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Prevalence and patterns of neuropathic pain in people with chronic post-surgical pain after total knee arthroplasty

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Aims

The aim of this study was to describe the prevalence and patterns of neuropathic pain over one year in a cohort of patients with chronic post-surgical pain at three months following total knee arthroplasty (TKA).

Methods

Between 2016 and 2019, 363 patients with troublesome pain, defined as a score of ≤ 14 on the Oxford Knee Score pain subscale, three months after TKA from eight UK NHS hospitals, were recruited into the Support and Treatment After Replacement (STAR) clinical trial. Self-reported neuropathic pain and postoperative pain was assessed at three, nine, and 15 months after surgery using the painDETECT and Douleur Neuropathique 4 (DN4) questionnaires collected by postal survey.

Results

Symptoms of neuropathic pain were common among patients reporting chronic pain at three months post-TKA, with half reporting neuropathic pain on painDETECT (191/363; 53%) and 74% (267/359) on DN4. Of those with neuropathic pain at three months, half continued to have symptoms over the next 12 months (148/262; 56%), one-quarter had improved (67/262; 26%), and for one-tenth their neuropathic symptoms fluctuated over time (24/262; 9%). However, a subgroup of participants reported new, late onset neuropathic symptoms (23/262; 9%). Prevalence of neuropathic symptoms was similar between the screening tools when the lower cut-off painDETECT score (≥ 13) was applied. Overall, mean neuropathic pain scores improved between three and 15 months after TKA.

Conclusion

Neuropathic pain is common in patients with chronic pain at three months after TKA. Although neuropathic symptoms improved over time, up to half continued to report painful neuropathic symptoms at 15 months after TKA. Postoperative care should include screening, assessment, and treatment of neuropathic pain in patients with early chronic postoperative pain after TKA.

Cite this article: *Bone Joint J* 2024;106-B(6):582–588.

Introduction

Total knee arthroplasty (TKA) is a successful operation for many patients; however, between 15% and 20% will continue to experience ongoing pain after surgery.[1,2] Chronic post-surgical pain (CPSP) is defined as pain of at least three months' duration after a surgical procedure when all other causes have been excluded.[3] Many patients with CPSP experience painful neuropathic symptoms. Neuropathic pain has been described as the result of either continuing inflammation or nerve injury or iatrogenic nerve damage.[4] The International Association for the Study of Pain (IASP) defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system."[5] Chronic neuropathic pain has been classified for the International Classification of Diseases (ICD)-11, with specific criteria for diagnosis.[6] Features of neuropathic pain following TKA may include pain that is diffuse and difficult to localize, pain that

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doi:10.1302/0301-620X.106B6.BJJ-2023-0889.R1 $2.00

Bone Joint J 2024;106-B(6):582–588.

radiates towards or away from the replaced knee, or feelings of pressure, numbness, sensitivity, burning, stinging, electric shocks, or rigidity.[6] The physical symptoms of neuropathic pain are often accompanied by psychological symptoms, including depression and anxiety, and are associated with reduced quality of life.[7-10] This is a complex condition that requires a multifaceted approach for assessment and treatment.

The prevalence of CPSP varies by type of surgery, with the incidence of neuropathic pain among those with CPSP ranging from 6% to 80%, depending on the procedure, method of assessment, and duration of follow-up.[11] Studies of neuropathic pain after TKA report incidences ranging from 39% at six weeks to 14% at five years postoperatively, measured using the painDETECT and Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionniares.[12-15] Although cross-sectional studies report the prevalence of neuropathic pain in the TKA population, few studies have followed a cohort of individuals with early indications of CPSP and neuropathic pain over time, to evaluate the patient recovery trajectory and the potential for the resolution of symptoms.[16-18]

We explored the prevalence and patterns of neuropathic pain over one year in a cohort of patients reporting early CPSP at three months after TKA. We measured painful neuropathic pain symptoms using two validated screening tools – painDETECT and Douleur Neuropathique 4 (DN4) – examining postoperative neuropathic pain and its trajectory from three to 15 months after TKA, and also examined the level of agreement between the screening tools.

Methods

Study design and setting. We report a secondary analysis of data from the Support and Treatment After Replacement (STAR) multicentre randomized controlled trial conducted at eight NHS hospitals in the UK (ISRCTN92545361). STAR evaluated the clinical effectiveness and cost-effectiveness of a new postoperative care pathway when compared with usual care, for people with early chronic pain after primary TKA for osteoarthritis.[19] A favourable ethical opinion was issued by the South West Central Bristol Research Ethics Committee (16/SW/0514) and approval was issued by the Health Research Authority (IRAS 204891). All participants provided written informed consent. Trial methods and results have been published previously.[20–23] This secondary analysis includes all trial participants from randomization (at three months postoperatively) to 15 months' follow-up. Data are reported according to STROBE statement guidelines for reporting of observational studies, as we report data from the full trial dataset rather than by treatment arm (Supplementary Material).[24]

Participants. Between 2016 and 2019, 363 patients with troublesome pain at three months post-TKA were recruited to the STAR trial.[21–23] Eligibility for inclusion was based on screening using the Oxford Knee Score (OKS)[25,26] pain component (scored 0 to 28, worst to best), using the validated score of ≤ 14 to identify those with troublesome postoperative pain likely to have a negative impact on health-related quality of life.[27] Trial screening procedures and baseline characteristics of recruited participants have been described previously.[21] Of 363 participants randomized at three months post surgery, mean participant age was 67 years (standard deviation (SD) 8.7), 60% were female, and 92% were White (Table I). Participant flow, including reasons for non-participation at each stage, were as published.[22] Follow-up rates were high, with 348 (96%) participants responding to postal data collection at nine months and 337 (93%) at 15 months postoperatively. PainDETECT data were completed by 363/363 participants (100%) at three months, 309/348 (89%) at nine months, and 292/337 (87%) at 15 months postoperatively. DN4 questionnaires were completed by 359/363 participants (99%) on recruitment, by 298/348 (86%) at nine months, and by 289/337 (79%) at 15 months postoperatively (Table II).

Table I. Participant characteristics.

Characteristic	Total
Patients, n	363
Mean age, yrs (SD)	67.2 (8.7)
Median age, yrs (IQR)	67 (61 to 73)
Sex, n (%)	
Female	217 (60)
Male	146 (40)
Marital status, n (%)	
Single	25 (7)
Married/partner	251 (71)
Divorced/separated	35 (10)
Widowed	45 (13)
Missing	7 (2)
Living arrangement, n (%)	
Lives alone	78 (22)
With spouse/partner	253 (71)
With someone else	22 (6)
Other	3 (1)
Missing	7 (2)
Ethnicity, n (%)	
White	335 (94)
Asian	13 (4)
Black	5 (1)
Mixed	1 (< 1)
Other	2 (< 1)
Missing	7 (2)
Education level, n (%)	
Left before age 16 years	22 (7)
Left at age 16 years	194 (61)
College	63 (20)
University	15 (5)
Other postgraduate	24 (8)
Missing	45 (12)

IQR, interquartile range; SD, standard deviation.

Outcomes. The prevalence and pattern of neuropathic pain was assessed using two patient-reported neuropathic pain screening tools: painDETECT and DN4.[28,29] PainDETECT measures the gradation of neuropathic pain using seven questions, with response options ranging from 0 (hardly noticed) to 5 (very strongly), a pain course pattern using four picture options, and a single question on radiating pain (yes/no). The self-completion DN4 questionnaire has seven items on pain characteristics with binary response options (yes/no), scored from 0 to 7. PainDETECT and DN4 were completed by trial participants by postal survey at baseline (three months after TKA) and six

Table II. Prevalence of neuropathic symptoms three to 15 months after total knee arthroplasty.

Timepoint	PainDETECT				Total
	Unlikely (-1 to 12)	Ambiguous (13 to 18)	Likely (19 to 38)	Missing	
3 mths, n (%)					
DN4 < 3	47 (13)	23 (6)	22 (6)	0	92 (25)
DN4 > 3	28 (8)	72 (20)	167 (47)	0	267 (74)
Missing	0	1	3	0	4 (1)
Total	75 (21)	95 (26)	189 (53)	4 (1)	363
9 mths, n (%)					
DN4 < 3	83 (27)	18 (6)	4 (1)	0	105 (31)
DN4 > 3	45 (15)	69 (22)	78 (25)	0	192 (56)
Missing	4	3	8	36	51 (9)
Total	132 (41)	90 (28)	90 (26)	36	348
15 mths, n (%)					
DN4 < 3	109 (37)	14 (5)	2 (0.7)	0	125 (43)
DN4 > 3	47 (16)	48 (16)	69 (24)	0	164 (56)
Missing	1	0	2	21	24
Total	157 (50)	62 (20)	73 (23)	21 (7)	313

DN4, Douleur Neuropathique 4.

and 12 months after randomization (nine and 15 months after TKA). Reminders were sent to non-responders after two weeks, and telephone contact was made to offer support in completing questionnaires.[23] As all participants were recruited postoperatively, no preoperative pain data were collected.

Statistical analysis. Validated scoring guidelines were followed for both neuropathic pain scales. A neuropathic pain component on painDETECT was considered as unlikely (-1 to 12), ambiguous (13 to 18), or likely (19 to 38). Positive scores (yes) on the DN4 for any three or more items indicated that pain was likely to have a neuropathic origin; scores of less than three were classified as nociceptive, non-neuropathic chronic pain. Pain trajectory over time was examined using the binary DN4 classification (neuropathic/non-neuropathic) and using two painDETECT cut-offs (> 13 and > 19).[28,29] Summary statistics for sociodemographic data were presented as mean, SD, and proportions. We examined level of agreement between screening tools using Cohen's kappa statistic, which measures agreement for categorical responses and percentage agreement, along with 95% confidence intervals (CIs). We used recommended interpretations of coefficients when comparing screening tools (< 0.20 indicates slight agreement; 0.21 to 0.40 fair; 0.41 to 0.60 moderate; 0.61 to 0.80 substantial; and 0.81 to 1 almost perfect agreement). Data completeness is reported in the tables and multiple imputation of data missingness was undertaken as a sensitivity analysis.

Results

The STAR trial found no evidence of a between-group difference in neuropathic symptoms at 15 months postoperatively as measured by painDETECT (-0.93 (95% CI -2.51 to 0.65); p = 0.249) or DN4 (-0.10 (95% CI -0.55 to 0.35); p = 0.653).[22]

Neuropathic pain at three months after TKA. Neuropathic pain characteristics among those reporting chronic pain at three months post-TKA were common (Table II). Half reported neuropathic pain using painDETECT (score > 19; 191/363; 53%), increasing to three-quarters of participants when using the DN4 questionnaire (score ≥ 3; 267/359; 74%). Neuropathic pain prevalence was similar across both screening tools using the lower painDETECT cut-off, including those with ambiguous and likely neuropathic components (score ≥ 13; 284/359; 79%). Symptoms most frequently reported at three months post-TKA in patients completing the painDETECT questionnaire were numbness (183/363; 50%), sudden pain attacks like electric shocks (129/363; 36%), and burning sensations (102/363, 28%). Similarly, painful characteristics reported on the DN4 at three months post-TKA included numbness (285/359; 79%), burning (262/359; 73%), tingling (228/359; 64%), and electric shocks (214/359; 60%) in or around the replaced knee.

Neuropathic pain at 15 months after TKA. The proportion of responding participants reporting neuropathic pain characteristics reduced over the follow-up period. Prevalence of neuropathic pain halved between three months and 15 months, with a reduction in prevalence from 79% to 46% on painDETECT (score ≥ 13; 133/289) and 74% to 57% on DN4 (score ≥ 3; 164/289). By 15 months, the commonest symptoms reported on painDETECT and DN4 were similar to those reported at three months postoperatively, namely numbness and burning sensations.

Sensitivity analysis using multiple imputation of painDETECT and DN4 missing data at the 15-month postoperative timepoint, using the 'best case' and 'worst case' scenarios to estimate prevalence, showed no substantial differences in imputed rates compared to the complete case analysis (Supplementary Material).

Patterns of neuropathic pain over time. Patterns of neuropathic pain were examined in the subset of patients who completed the DN4 at all three timepoints (262/363; 72%). Half (148/262; 56%) did not report a change in symptoms; of the patients not reporting change, 108/262 (41%) continued to experience painful neuropathic symptoms over the next year and 40/262 (15%) did not experience neuropathic symptoms. For the remainder, some improved (67/262; 26%) or their symptoms fluctuated (24/262; 9%), but a subgroup developed late onset neuropathic pain (23/262; 9%).

Patterns were also examined in the subset of patients who completed the painDETECT questionnaire at all three

Table III. Agreement between Douleur Neuropathique 4 and PainDETECT (score 13 to 38) after total knee arthroplasty.

Timepoint	PainDETECT				Agreement, %	Kappa (95% CI)
	No NeuP	NeuP	Missing	Total		
3 mths, n (%)					80	0.43 (0.32 to 0.54)
DN4 < 3	47 (13)	45 (12)	0	92		
DN4 > 3	28 (8)	239 (66)	0	267		
Missing	0	4	0	4		
Total	75	288	0	363		
9 mths, n (%)					77	0.53 (0.43 to 0.63)
DN4 < 3	83 (27)	22 (6)	0	105		
DN4 > 3	45 (15)	147 (42)	0	192		
Missing	4	11	36	32		
Total	132	180	36	348		
15 mths, n (%)					78	0.57 (0.48 to 0.66)
DN4 < 3	109 (37)	16 (5)	0	125		
DN4 > 3	47 (16)	117 (37)	0	164		
Missing	1	2	21	24		
Total	157	135	21	313		

CI, confidence interval; DN4, Douleur Neuropathique 4; NeuP, neuropathic pain.

timepoints (277/363; 76%). Many reported no change in symptoms (90/277; 32%), while others reported improvement (123/27; 44%), fluctuation of symptoms (47/277; 17%), or development of late onset neuropathic pain (17/277; 6%). There was moderate agreement between the DN4 and painDETECT screening tools at all postoperative timepoints, with kappa values of 0.43 (95% CI 0.32 to 0.54), 0.53 (95% CI 0.43 to 0.63), and 0.57 (95% CI 0.48 to 0.66) at three, nine, and 15 months, respectively (Table III).

Discussion

We examined neuropathic pain symptoms in a cohort of patients reporting chronic pain at three months after TKA. This UK study screened over 5,000 patients for pain-related outcomes at ten weeks post-TKA, and 363 with troublesome pain were recruited into the STAR trial. We found that neuropathic pain was common among the recruited patients with CPSP at three months post-TKA. Three-quarters of patients reported symptoms indicative of neuropathic pain at three months after TKA when using either the painDETECT (cut-off point ≥ 13) or the DN4 screening questionnaire. Overall, rates of neuropathic pain declined over the following year of follow-up. We found a small subset of patients who were free of neuropathic symptoms at three months post-TKA who then went on to develop late onset neuropathic pain. Although neuropathic pain symptoms improved over time, the prevalence of neuropathic pain is higher in this cohort of patients with CPSP than in the overall population of postoperative TKA patients.

This study group comprises a subset of the overall TKA population who have CPSP, which is estimated to have a prevalence of 20%.[1] The prevalence of neuropathic pain after TKA has been reported in the overall TKA population at several timepoints from one month to five years after surgery.[12-15] Prevalence varies widely in the literature (from 2% to 39%), due to differences in definitions, timing of postoperative assessment, methods used, and classification cut-off points.[12–15,30]

The strengths of this study include a large cohort of patients undergoing knee surgery recruited from eight major teaching hospitals in the UK. We used rigorous data collection procedures and achieved high rates of postal survey completion (80%) at 15 months postoperatively. The presence of neuropathic pain was assessed using two widely used, validated screening tools with comparison of two outcome measures collected at three timepoints. Using data from 2003 to 2012, the National Joint Registry reported that patients undergoing knee arthroplasty in the UK have a mean age of 69 years, 57% are female, and 95% are white.[31] Our trial sample broadly reflects the demographics of the national population having knee arthroplasty. However, in comparison to the 2021 Census, which reports the ethnicity of residents of England and Wales as 81.7% White, our study sample lacks ethnic diversity.[32]

Study participants were recruited postoperatively, thus one limitation is the lack of preoperative and surgical data, including relevant data on preoperative pain. The aim of this secondary analysis was to report the prevalence of neuropathic pain in patients with troublesome and persistent pain three months after TKA. Identifying risk factors or causes for postoperative neuropathic pain was beyond the scope of this study. We also acknowledge that our findings are based on screening questionnaires rather than detailed clinical examination, which involves bedside quantitative sensory testing to confirm neurological dysfunction. Although over 5,000 people returned short postal questionnaires at eight to ten weeks after their joint arthroplasty, the OKS was used to determine eligibility for inclusion in the STAR trial, thus assessment of neuropathic pain scores were only captured on the consented population reporting chronic post-surgical pain. We cannot exclude the possibility that some patients reporting OKS pain subscale scores > 14 have neuropathic symptoms. We followed the cohort to 15 months postoperatively, thus our estimates of prevalence cannot be compared to studies of longer duration. However, longer-term follow-up of STAR trial participants is underway to investigate outcomes at four years postoperatively.

We found marked differences in the prevalence of neuropathic pain using the two tools. These differences were impacted by the three-tiered scoring system for painDETECT (unlikely,

possible, and likely) compared with the binary (likely, unlikely) scoring of DN4. When painDETECT scores were lowered to include the 'ambiguous' cut-off scores of ≥ 13, prevalence estimates were very similar to the DN4, indicating a likely neuropathic component. Patients may prefer multiple categorical options for describing their pain (never, hardly noticed, slightly, moderately, strongly, very strongly), as provided in the painDETECT, compared to the binary 'yes' or 'no' options in the DN4. In this study, we found that completion rates for these postal screening tools were broadly similar. Postal screening is an efficient approach for screening large samples of people at risk of developing neuropathic pain; nevertheless, a limitation of this study was the use of self-reported neuropathic screening questionnaires rather than detailed clinical assessment to establish a confirmatory diagnosis of neuropathic pain. The consistency observed between DN4 and painDETECT (score ≥ 13) and evidence of moderate statistical agreement (kappa: 0.41 to 0.60) suggests that these tools were appropriate and valid screening measures to use in this surgical population. We encourage future studies to consider assessment of neuropathic pain and encourage awareness of screening for neuropathic features relevant to the clinical care of these patients.

Screening questionnaires have improved diagnosis of neuropathic pain in the post-surgical setting, leading to better medical treatment and management, and these tools have been translated and linguistically validated in over 90 languages.[33] Screening using more than one tool has been shown to be helpful in detection of neuropathic pain in patients with other conditions such as cancer.[34,35] Management of expectations is important for patients suffering from chronic pain. Furthermore, there is an association between expectations of treatment and clinical outcomes for patients with chronic pain.[36] Unmet expectations in relation to pain relief and function can result in patient dissatisfaction with TKA.[37–39] Satisfaction is independent of clinical features and more reliant on the care process.[40] Screening, assessment, and treatment of neuropathic pain after knee arthroplasty combined with management of expectations for recovery may lead to improved patient satisfaction.

Neuropathic pain has a negative impact on health-related quality-of-life domains, including sleep and physical, emotional, and social function.[9] Patients with neuropathic pain have significantly poorer OKS at two months postoperatively than those without neuropathic symptoms.[41] Both the painDETECT and DN4 are useful tools for screening of patients with neuropathic features of pain after TKA. Although based on a small cohort of patients reporting chronic pain after TKA, we consider it appropriate to use a cut-off score of ≥ 13 on painDETECT to screen for postoperative neuropathic pain. We recommend that a neuropathic component should be considered in the assessment of patients describing persistent, chronic pain after their TKA. One management option is the STAR care pathway, which was found to be a clinically important and a cost-effective support and treatment intervention for patients with CPSP after TKA, and which successfully screened for patients with neuropathic symptoms after surgery and enabled referral for appropriate specialist treatment.

In conclusion, neuropathic pain was common among a cohort of patients reporting chronic post-surgical pain at three months after TKA. Although the proportion of patients reporting neuropathic pain symptoms decreased over 15 months, prevalence was still higher for those with chronic pain after surgery when compared with reported prevalence for TKA patients as a whole. Clinicians could consider a multimodal approach to identification, assessment, and treatment of patients with CPSP after TKA, such as the STAR care pathway, which includes a component for the screening, assessment, and management of neuropathic pain. An understanding of the prevalence and patterns of neuropathic pain in these patients will assist clinicians in the management of patients' expectations for recovery after TKA.

Take home message

- Up to three-quarters of participants reporting chronic pain at three months after total knee arthroplasty (TKA) reported painful neuropathic symptoms, with between one-quarter and half continuing to experience painful neuropathic symptoms up to 15 months after TKA.
- Both the painDETECT and Douleur Neuropathique 4 outcome measures are useful tools for screening for neuropathic features of pain after TKA. For people reporting chronic pain after TKA, we suggest a cut off score of ≥ 13 on painDETECT to screen for postoperative neuropathic pain.
- Clinical teams should be aware of the frequency of persistent, neuropathic symptoms after TKA.

Supplementary material

STROBE checklist, and sensitivity analysis for missing data at 15 months postoperatively.

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Funding statement:
The authors disclose receipt of the following financial or material support for the research, authorship, and/or publication of this article: this study is funded by the National Institute for Health Research (NIHR) (Programme Grant for Applied Research (Grant Reference Number RP-PG-0613-20001)). The study was also supported by the NIHR Biomedical Research Centre at the University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. J. Bruce is supported by NIHR Research Capability Funding via University Hospitals Coventry and Warwickshire.

ICMJE COI statement:
This study is funded by the National Institute for Health Research (NIHR) (Programme Grant for Applied Research (Grant Reference Number RP-PG-0613-20001)). The study was also supported by the NIHR Biomedical Research Centre at the University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol. The views expressed are those of the authors and not necessarily those of the NIHR or the

Department of Health and Social Care. J. Bruce is supported by NIHR Research Capability Funding via University Hospitals Coventry and Warwickshire. R. Gooberman-Hill is Co-Chair of the UK Committee on Research Integrity. N. Howells reports payment from Smith & Nephew for lectures related to knee surgery, and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Joint Operations, all of which are unrelated to this study. E. Lenguerrand reports institutional payments from NIHR PGfAR, HQIP, NIHR AI, NIHR RfPB, CeramTec, and Tommy's National Centre for Improving Maternity Care, all of which are unrelated to this study. E. Lenguerrand is also an unfunded member of the NIHR Steering Committee, an unfunded College of Experts member for Versus Arthritis, Bone and Joint Infection Registry Scientific Committee Member, SouthWest-Frenchay Research Ethics Committee member, and NIHR Grant Committee member. V. Wylde is Chair of trial steering committees, unrelated to this study.

Data sharing:
The data sets generated during the present study will be available in the University of Bristol Research Data Repository (https://data.bris.ac.uk/data/. Access to the data will be restricted to ensure that data are only made available to bona fide researchers for ethically approved research projects, on the understanding that confidentiality will be maintained and after a data access agreement has been signed by an institutional signatory.

Acknowledgements:
The STAR team would like to thank the study participants and our patient partners for their help and input. The research team acknowledges the support of the NIHR, through the Clinical Research Network. This work was also supported by the NIHR Biomedical Research Centre at University Hospitals Bristol and Weston NHS Foundation Trust and the University of Bristol. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. The Bristol Trials Centre (formed through a merger of the Bristol Randomised Trials Collaboration with another UK Clinical Research Collaboration registered Clinical Trials Unit [CTU]) receives NIHR CTU Support Funding to underpin the development and conduct of NIHR-funded trials.

Ethical review statement:
A favourable ethical opinion was issued by the South West Central Bristol Research Ethics Committee (16/SW/0514). HRA approval was issued bu the Health Research Authority (IRAS 204891).

Open access funding:
Open access is funded by the a Programme Grant for Applied Research (Grant Reference Number RP-PG-0613-20001) from the National Institute for Health and Care Research (NIHR).

Trial registration number:
The STAR Trial was prospectively registered with ISRCTN: https://doi.org/10.1186/ISRCTN92545361.

This article was primary edited by D. Johnstone.