10 | 2,918 |
| S12 | S1 OR S2 OR S3 OR S11 | 28,212 |
| S13 | (MH "Neuralgia+") | 8,044 |
| S14 | (pain* or discomfort*) n10 (central or complex or myofasci* or nerv* or neuralg* or neuropath*) | 27,343 |
| S15 | (neur* or nerv*) n6 (compress* or damag*) | 13,114 |
| S16 | (MH "Postoperative Pain") | 21,497 |
| S17 | S13 OR S14 OR S15 OR S16 | 62,340 |

| | | |
|---|---|---|
| S18 | S12 AND S17 | 2,105 |
| S19 | MH randomized controlled trials OR MH “double-blind studies” OR MH “single-blind studies” OR MH random assignment OR MH “pretest-posttest design” OR MH cluster sample OR TI ( (randomised OR randomized) ) OR AB random* OR TI trial OR ( (MH "sample size") AND (assigned OR allocated OR control) ) OR MH placebos OR PT randomized controlled trial | 632,777 |
| S20 | AB control n5 group OR MH crossover design OR MH comparative studies OR AB cluster n3 RCT | 635,141 |
| S21 | S19 OR S20 | 1,078,708 |
| S22 | (MH "Animals+") | 100,544 |
| S23 | MW animal studies OR TI animal model* | 159,651 |
| S24 | S22 OR S23 | 249,186 |

| | | |
|---|---|---|
| S25 | MH human | 2,825,160 |
| S26 | S24 not S25 | 214,715 |
| S27 | s21 not s26 | 1,028,151 |
| S28 | S18 AND S27 | 1,030 |

## Cochrane CENTRAL

Search Name: Neuropathic pain TKR

Date Run: 09/12/2024 15:39:27

| ID | Search | Hits |
|---|---|---|
| #1 | (knee* near/3 (replace* or arthroplast* or prosthe* or endoprosthe* or implant*)) | 12138 |
| #2 | (tkr or tka) | 5164 |

#3 MeSH descriptor: [Arthroplasty, Replacement, Knee] 3 tree(s) exploded 4112

#4 MeSH descriptor: [Knee Prosthesis] explode all trees 1020

#5 MeSH descriptor: [Arthroplasty] 2 tree(s) exploded 8229

#6 MeSH descriptor: [Joint Prosthesis] explode all trees 2539

#7 MeSH descriptor: [Prostheses and Implants] explode all trees 26436

#8 MeSH descriptor: [Knee] explode all trees 1128

#9 MeSH descriptor: [Knee Joint] explode all trees 5075

#10 #8 or #9 5976

#11 {or #5-#7}[1] 32882

#12 #10 and #11 1795

#13 {or #1-#4, #12} 12823

#14 MeSH descriptor: [Neuralgia] explode all trees 2512

#15 (pain* or discomfort*) near/10 (central or complex or myofasci* or nerv* or neuralg* or neuropath*) 42743

#16 ((neur* or nerv*) near/6 (compress* or damag*)) 4542

119956-supplementary-material

#17 MeSH descriptor: [Pain, Postoperative] explode all trees 22237

#18 {or #14-#17} 63967

#19 #13 and #18 with Cochrane Library in Trials 2355

## *Systematic Review Search Strategy 19/08/2021*

Full Search strategy for this protocol

| # | Database | Search term | Results |
|---|---|---|---|
| 1 | Medline | (knee* ADJ3 (replace* OR arthroplast* OR prosthe* OR endoprosthe* OR implant*)).ti,ab | 27332 |
| 2 | Medline | (tkr OR tka).ti,ab | 8820 |
| 3 | Medline | "ARTHROPLASTY, REPLACEMENT, KNEE"/ | 17506 |
| 4 | Medline | "KNEE PROSTHESIS"/ | 10036 |

| | | | |
|---|---|---|---|
| 5 | Medline | exp ARTHROPLASTY/ | 52705 |
| 6 | Medline | "JOINT PROSTHESIS"/ | 9596 |
| 7 | Medline | exp "PROSTHESES AND IMPLANTS"/ | 453148 |
| 8 | Medline | KNEE/ | 12572 |
| 9 | Medline | "KNEE JOINT"/ | 46241 |
| 10 | Medline | (5 OR 6 OR 7) | 490104 |
| 11 | Medline | (8 OR 9) | 56538 |
| 12 | Medline | (10 AND 11) | 11928 |
| 13 | Medline | (1 OR 2 OR 3 OR 4 OR 12) | 35843 |
| 15 | Medline | exp NEURALGIA/ | 18961 |
| 16 | Medline | ((pain* OR discomfort*) ADJ10 (central OR complex OR myofasci* OR nerv* OR neuralg* OR neuropath*)).ti,ab | 53579 |

| | | | |
|---|---|---|---|
| 17 | Medline | ((neur* OR nerv*) ADJ6 (compress* OR damag*)).ti,ab | 47311 |
| 18 | Medline | PAIN/ | 128291 |
| 19 | Medline | (15 OR 16 OR 17 OR 18) | 223574 |
| 20 | Medline | (lidocaine OR Lidocain OR Lidocaina OR Lidocainum OR Lidokaiini OR Lidokain OR Lidokaina OR Lidokainas orLignocaina OR Lignocaine).ti,ab | 23254 |
| 21 | Medline | LIDOCAINE/ | 23760 |
| 22 | Medline | CAPSAICIN/ | 10070 |
| 23 | Medline | (Capsaicin* OR Axsain OR Zacin OR Capsicum OR Capsidol OR Zostrix OR Capzasin OR Gelcen OR Katrum OR Capsin).ti,ab | 15458 |

| | | | |
|---|---|---|---|
| 24 | Medline | (20 OR 21 OR 22 OR 23) | 48353 |
| 25 | Medline | "ADMINISTRATION, TOPICAL"/ | 37094 |
| 26 | Medline | (topical).ti,ab | 90232 |
| 27 | Medline | (25 OR 26) | 105439 |
| 28 | Medline | (13 AND 19 AND 24 AND 27) | 1 |
| 29 | Medline | (desensiti*).ti,ab | 9016 |
| 30 | Medline | exp "ORTHOPEDIC PROCEDURES"/ | 286312 |
| 31 | Medline | (surg* OR operat*).ti,ab | 2388344 |
| 32 | Medline | (29 OR 30 OR 31) | 2538678 |
| 33 | Medline | (24 OR 27 OR 32) | 2666841 |
| 34 | Medline | (13 AND 19 AND 33) | 1101 |

| | | | |
|---|---|---|---|
| 35 | Medline | 34 [Languages English] [Humans] | 968 |
| 36 | Medline | 34 [Document type Clinical Trial OR Meta-analysis OR Randomized Controlled Trial] | 210 |
| 37 | EMBASE | (((knee* ADJ3 (replace* OR arthroplast* OR prosthe* OR endoprosthe* OR implant*)).ti,ab OR (tkr OR tka).ti,ab OR "ARTHROPLASTY, REPLACEMENT, KNEE"/ OR "KNEE PROSTHESIS"/ OR ((exp ARTHROPLASTY/ OR "JOINT PROSTHESIS"/ OR exp "PROSTHESES AND IMPLANTS"/) AND (KNEE/ OR "KNEE JOINT"/))) AND (exp NEURALGIA/ OR ((pain* OR discomfort*) ADJ10 (central OR | 3209 |

complex OR myofasci* OR
nerv* OR neuralg* OR
neuropath*)).ti,ab OR ((neur*
OR nerv*) ADJ6 (compress*
OR damag*)).ti,ab OR PAIN/))
AND ((lidocaine OR Lidocain
OR Lidocaina OR Lidocainum
OR Lidokaiini OR Lidokain OR
Lidokaina OR Lidokainas
orLignocaina OR
Lignocaine).ti,ab OR
LIDOCAINE/ OR CAPSAICIN/
OR (Capsaicin* OR Axsain OR
Zacin OR Capsicum OR
Capsidol OR Zostrix OR
Capzasin OR Gelcen OR
Katrum OR Capsin).ti,ab OR
"ADMINISTRATION,
TOPICAL"/ OR (topical).ti,ab
OR (desensiti*).ti,ab OR exp
"ORTHOPEDIC

| | | | |
|---|---|---|---|
| | | PROCEDURES"/ OR (surg* OR operat*).ti,ab) | |
| 38 | EMBASE | 37 [Exclude medline journals] [English language] [Humans] [Clinical queries Therapy maximizes sensitivity] | 96 |

## Appendix S2: Risk of Bias

Rienstra et al.[2], is a planned randomised controlled trial using pre-operative Duloxetine for ten weeks in 118 patients having TKR and THR aiming to detect a 10 point difference in the HOOS/KOOS pain subscale at six months. 111 were randomised and 11 were lost to follow-up in the treatment arm and three in the control arm. `There was concern that despite randomisation there were significant differences between the control and intervention arms in both VAS and HOOS/KOOS pain subscales at baseline, favouring the intervention group. Patients own medications were not controlled for as part of usual care received. Participant's outcomes were assessed independent of investigators through mailed questionnaires. The overall risk of bias was low.

Buvanendran et al.[3], 2010, is a randomised placebo controlled trial of the effectiveness of pre-operative pregabalin in 240 patients having TKR powered to detect a 9.5% reduction in the proportion reporting neuropathic pain. Following randomisation there was blinding to the intervention to the patient and those healthcare staff involved preoperatively. There were only 12 of 240 patients lost to follow up. Investigators were blinded when analysing outcomes using the chi squared test. It was assumed there was no selection of the result that deviated from the original plan. Patients who had pregabalin had a 5.2% reduction in the proportion with neuropathic pain at six months. We assessed overall a low risk of bias.

The study (Albayrak et al. [4], 2017) investigating Radio-Frequency to the Dorsal Root Ganglion was a retrospective review which did specify the outcome but was confounded by including only those patients that came to clinic, excluding 10 participants. Data from six patients with incomplete forms were excluded. Only patients showing response to the diagnostic nerve blocks had the intervention which favoured the intervention group. So there was a difference in the comparator group which made the conclusion questionable.

Kretschmar[5] reported a retrospective observational study of dorsal root ganglion stimulators in nine patients after TKR with sustained improvement in pain to 36 months. There was no information on how these patients were selected and there was no comparator.

Yang et al.[6], 2021, was a retrospective comparative study. Only 37 of 55 patients who responded to selective nerve block were offered surgery on the infrapatellar nerve and 24 had surgery to transect and bury the nerve in the Vastus Medialis muscle. Two had cryoablation. It was not possible to extract data for patients only having TKR (26 of 37 responders, and 16 of 18 non-responders). Patients were also offered other neuropathic pain management.

Zhong et al.[7], 2017, is a retrospective comparative study of selective peripheral nerve resection which was confounded by including only the 22 patients who wanted surgery and had a 50% improvement in their pain VAS in the intervention group. The remaining 38 patients were the controls. It is unclear how many patients were excluded based on their criteria. This selection favoured the intervention group in the study.

Clenenden et al.[8], 2014, was a retrospective observational study in 16 patients after TKR. The Infrapatellar branch of the saphenous nerve was assumed to be the cause of the neuropathic pain but this was not assessed in patients prior to treatment which was a steroid injection, two had Radio-Frequency ablation. There was no comparator, which favoured the intervention group with the study reporting pain improvement in nine patients.

## Appendix S3: PRISMA 2020 Checklists

The completed PRISMA checklist{Page, 2021 #11903} is presented below.

### PRISMA 2020

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | y, Title |

| | | | |
|---|---|---|---|
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | y,Abstract |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | y, Introduction |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | y, Introduction paragraph 7 |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | y, Method paragraph 3,4 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | y, Method, paragraph 2, and Appendix S1 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | y, Method, Appendix S1 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | y, Method paragraph 6 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | y, Method paragraph 10 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | y, Method paragraph 10 |

| | | | |
|---|---|---|---|
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | y, Method paragraph 10 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | y, Method paragraph 9 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | y, Method paragraph 10, Appendix S4 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | y,planned: Appendix S4: Analysis, paragraph 2 |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | y, Method paragraph 10 |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | y, Results Figure 2 |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | y,planned: Appendix S4: Analysis |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | n |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | n |

| | | | |
|---|---|---|---|
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | n |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | Not Applicable, |
| **RESULTS** | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | y, Results Paragraphs 1 & 2 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | y, Figure 1 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | y, Results Table 1 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | y, Results Table 2 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | y, Results Table 3 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | Not Applicable, risk of bias overall- Results Table 2 |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Not Applicable, |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Not Applicable, |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | Not Applicable, |

| | | | |
|---|---|---|---|
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | NA, risk of bias overall- Results Table 2. Numbers not followed up:Table 3 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Not Applicable, |
| **DISCUSSION** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | Not Applicable, |
| | 23b | Discuss any limitations of the evidence included in the review. | y, Discussion "Limitations" |
| | 23c | Discuss any limitations of the review processes used. | y, Discussion "Limitations" |
| | 23d | Discuss implications of the results for practice, policy, and future research. | y, Discussion Parahraph 12 |
| **OTHER INFORMATION** | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | y,Method paragraph 1 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | y, Appendix S4 |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | No amendment |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | y, Funding statement |
| Competing interests | 26 | Declare any competing interests of review authors. | y, submitted |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Not Applicable, |

## PRISMA 2020 for Abstract

Checklist for Abstract was completed.[1]

| Section and Topic | Item # | Checklist item | Reported (Yes/No) |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | Yes |
| **BACKGROUND** | | | |
| Objectives | 2 | Provide an explicit statement of the main objective(s) or question(s) the review addresses. | Yes |
| **METHODS** | | | |
| Eligibility criteria | 3 | Specify the inclusion and exclusion criteria for the review. | Yes |
| Information sources | 4 | Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched. | Yes |
| Risk of bias | 5 | Specify the methods used to assess risk of bias in the included studies. | |
| Synthesis of results | 6 | Specify the methods used to present and synthesise results. | Yes |
| **RESULTS** | | | |
| Included studies | 7 | Give the total number of included studies and participants and summarise relevant characteristics of studies. | |
| Synthesis of results | 8 | Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured). | Yes |

| Section and Topic | Item # | Checklist item | Reported (Yes/No) |
|---|---|---|---|
| **DISCUSSION** | | | |
| Limitations of evidence | 9 | Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision). | Yes |
| Interpretation | 10 | Provide a general interpretation of the results and important implications. | Yes |
| **OTHER** | | | |
| Funding | 11 | Specify the primary source of funding for the review. | Yes |
| Registration | 12 | Provide the register name and registration number. | Yes |

## PRISMA Checklist for Searches

| Section/topic | # | Checklist item | Location(s) Reported |
|---|---|---|---|
| **INFORMATION SOURCES AND METHODS** | | | |
| Database name | 1 | Name each individual database searched, stating the platform for each. | Page 4, Method, Paragraph 1 |
| Multi-database searching | 2 | If databases were searched simultaneously on a single platform, state the name of the platform, listing all of the databases searched. | NA |

| | | | |
|---|---|---|---|
| Study registries | 3 | List any study registries searched. | Page 4, Method, Paragraph 1 |
| Online resources and browsing | 4 | Describe any online or print source purposefully searched or browsed (e.g., tables of contents, print conference proceedings, web sites), and how this was done. | NA |
| Citation searching | 5 | Indicate whether cited references or citing references were examined, and describe any methods used for locating cited/citing references (e.g., browsing reference lists, using a citation index, setting up email alerts for references citing included studies). | Page 4, Method, Paragraph 1 |
| Contacts | 6 | Indicate whether additional studies or data were sought by contacting authors, experts, manufacturers, or others. | None |
| Other methods | 7 | Describe any additional information sources or search methods used. | NA |
| **SEARCH STRATEGIES** | | | |
| Full search strategies | 8 | Include the search strategies for each database and information source, copied and pasted exactly as run. | Yes, in the supplementary material |

| | | | |
|---|---|---|---|
| Limits and restrictions | 9 | Specify that no limits were used, or describe any limits or restrictions applied to a search (e.g., date or time period, language, study design) and provide justification for their use. | No Limits used, Page 4, Method, Paragraph 1 |
| Search filters | 10 | Indicate whether published search filters were used (as originally designed or modified), and if so, cite the filter(s) used. | See Search Strategy, in the supplementary material |
| Prior work | 11 | Indicate when search strategies from other literature reviews were adapted or reused for a substantive part or all of the search, citing the previous review(s). | None |
| Updates | 12 | Report the methods used to update the search(es) (e.g., rerunning searches, email alerts). | |
| Dates of searches | 13 | For each search strategy, provide the date when the last search occurred. | Page 4, Method, Paragraph 1, line 3 |

| | | | |
|---|---|---|---|
| **PEER REVIEW** | | | |
| Peer review | 14 | Describe any search peer review process. | Review team meetings |
| **MANAGING RECORDS** | | | |
| Total Records | 15 | Document the total number of records identified from each database and other information sources. | in the supplementary material and PRISMA flow diagram |
| Deduplication | 16 | Describe the processes and any software used to deduplicate records from multiple database searches and other information sources. | Search Strategy, in the supplementary material |

PRISMA-S: An Extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews

Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, Koffel JB, PRISMA-S Group.

Last updated February 27, 2020.

## SWiM Checcklist

# Synthesis Without Meta-analysis (SWiM) reporting items

The citation for the Synthesis Without Meta-analysis explanation and elaboration article is: Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, Hartmann-Boyce J, Ryan R, Shepperd S, Thomas J, Welch V, Thomson H. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline BMJ 2020;368:l6890 http://dx.doi.org/10.1136/bmj.l6890

| **SWiM is intended to complement and be used as an extension to PRISMA** | | | |
|---|---|---|---|
| **SWiM reporting item** | **Item description** | **Page in manuscript where item is reported** | **Other*** |
| *Methods* | | | |
| **1** Grouping studies for synthesis | 1a) Provide a description of, and rationale for, the groups used in the synthesis (e.g., groupings of populations, interventions, outcomes, study design) | Appendix S4, Analysis, Page 42-43 | |
| | 1b) Detail and provide rationale for any changes made subsequent to the protocol in the groups used in the synthesis | None | |

| | | | |
|---|---|---|---|
| **2** Describe the standardised metric and transformation methods used | Describe the standardised metric for each outcome. Explain why the metric(s) was chosen, and describe any methods used to transform the intervention effects, as reported in the study, to the standardised metric, citing any methodological guidance consulted | Appendix S4, Analysis Page 42-43 | |
| **3** Describe the synthesis methods | Describe and justify the methods used to synthesise the effects for each outcome when it was not possible to undertake a meta-analysis of effect estimates | Appendix S4, Analysis Page 42-43 | |
| **4** Criteria used to prioritise results for summary and synthesis | Where applicable, provide the criteria used, with supporting justification, to select the particular studies, or a particular study, for the main synthesis or to draw conclusions from the synthesis (e.g., based on study design, risk of bias assessments, directness in relation to the review question) | Figure 2a and 2b, with text in figure legend | |
| **SWiM reporting item** | **Item description** | **Page in manuscript where item is reported** | **Other*** |

| | | | |
|---|---|---|---|
| **5** Investigation of heterogeneity in reported effects | State the method(s) used to examine heterogeneity in reported effects when it was not possible to undertake a meta-analysis of effect estimates and its extensions to investigate heterogeneity | Appendix S4, Analysis Page 43 | |
| **6** Certainty of evidence | Describe the methods used to assess certainty of the synthesis findings | Figure 2a and 2b and text in Figure legend | |
| **7** Data presentation methods | Describe the graphical and tabular methods used to present the effects (e.g., tables, forest plots, harvest plots).<br><br>Specify key study characteristics (e.g., study design, risk of bias) used to order the studies, in the text and any tables or graphs, clearly referencing the studies included | Appendix S4, Analysis Page 43 | |
| *Results* | | | |
| **8** Reporting results | For each comparison and outcome, provide a description of the synthesised findings, and the certainty of the findings. Describe the result in language that is consistent with the question the synthesis addresses, and indicate which studies contribute to the synthesis | Table 3, Results Paragraph 12 | |
| *Discussion* | | | |
| **9** Limitations of the synthesis | Report the limitations of the synthesis methods used and/or the groupings used in the synthesis, and how these affect the conclusions that can be drawn in relation to the original review question | Discussion, Limitations in Paragraph 13 | |

| | | | |
|---|---|---|---|
| | | | |

PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
*If the information is not provided in the systematic review, give details of where this information is available (e.g., protocol, other published papers (provide citation details), or website (provide the URL)).

# Appendix S4: Protocol

## Background

1. What is neuropathic pain

   Neuropathic pain is defined as pain 'arising as a direct consequence of a lesion or disease affecting the somatosensory system'.[9] Clinically, it can present with burning and shooting pain as well as allodynia and/or hyperalgesia.[10] Patients affected by neuropathic pain have a poorer quality of life compared to those with non-neuropathic pain.

   Neuropathic pain can be diagnosed using a variety of questionnaires – the DN4[11], S-LANSS[12] and 'ID Pain"[13] questionnaires are three screening tools and the painDETECT[14] score can be used both for screening and also to assess severity.

   Neuropathic pain is not effectively treated with standard analgesia and more specific management is required including the use of medications such as pregabalin and gabapentin, topical agents such as capsaicin creams, lidocaine plasters, and surgical interventions. It is important to first identify the cause and manage it if possible. The rate could be influenced by surgical techniques to minimise the incidence of neuropathic pain.
2. The rate of NP after TKR

Chronic pain post TKR is documented as being between 8% and 34%. Neuropathic pain has been documented post TKR at a rate of 5% after six months, and postsurgical pain with neuropathic characteristics has been reported in up to 50% of patients post TKR[15] . Another study reported 43% neuropathic pain at 3 months of 620 who had chronic pain at 3 months after orthopaedic surgery. [16]

3. NP severity and improvement: Phillips reported the peak incidence of neuropathic pain post TKR is at 6 weeks post-op with 35% (30 of 85) respondents have possible or likely neuropathic pain on painDETECT score.[17] At 46 months, this had decreased to 14% of respondents with possible or likely neuropathic pain.[17] Pain reduction of around 30% is considered meaningful improvement.[10]

After TKR neuropathic pain detection, assessment of severity, natural history, expected benefits and harms of interventions remain unclear.

## Review question:

The aim of this systematic review was to review the literature on the diagnosis and management of neuropathic pain after a total knee replacement to ascertain whether there were standard treatment protocols with satisfactory neuropathic pain outcomes.

## Identify evidence

We plan to search the following databases MEDLINE, Cochrane CENTRAL, EMBASE, CINAHL, EMCARE, Clinicaltrials.gov and WHO International Clinical Trials Registry. The reference lists of eligible studies will be reviewed for further studies.

## Study selection and data extraction

### Types of study to be included:

Randomised controlled trials, Cross-sectional studies, Retrospective cohort studies Prospective cohort studies, Comparative study,

### Condition or domain being studied:

Aim is to investigate the *diagnosis, management and outcomes* of neuropathic pain after total knee replacement.

The primary aim is to investigate:

1. Management – do the studies involve investigating a specific intervention for neuropathic pain?
2. Outcomes – do the studies measure the outcomes of neuropathic pain before and after intervention?

The secondary aims are to explore the following aspects of neuropathic pain which could explain heterogeneity in addition to patient factors:

3. Diagnosis – Do the studies have set diagnostic criteria to detect neuropathic pain and are these comparable?
4. Rate: do the studies report the rate of neuropathic pain post total knee replacement and is there an explanation for differences?
5. Timing: do studies report the interval at which neuropathic pain was detected (3months / 6months/ 12 months)
6. Natural history: do the studies report a change in neuropathic pain post TKR over time?
7. Severity: do the studies document the severity of the neuropathic pain after TKR and how is this done (e.g. scores or examination)?
8. Causes – did the studies report potential causes of the neuropathic pain post TKR?
9. Cost: do the studies report cost effectiveness of treatment?

## Participants/population

*Inclusion criteria:*

- Studies reporting the management of neuropathic pain post total knee replacement
- **Languages:** Unrestricted. Every effort will be made to obtain the English translation for foreign language papers
- **Timeframe:** Papers after 1990. Any papers prior to this date will only be included with the agreement of all authors
- **Patients:** All adult patients (above the age of 18 years) who had a total knee replacement.

*Exclusion criteria:*

- Papers that do not mention neuropathic pain specifically
- Case reports, Conference papers, study protocols, review articles, and foreign language papers where we are unable to obtain an English translation
- Systematic Reviews and Meta Analyses (however, these will be collected for review to check references and inform discussion)

## Intervention(s), exposure(s)

Management – do the studies involve investigating a specific treatment intervention in the context of neuropathic pain. For example, perioperative pregabalin, 5% lidocaine plasters, perioperative nefopam or ketamine, or other interventions.

Are desensitisation techniques, specific medicinal applications, nerve blocks or surgical managements e.g., release of a trapped nerve / re-siting or other neuroma management investigated?

## Context

### *Main outcome(s)*

The considerations for neuropathic pain post total knee replacement:

1) Is there effective management of neuropathic pain after total knee replacement?
2) What is the severity of neuropathic pain post total knee replacement? How is it graded?
3) What is the rate of occurrence of neuropathic pain after total knee replacement?
4) Does neuropathic pain post total knee replacement change in time
5) What is the cost of treating neuropathic pain post total knee replacement?
6) What will be the future impact of neuropathic pain on the patient? Does neuropathic pain resolve or leave residual disability?

### *Additional outcomes*

The secondary aims will provide the additional information to inform interpretation.

## Study screening and selection

### *Stage 1: Review of all studies*

Papers will be retrieved following the search strategy, undertaken by an experienced clinical librarian. The titles and/or abstracts of these papers will be independently screened by three independent reviewers to identify studies that meet the inclusion criteria

All papers will be filtered if they are deemed:

a) Irrelevant titles/abstracts

b) Do not mention neuropathic pain

c) Do not meet our inclusion criteria

d) Meet the exclusion criteria.

### *Stage 2: Eligibility*

The full paper of identified studies will be obtained and independently reviewed by at three reviewers for eligibility. Any disagreements between reviewers will be resolved through a team discussion. The quality of eligible studies will then be assessed using the Colman method.[18] We will create a PRISMA[19] flowchart to summarise the screening process.

### *Stage 3. Study quality assessment*

Three reviewers will independently score each selected study against pre-defined modified Coleman criteria.[18] Coleman A will be used to help stratify studies and narrow down to high quality papers for our study questions. Coleman B will assist with more specific study questions and an additional point to ensure we identify all studies which could provide data to extract and analyse. Discussion of selection will be by study group consensus. The review team will have several meetings scheduled to discuss conflicts, review quality, and agree courses of action through the review process.

### *Stage 4: Risk of bias assessment*

Bias will be assessed using the ROB 2.0[20] and ROBINS-I[21] tools for RCT and non-RCT studies respectively. These assess bias across several domains including methods, patient allocation, blinding, reporting bias and others. Outcomes of the bias assessments will be discussed in a team

meeting and differences between reviewers will be resolved through group discussion. A traffic-light diagram will be constructed to present the outcomes of the bias assessments.

### *Stage 5: Extraction of Data*

Once studies to be included have been decided upon an extraction form for the data to be included will be created in Microsoft Excel and piloted on a small selection of papers and adjusted if needed. Extracted data will comprise the outcome domains mentioned previously. The raw text can also be copied to help with efficiency of classification. The extraction will be carried out independently by three reviewers and cross checked for any differences. These differences will be discussed at review meetings to help resolution of queries. The reasons for excluding studies will be recorded. The three independent reviewers will not be blind to the journal articles or to the study authors or institutions. The extracted data will be checked by the other clinical team members and discrepancies will be resolved by discussion at the team meeting. Authors will be contacted if data in the publication is considered inadequate but essential for pooling.

Data we plan to extract will include:

- Study – Type, country, setting, study period
- Patients and population – Total number of patients randomised or included, number and severity of neuropathic pain and interventions, age, gender, follow up period, exclusion criteria applied, and attrition rate
- Outcomes – We will collect the change in pain and/or rate of NP, interval between assessments and complications of treatments.

## Strategy for data analysis

Studies will be summarised.[22] Data will be synthesised qualitatively and quantitatively where appropriate. Statistical analysis, where possible based upon the quality of the source data, will be performed using appropriate statistical software. Consideration of a network meta-analysis for

comparison of interventions may also be considered if appropriate. The review team will discuss this at a review meeting to decide on the appropriate steps consensually. Results for some aspects are expected to be mainly qualitative and follow a narrative review.

We anticipate continuous (change in pain severity, interval between assessments) or dichotomous outcomes (proportion of subjects classified as having neuropathic pain). The sample size for each intervention and symptom improvement reported will be extracted. When the number of participants is not stated, the number randomised minus dropouts will be used. We anticipate extracting a risk ratio or the odds ratio with 95% confidence intervals. If continuous data, such as duration and pain improvement are available, we will extract the mean and standard deviation (SD). If data cannot be extracted easily, we will attempt to contact authors, but graph data will be extracted using established techniques. Standard data imputation methods will be used, if required, to calculate SDs from standard errors (SE) or 95% CI. If only median and (interquartile) ranges are reported, these will be extracted and converted to mean and SD where possible using published formulae.[23]

## Analysis

If sufficient studies are not available for a meta-analysis, a narrative synthesis will be carried out and results tabulated following the nine items of the SWiM guideline[24] and describing the limitations of the synthesis. Key study characteristics will be presented in narrative and tabular form and quality assessment reported. This will include the baseline population detail; intervention details; study methods (e.g., study design, how and when outcomes were measured and defined); and risk of bias.

We will group studies for synthesis by treatments (medication, local treatments, and surgical interventions) and order these by interval after TKR and between assessments. We will report heterogeneity in patient factors, interval since TKR, definitions of neuropathic pain, Interval between

treatment and final assessment, and assessment methods used across the study. We anticipate addressing the certainty of the evidence by looking at the consistency of effects across studies reporting each intervention group for neuropathic pain and will present this data in the table.

If sufficient homogenous studies are available for each intervention a quantitative synthesis will be performed via a random-effects meta-analysis (using a generalised linear mixed model (GLMM) approach with the logit transformation) which will take into consideration that the studies may not be homogenous. For proportions we anticipate dichotomous outcomes of number of subjects classified as having neuropathic pain at different time points. The number reviewed will be used. When the number of participants is not stated, the number randomised minus dropouts will be used.

The post-intervention mean (and SD) and/or the mean change from baseline for each group will be extracted for continuous outcomes (e.g. change in neuropathic pain severity), and these will be analysed using the standardized mean difference.

Statistical heterogeneity will be assessed using the chi-squared test and quantified using the $I^2$ statistic and estimating the between-study variance ($\tau^2$). We will seek explain heterogeneity if possible.

For each common treatment of neuropathic pain after TKR, if sufficient studies are available to create a connected network, a network meta-analysis will be performed to directly compare proportion of subjects with neuropathic pain between interventions. Bayesian methods will be

used to obtain comparative odds ratios (with 95% CI), using MetaInsight.[7] To ensure results are robust, different priors will be tested. Model checks will include convergence, network inconsistency, and leverage of individual data points.

The impact of risk of bias on the effect size will be explored in a sensitivity analysis, if there are sufficient studies, by omitting studies that are judged to be at high risk. The potential for reporting bias will be explored using funnel plots. We do not anticipate subgroup analyses but if there is sufficient data, we will explore subgroups to explain heterogeneity.

## Dissemination

The review will be structured around the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement[25] template if data permits and findings will be presented at appropriate meetings.

## Full Search strategy for this protocol

Given above

## References

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## Appendix S5: Neuropathic pain questionnaires

The DN4[2] addresses four domains assessed by 10 questions (7 on symptoms and 3 on signs) each answered “yes”=1 or “no”=0. A score ≥4 defines neuropathic pain. The ID_pain[4] is a screening tool of six questions with a “yes”=1 and “no”=0, with a score ≥3 identifies neuropathic pain.

The S-LANSS score[3] has seven questions on pain characteristics with 5-points given per "yes" answer, summed generating a score. Five are related to symptoms identifying paraesthesia and allodynia and two to response to touch identifying numbness or hypersensitivity. A score ≥ 12 identifies neuropathic pain. It includes a pain-VAS. PainDETECT[5] is a screening questionnaire with seven questions: five on paraesthesia and allodynia symptoms and two on hypersensitivity to touch. Each is scored from 0=normal to 5=worst. It also notes pain-patterns. A score ≥19 identifies neuropathic pain.