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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Konstantinou K, Lewis M, Dunn KM, et al. Stratified care versus usual care for management of patients presenting with sciatica in primary care (SCOPiC): a randomised controlled trial. *Lancet Rheumatol* 2020; **2:** e401–11.

Table 1. Outcome measures in self-completed questionnaires and their time-points

Outcomes	**Instrument**	**Time-points**		
		0	**4mth**	**12mth**
Global Perceived Change	6-point ordinal scale		✓	✓
Physical function	Modified Roland Morris Disability Questionnaire	✓	✓	✓
Sciatica symptoms	Sciatica Bothersomeness Index	✓	✓	✓
Pain intensity (usual pain)	Numerical Rating Scale (NRS) for back & leg pain	✓	✓	✓
Sleep interference	Jenkins Sleep Questionnaire	✓	✓	✓
Risk of persistent pain-related disability	STarT Back Tool	✓	✓	✓
Anxiety and depression	Hospital Anxiety and Depression scale (HADs)	✓	✓	✓
Fear of movement	Tampa Scale of Kinesphobia (TSK)	✓	✓	✓
Neuropathic pain	Self-report Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS)	✓	✓	✓
Employment	Questions on employment status and work absence (days)	✓	✓	✓
Presenteeism (Productivity)	Performance at work – single question with NRS response (0-10 scale)	✓	✓	✓
General health	Short Form 1 (SF1)	✓	✓	✓
Serious adverse events, adverse events	Identified by clinicians and through Patient Self-report via their Questionnaires		✓	✓
Patient satisfaction with care and results of care	5-point scale		✓	✓
Health economic measures	EQ-5D-5L	✓	✓	✓
	Healthcare use questions		✓	✓

Additional questions; duration of symptoms (back pain, sciatica) at baseline.
Minimal data collection at 4 and 12 months (for those patients not responding to the full questionnaire) included; Global Perceived Change, Physical function, EQ-5D-5L.

Table 2. Key baseline characteristics of participants followed-up and those lost to follow-up at 4 and 12 months

Key baseline characteristics	**Completed follow-up at 4m (n=393)**	**Lost to follow-up at 4m (n=83)**	**Completed follow-up at 12m (n=359)**	**Lost to follow-up at 12m (n=117)**
Age, mean (SD)	53·9 (13·7)	43·1 (12·3)	54·1 (13·7)	45·6 (13·3)
Females, n (%)	214 (54·5)	48 (57·8)	192 (53·5)	70 (59·9)
IMD, median (IQR)	15619 (8958-21903)	10569 (3272-18294)	15619 (8920-21890)	12393 (3558-21427)
Employed, n (%)	263 (67·3)	61 (75·3)	240 (67·2)	84 (73·0)
Pain duration >12 weeks, n (%)	191 (48·6)	39 (47·6)	168 (46·8)	62 (53·4)
Algorithm sciatica group, n (%)				
1	95 (24·2)	12 (14·5)	92 (25·6)	15 (12·8)
2	171 (43·5)	40 (48·2)	152 (42·3)	59 (50·4)
3	127 (32·3)	31 (37·3)	115 (32·0)	43 (36·8)
Usual back pain (0-10 NRS), mean (SD)	5·7 (2·9)	6·3 (2·5)	5·6 (2·9)	6·5 (2·4)
Usual leg pain (0-10 NRS), mean (SD)	6·8 (2·3)	7·0 (2·1)	6·8 (2·3)	6·9 (2·1)

Physical function (RMDQ, 0-23), mean (SD)	10·9 (5·2)	12·7 (5·7)	10·8 (5·2)	12·6 (5·4)

SD=Standard Deviation; IMD=Index of Multiple Deprivation (1-32,844, with higher scores indicating lower levels of deprivation); IQR= Inter-Quartile Range; NRS=Numerical Rating Scale (0-10, with higher scores indicating worse symptoms); RMDQ=Roland-Morris Disability Questionnaire (0-23, with higher scores indicating higher levels of disability).

Table 3. 'Life Table' summarising primary outcome event (first resolution of sciatica symptoms) over the follow-up period

Arm	Interval start time	No. entering interval	No. censored during Interval	No. exposed to having event	No. of events[†]	Proportion resolved	Cumulative proportion with resolution
SC	0[#]	238	1	237·5	4	0·02	0·02
	1	233	0	233	11	0·05	0·06
	2	222	0	222	21	0·09	0·15
	3	201	3	199·5	14	0·07	0·21
	4	184	1	183·5	16	0·09	0·28
	5	167	1	166·5	19	0·11	0·36
	6	147	0	147	9	0·06	0·40
	7	138	0	138	6	0·04	0·43
	8	132	0	132	6	0·05	0·45
	9	126	0	126	7	0·06	0·48
	10	119	0	119	6	0·05	0·51
	11	113	0	113	2	0·02	0·52
	12	111	1	110·5	3	0·03	0·53
	13	107	0	107	2	0·02	0·54
	14	105	2	104	3	0·03	0·55
	15	100	1	99·5	6	0·06	0·58
	16	93	2	92	2	0·02	0·59
	20	89	2	88	8	0·09	0·63
	24	79	2	78	6	0·08	0·66
	28	71	0	71	8	0·11	0·69
	32	63	4	61	7	0·11	0·73
	36	52	0	52	2	0·04	0·74
	40	50	0	50	4	0·08	0·76
	44	46	0	46	4	0·09	0·78
	48[##]	42	42	21	0	0	0·78
UC	0[#]	238	2	237	11	0·05	0·05
	1	225	0	225	16	0·07	0·11
	2	209	1	208·5	11	0·05	0·16
	3	197	0	197	10	0·05	0·20
	4	187	0	187	8	0·04	0·24
	5	179	0	179	11	0·06	0·28
	6	168	1	167·5	11	0·07	0·33
	7	156	0	156	9	0·06	0·37
	8	147	0	147	8	0·05	0·40
	9	139	1	138·5	8	0·06	0·44

	10	130	0	130	6	0·05	0·46
	11	124	0	124	8	0·06	0·50
	12	116	0	116	4	0·03	0·52
	13	112	0	112	4	0·04	0·53
	14	108	1	107·5	6	0·06	0·56
	15	101	0	101	2	0·02	0·57
	16	99	2	98	4	0·04	0·59
	20	93	1	92·5	7	0·08	0·62
	24	85	2	84	7	0·08	0·65
	28	76	2	75	6	0·08	0·68
	32	68	1	67·5	5	0·07	0·70
	36	62	0	62	3	0·05	0·72
	40	59	2	58	1	0·02	0·72
	44	56	1	55·5	0	0	0·72
	48[##]	55	53	28·5	2	0·07	0·74

SC=Stratified Care; UC=Usual Care· [†]Event=First resolution of sciatica symptoms ('completely recovered' / 'much better'). Times shown follow the periods of text data collection in the trial (i.e. weekly for the first 16 weeks, monthly from week 16 through to week 48 (or until 2 consecutive months of resolution).
[#] There were no text responses from 2 participants (1 in the SC arm (who was withdrawn as they had been randomised in error) and 1 in the UC arm). One further participant in the UC arm was censored before week 1 as the participant only provided 1 text response (response category of 'worse' on the first text response at week 0).
[##] A total of 95 participants (42 in SC and 53 in UC) were censored at week 48 having been followed-up throughout the trial period and not reporting resolution of symptoms ('completely recovered' or 'much better') at any time.

Table 4. Sensitivity analyses of primary outcome measure

	HR (95% CI) (P-value)
Stable resolution*	1·11 (0·87, 1·43) (P=0·39)
Improvement**	0·95 (0·79, 1·15) (P=0·59)
Stable improvement***	1·05 (0·86, 1·29) (P=0·61)
Resolution: missing (mean imputation)	1·15 (0·90, 1·47) (P=0·27)
Resolution: missing (resolved imputation)	1·12 (0·89, 1·41) (P=0·32)
Stable resolution: missing (mean imputation)	1·12 (0·87, 1·43) (P=0·38)
Stable resolution: missing (resolved imputation)	1·11 (0·89, 1·39) (P=0·34)
Improvement: missing (mean imputation)	0·95 (0·79, 1·15) (P=0·62)
Improvement: missing (resolved imputation)	0·92 (0·77, 1·11) (P=0·39)
Stable improvement: missing (mean imputation)	1·06 (0·86, 1·29) (P=0·60)
Stable improvement: missing (resolved imputation)	1·07 (0·88, 1·29) (P=0·51)
Parametric – Weibull model	1·16 (0·91, 1·50) (P=0·24)
Parametric – Exponential model	1·19 (0·89, 1·59) (P=0·25)
Parametric – Lognormal model	0·88 (0·65, 1·18) (P=0·38)
Interval censoring - Weibull	1·17 (0·91, 1·49) (P=0·22)
Interval censoring - Exponential	1·20 (0·89, 1·62) (P=0·24)
Interval censoring - Lognormal	0·86 (0·62, 1·19) (P=0·36)

Log Rank (non-parametric) test	(P=0·37)
Breslow (non-parametric) test	(P=0·49)
Tarone-Ware (non-parametric) test	(P=0·43)
Complete case analysis[#]	1·22 (0·89, 1·66) (P=0·21)

* 286/476 (60·1% Stable Resolution by week 48) (Stratified Care, SC=61·3%; Usual Care, UC=58·8%)
** 437/476 (91·8% Improvement by week 48) (SC=92·0%; UC=91·6%)
*** 396/476 (83·2% Stable improvement by week 48) (SC=83·2%; UC=83·2%)
# Analysis of 286 complete responders
HR=Hazard Ratio; CI=Confidence Interval

Table 5. Satisfaction with (i) care received and (ii) results of care received

Satisfaction with:	**All**		**Group 1**		**Group 2**		**Group 3**	
	SC	**UC**	**SC**	**UC**	**SC**	**UC**	**SC**	**UC**
(i) Care								
4 months								
Very satisfied	65 (43)	57 (36)	18 (45)	18 (47)	31 (46)	25 (34)	16 (35)	14 (30)
Quite satisfied	42 (27)	48 (30)	12 (30)	9 (24)	18 (27)	27 (37)	12 (26)	12 (26)
No opinion	22 (14)	27 (17)	6 (15)	5 (13)	7 (10)	14 (19)	9 (20)	8 (17)
Not satisfied	24 (16)	26 (16)	4 (10)	6 (16)	11 (16)	8 (11)	9 (19)	12 (26)
Total n	153	158	40	38	67	74	46	46
	P=0·21		P=0·78		P=0·30		P=0·47	
12 months								
Very satisfied	42 (34)	50 (38)	14 (47)	18 (44)	17 (30)	19 (38)	11 (30)	13 (32)
Quite satisfied	32 (26)	36 (27)	7 (23)	11 (27)	15 (27)	14 (28)	10 (27)	11 (27)
No opinion	32 (26)	28 (21)	7 (23)	6 (15)	17 (30)	12 (24)	8 (22)	10 (24)
Not satisfied	17 (14)	18 (14)	2 (7)	3 (15)	7 (13)	5 (10)	8 (22)	7 (17)
Total n	123	132	30	38	56	50	37	41
	P=0·87		P=0·93		P=0·56		P=0·65	
(ii) Results								
4 months								
Very satisfied	62 (41)	42 (27)	18 (45)	15 (40)	29 (44)	16 (22)	15 (33)	11 (24)
Quite satisfied	43 (28)	58 (37)	12 (30)	10 (26)	19 (29)	33 (45)	12 (26)	15 (33)
No opinion	20 (13)	30 (19)	5 (13)	6 (16)	7 (11)	17 (23)	8 (17)	7 (15)
Not satisfied	27 (18)	28 (18)	5 (13)	7 (18)	11 (17)	8 (11)	11 (24)	13 (28)
Total n	152	158	40	38	66	74	46	46
	P=0·030		P=0·38		P=0·065		P=0·37	
12 months								
Very satisfied	37 (30)	49 (37)	15 (52)	18 (44)	12 (21)	19 (38)	10 (27)	12 (29)

Quite satisfied	36 (30)	37 (28)	7 (24)	9 (22)	19 (34)	15 (30)	10 (27)	13 (32)
No opinion	33 (27)	27 (20)	6 (21)	7 (17)	17 (30)	11 (22)	10 (27)	9 (22)
Not satisfied	16 (13)	19 (14)	1 (3)	7 (17)	8 (14)	5 (10)	7 (19)	7 (17)
Total n	122	132	29	41	56	50	37	41
	P=0·94		P=0·32		P=0·27		P=0·59	

SC=Stratified Care; UC=Usual Care. Numbers shown are frequency count (percentage).

Table 6. Summary data from hospital records review

	All (n=427)†	**SC (n=215)**	**UC (n=212)**
Numbers attended Spinal Interface[**] Clinic and time to appointment (median (IQR) days to be seen from randomisation time point)	104 (14, 10-69)	80 (12, 9-15)	24 (115, 32-191)
- Sciatica group 1 - Sciatica group 2 - Sciatica group 3	2 (1·2%) (115, 48-181) 23 (22·1%) (88, 34-146) 79 (76·0%) (12, 9-15)	1 (1·25%) (48, -) 14 (17.5%) (83, 50-146) 65 (81.25%) (11, 8-13)	1 (4·2%) (181, -) 9 (37·5) (88, 25-120) 14 (58·3%) (119, 51-245)
Outcome of Spinal Interface Clinic appointment (numbers referred to other services/interventions)			
Referred to physiotherapy	47 (46·5%)	44 (54·3%)	3 (15·0%)
Referred to orthopaedics	32 (31·7%)	22 (27·2)	10 (50·0%)
Referred to pain clinic	4 (4·0%)	2 (2·5%)	2 (10·0%)
Referred for spinal epidural injection	18 (17·8%)	13 (16·0%)	5 (25·0%)
Total referrals[*] *(denominator)*	101	81	20

SC=Stratified Care; UC=Usual Care; IQR= Inter-Quartile Range. [*]This number excludes patients who were discharged or referred to any other services.

[**] In the UK, patients with back pain and/or sciatica who do not improve with primary care based interventions and require specialist assessment, before they are referred to see medical or surgical spinal specialists in secondary care settings, they are first referred to intermediate care settings, called Interface Spinal Clinics, for initial assessment and tests (for example, MRIs, x-rays).

Table 7. Health outcome data over the 12 month period (mean, SD).

Health outcomes	SC (n=238)	UC (n=238)	Difference[b] (CI)(SC-UC)
Base-case (Imputed) analysis [a]			
Baseline EQ-5D	0·5168 (0·2109)	0·5201 (0·2300)	-0·003 (-0·043, 0·037)
4 month EQ-5D	0·6710 (0·2006)	0·6806 (0·1955)	-0·009 (-0·046, 0·026)
12 month EQ-5D	0·7138 (0·2137)	0·7320 (0·1879)	-0·018 (-0·054, 0·0176)
Unadjusted QALYs[c]	0·6599 (0·1731)	0·6713 (0·1685)	-0·011 (-0·042, 0·019)

Adjusted QALYs[c]	-	-	-0·011 (-0·035, 0·013)

SC=Stratified care. UC=Usual care. QALYs=quality-adjusted-life-years. MDC=Minimum data collection. [a] Values are mean (SD) scores unless stated otherwise, [b]Difference=SC-UC. Reported CIs were generated using regression methods. [c]Incremental QALY estimates following multiple regression-based adjustment for age, gender, and baseline EQ-5D scores. *Values reported represent number (percentage).

Table 8. Mean per-participant sciatica-related resource use and costs over 12 months, by intervention arm

Healthcare resource	SC (n=114)		UC (n=122)	
	Average number of visits per participant (SD)	Mean cost per participant (SD)	Average number of visits per participant (SD)	Mean cost per participant (SD)
Intervention costs		155·79 (142·64)		54·48 (56·98)
Primary care general practitioner	1.44 (1·88)	52·58 (69·62)	1·53 (2·01)	56·71 (74·49)
Primary care nurse	0·09 (0·39)	0·97 (4·28)	0·13 (0·49)	1·44 (5·47)
Primary care other [l]	0·05 (0·39)	2·58 (19·38)	0·23 (0·98)	11·25 (48·30)
Prescriptions	4·70 (8·50)	15·51 (29·04)	3·79 (5·79)	12·81 (20·68)
NHS consultant	0·57 (1·28)	77·57 (173·07)	0·43 (1·33)	65·34 (222·93)
Private consultant	0·03 (0·20)	3·26 (25·87)	0·04 (0·37)	5·08 (46·19)
NHS Physiotherapist	1·57 (2·88)	76·93 (141·17)	2·79 (3·08)*	136·55 (151·09)
Private Physiotherapist	0·32 (1·69)	15·47 (82·79)	0·61 (2·15)	29·72 (105·33)
NHS Hospital nurse	0·15 (1·05)	16·40 (116·36)	0·01 (0·09)	0·90 (9·95)
Private Hospital nurse	0·02 (0·18)	1·93 (20·60)	0·00 (0·00)	0·00 (0·00)
NHS Chiropractor	0·03 (0·28)	1·29 (13·76)	0·05 (0·54)	2·41 (26·61)
Private Chiropractor	0·67 (3·08)*	32·67 (151·29)	0·12 (0·71)	5·62 (34·61)
NHS Acupuncturist	0·03 (0·16)	1·29 (7·88)	0·07 (0·53)	3·21 (25·77)
Private Acupuncturist	0·54 (3·25)*	26·64 (159·43)	0·03 (0·20)	1·21 (9·88)
NHS Osteopath	0·02 (0·13)	0·86 (6·46)	0·03 (0·27)	1·21 (13·30)
Private Osteopath	0·08 (0·66)	3·86 (32·68)	0·07 (0·37)	3·62 (18·00)
NHS X-rays	0·09 (0·28)	2·72 (8·80)	0·11 (0·42)	3·30 (13·10)
NHS Scans	0·07 (0·29)	7·23 (29·76)	0·01 (0·09)	0·84 (9·33)
NHS Blood tests	0·16 (0·18)	0·95 (2·59)	0·10 (0·37)	0·59 (2·24)
NHS MRI investigations	0·32 (0·64)	53·37 (108·56)	0·33 (0·65)	55·41 (109·59)
Private MRI investigation	0·02 (0·13)	2·97 (22·28)	0·02 (0·18)	2·77 (30·60)
NHS epidural injections	0·14 (0·44)	80·70 (252·29)	0·10 (0·35)	56·56 (201·23)
Resource use other (%)				
NHS Sciatica-related surgery	1 (0·9%)	46·47(496·20)	3 (2·5%)	130·27 (823·89)
Prescriptions	40 (35·09%)		36 (29·51%)	
"Over-the-counter" treatments	28 (24·56%)	4·78 (10·35)	31 (25·41%)	10·00 (21·81)
Mean Costs (SD) (base-case):		663·58 (737·14)		617·37 (935·50)
Cost Difference (CI)		46·21 (-110·60, 187·06)		
QALY Difference (CI)		-0·011 (-0·035, 0·013)		
ICER		Dominated.		

[l] Includes visits to other professionals such as community physiotherapists. *Significant differences between the groups as the value zero is not contained in the 95% confidence interval. Confidence intervals for mean

differences in resource use (not reported here) were obtained by bootstrapping using 1000 replications. SC=Stratified Care. UC=Usual Care. MRI=magnetic resonance imaging. NHS=National Health Service. ICER=incremental cost-effectiveness ratio.

Table 9. Sensitivity analysis: Cost-Utility analysis results, by intervention arm

SC (£)	**UC (£)**	
Mean cost difference over 12 months (95% CI), £	Mean cost QALYs (95% CI), £	ICER
Healthcare perspective		
77·67 (-70·49, 232·94)	-0·011 (-0·035, 0·013)	Dominated[3]
Societal perspective		
-16·73 (-422·66, 337·76)	-0·011 (-0·035, 0·013)	1520[2]
NHS costs including hospital records data[4]		
40·72 (-168·20, 250·08)	-0·011 (-0·035, 0·013)	Dominated[3]
Healthcare costs including hospital records data		
72·18 (-150·36, 276·88)	-0·011 (-0·035, 0·013)	Dominated[3]
Complete-case analysis		
-14·03 (-310, 254)	-0·0255 (-0·061,0·008)	550.20[2]

ICER=incremental cost-effectiveness ratio. QALY=quality-adjusted life-year. *Adjusted for baseline utility. SC=Stratified Care. UC=Usual Care. ICER=incremental cost-effectiveness ration ICER relates to SC-UC. CI=confidence interval Difference=SC - UC. NHS=National Health Service.
[1]Adjusted for age, gender, trial arm and baseline health-related quality of life [2]Mean ICER in south-west quadrant of the cost-effectiveness plane where stratified care was less costly but less effective [3]Mean ICERs fell in the north-west quadrant of the cost-effectiveness plane where stratified care was more costly and less effective. [4]Total costs including MRIs, spinal injections and spinal surgeries for sciatica from hospital records review.

Table 10. Sensitivity analysis: Description of work-related outcomes for participants in paid employment (absence, reduced productivity, and costs) by intervention arm (mean, SD).

	Trial arm		
Work-related outcomes[a]	SC	UC	Difference (CI) (SC-UC)
Performance at work at 12 months[b]	3·01 (2·75)	3·00 (2·60)	0·01 (-0·72,0·92)
Days off work over 12 months	5·48 (18·14)	5·67 (17·08)	-0·18 (-5·67,5·39)
Productivity costs[c]	590·42 (1955·13)	610·53 (1840·98)	-20·11 (-623·53,557·06)

[a]The evaluation of work-related outcomes and the estimation of indirect costs focussed on the subsample of respondents in paid employment at 12 months (156/476). [b] Mean performance at work on a scale of 0 to 10 where 0 indicates work performance not affected. SC=Stratified Care; UC=Usual Care. SD=standard deviation. [c]Productivity costs obtained from days off-work at 12 months.

Table 11. Subgroup analysis: Cost-utility analysis results by, intervention arm

	Mean incremental[1] costs (CI) (SC-UC), £	**Mean incremental[1] QALYs** (CI) (SC-UC)	**ICER**
NHS Perspective			
Sciatica group 1 (n=107)	-9·45 (-205·67, 203·42)	-0·0004 (-0·0447, 0·0392)	23048[2]
Sciatica group 2 (n=211)	-54·45 (-274·91,141·32)	-0·0198 (-0·0513,0·0110)	2748[2]
Sciatica group 3 (n=158)	209·56 (-142·47,521·72)	-0·0084 (-0·0567, 0·0433)	Dominated[3]
NHS Perspective including hospital records data			
Sciatica group 1 (n=107)	104·54 (-141·18,475·53)	-0·0004 (-0·0447, 0·0392)	Dominated[3]
Sciatica group 2 (n=211)	-4·53 (-308·90,259·97)	-0·0198 (-0·0513,0·0110)	228[2]
Sciatica group 3 (n=158)	47·61 (-361·53, 459·75)	-0·0084 (-0·0567, 0·0433)	Dominated[3]

SC=Stratified care. UC=Usual care. Difference=SC – UC. NHS=National Health Service. QALYs=quality-adjusted-life-years. ICER=incremental cost-effectiveness ratio.[1]Adjusted for age, gender, intervention arm and baseline health-related quality of life. [2]Mean ICER in south-west quadrant of the cost-effectiveness plane where stratified care is less costly but less effective. [3]Mean ICERs fell in the north-west quadrant of the cost-effectiveness plane where stratified care is more costly and less effective.

Figure 1 STarT Back tool

The Keele STarT Back Screening Tool

Thinking about the **last 2 weeks** tick your response to the following questions:

		Disagree 0	**Agree** 1
1	My back pain has **spread down my leg(s)** at some time in the last 2 weeks	☐	☐
2	I have had pain in the **shoulder** or **neck** at some time in the last 2 weeks	☐	☐
3	I have only **walked short distances** because of my back or leg pain	☐	☐
4	In the last 2 weeks, I have **dressed more slowly** than usual because of back or leg pain	☐	☐
5	It's not really safe for a person with a condition like mine to be physically active	☐	☐
6	**Worrying thoughts** have been going through my mind a lot of the time	☐	☐
7	I feel that **my back or leg pain is terrible** and **it's never going to get any better**	☐	☐
8	In general I have **not enjoyed** all the things I used to enjoy	☐	☐

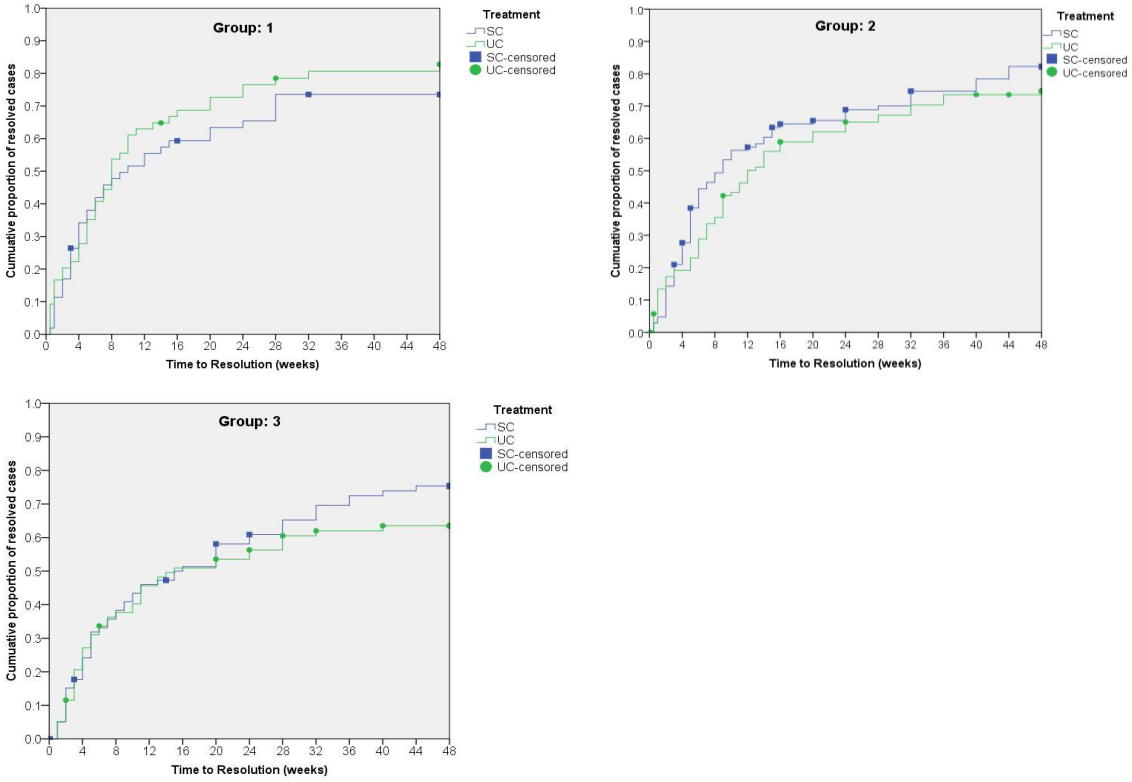
9 Overall, how **bothersome** has your back or leg pain been in the **last 2 weeks**?

Not at all	Slightly	Moderately	Very much	Extremely
☐	☐	☐	☐	☐
0	0	0	1	1

Total score (all 9): _____ Ψx Subscale Score (Q5-9):_____

Funded by Arthritis Research UK

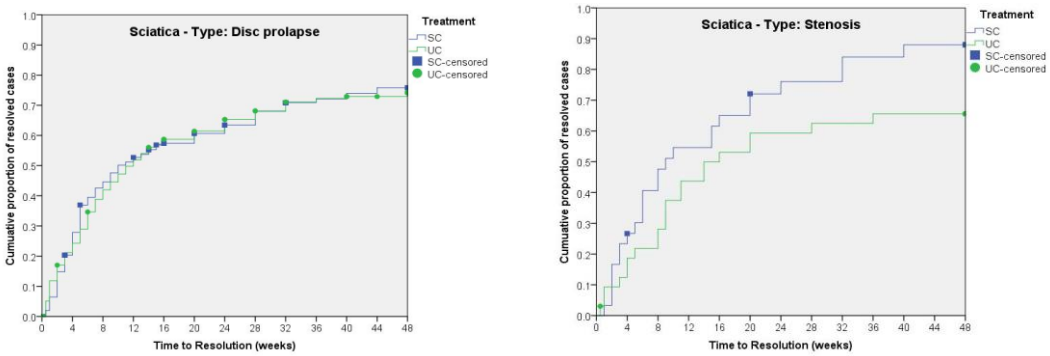
Figure 2. Time-to-event (time to first resolution of sciatica symptoms) in each of the sciatica groups 1, 2, and 3



HR (Group 2 vs Group1) = 1·46 (95% CI; 0·84, 2·54)
HR (Group 3 vs Group1) = 1·43 (95% CI; 0·78-2·62)

SC=Stratified Care; UC=Usual Care; HR=Hazard Ratio.

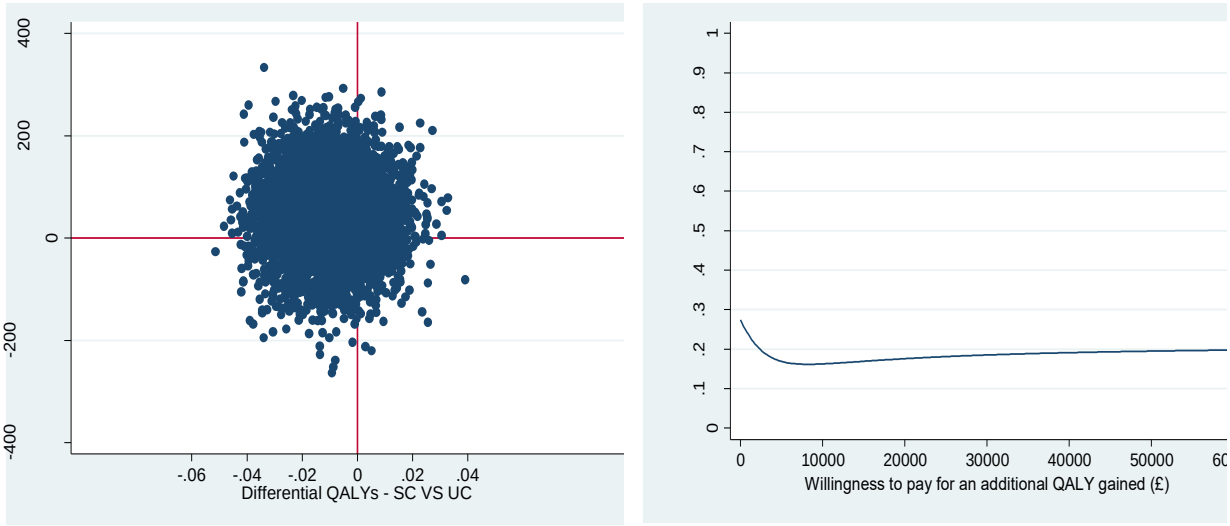
Figure 3. Time-to-event (time to first resolution of sciatica symptoms) in those with a clinical diagnosis of disc-related sciatica and those with clinical diagnosis of spinal stenosis



HR (stenosis vs disc prolapse) = 1·92 (95% CI: 1·01, 3·65)

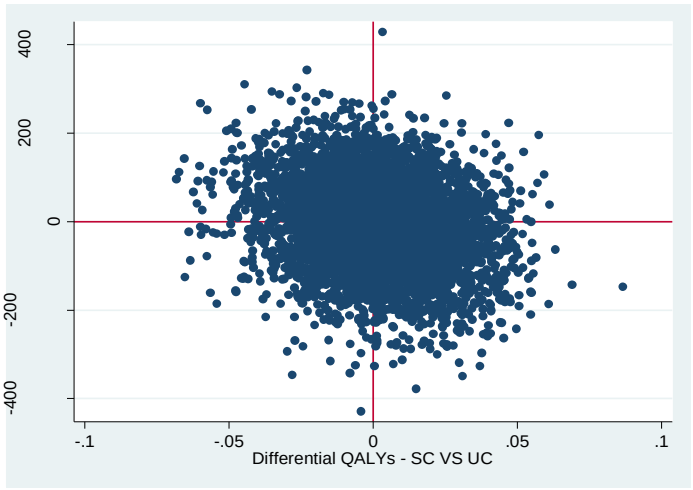
SC=Stratified Care; UC=Usual Care; HR=Hazard Ratio.

Figure 4: Cost-effectiveness from the NHS perspective. (a) Cost-effectiveness plane comparing the SC intervention with UC, showing 5000 bootstrapped replicates of the ICER; and (b) CEAC for SC (intervention) compared with UC.



SC=Stratified care, UC=Usual care, QALY=quality-adjusted life year. QALYs (NHS perspective). ICER=incremental cost-effectiveness ratio.

Figure 5a Sciatica group 1: comparing SC with UC. (a) Cost-effectiveness plane; and (b) CEAC.



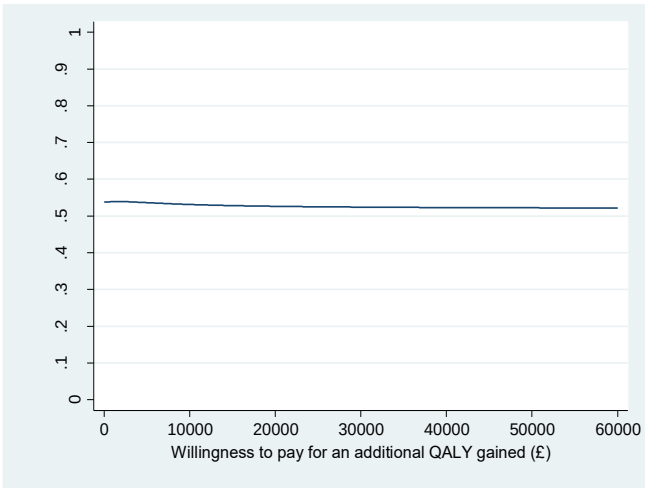
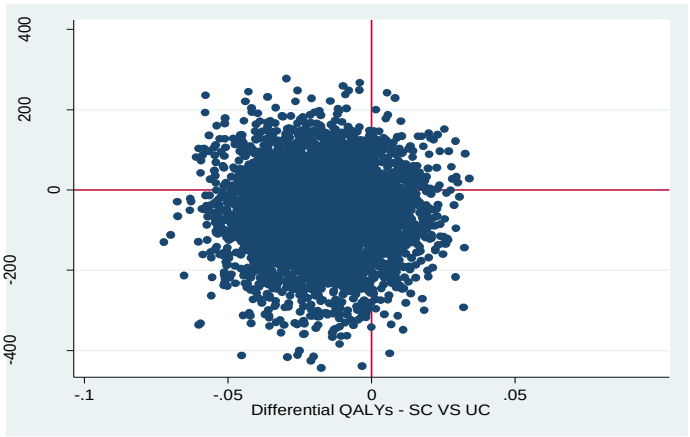


Figure 5b. Sciatica group 2: comparing SC with UC. (a) Cost- effectiveness plane; and (b) CEAC.



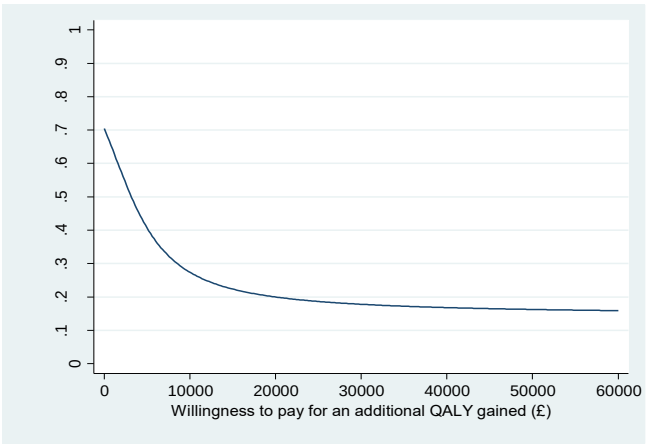
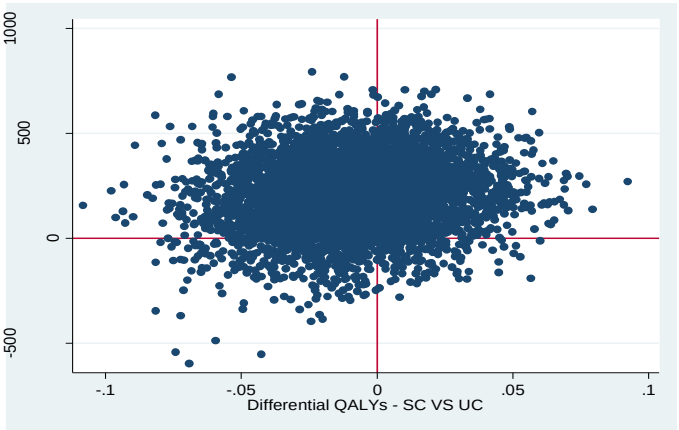
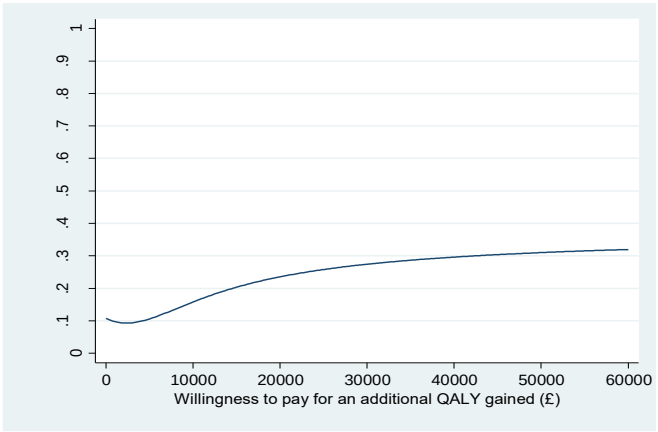


Figure 5c. Sciatica group 3: comparing SC with UC. (a) Cost-effectiveness plane; and (b) CEAC.





SC=Stratified care. UC=Usual care. QALYs=quality-adjusted-life-years.

Statistical Analysis Plan

Version 1.0 (16th February 2018)

Authors

Dr Martyn Lewis / Dr Reuben Ogollah / Dr Kika Konstantinou / Professor Nadine Foster / Dr Jesse Kigozi / Dr Sue Jowett

Trial Registration Number: ISRCTN75449581

Reference to Protocol Version 1 (Ref. 12/201/09 (dated, 12/2/2015))

1. Background and rationale

Sciatica is a common variation of low back pain (LBP) (Koes et al 2007) and although it is generally believed that many patients with sciatica have a favourable outcome, research evidence indicates that recovery rates, over a year, vary from 49-58% depending on the definition of recovery (Haugen et al 2011) . The condition is associated with significant pain and disability, leads to lower quality of life and increased use of healthcare resources, as well as lost workdays and it is responsible for much of the indirect costs and lost workdays associated with LBP (Konstantinou et al 2013, van Tulder et al 1995).

In contrast to LBP, there is no UK National Institute of Health and Clinical Excellence (NICE) guidance to date about the best way to treat sciatica patients, and little previous research specifically on this patient population in the primary care setting, where most patients are managed. In practical terms, current treatments range from information and advice, medications, exercise, traction, acupuncture and manual therapy, to more invasive treatments such as spinal injections and surgery, and although there is variation across clinicians, generally the current model of care followed for sciatica is 'stepped' (Lewis et al 2011). This typically means that initially there is a 'wait and see' policy in primary care with advice and pain medication, then for those patients not improving a referral to a primary clinician (such as a physiotherapist) might be considered for further treatments. Subsequently, patients failing to improve might be referred to specialist spinal services for investigations and specialist management. Currently the only patients who are fast-tracked from primary care to spinal specialist opinion are those with suspected serious spinal pathologies, who are treated as emergency cases.

A UK Spinal Taskforce highlighted the need for better information about the clinical and cost effectiveness of early referral of sciatica patients with severe symptoms for consideration of secondary care treatments such as surgery or spinal injections (National Spinal Taskforce, Jan 2013). Several specialist UK Health Boards have suggested a need for a model of care that does not over-treat those with a good natural history yet spots the patients who do need more active treatment to help with symptoms, prevent chronicity and return to work (Commissioning Guide for Radicular Pain, May 2013). Stratified care, which is the model of better and earlier identification of patient subgroups for matched treatments, was found to be clinically superior and cost-effective for the broader population of patients with LBP with or without leg pain in primary care, compared to usual, non-stratified care (Hill et al 2011, Foster et al 2014). We are now adapting and extending the stratified care model in sciatica patients seeking treatment in primary care. The SCOPiC stratified care model combines key prognostic indicators with key clinical indicators of sciatica severity and allocates patients into one of three subgroups; for matched treatment. Patients in group 1 receive brief

education and self-management support in up to two physiotherapy treatment visits, patients in group 2 receive a course of evidence-based physiotherapy care, and patients in group 3 have a fast-track referral (including MRI scan) to spinal specialist assessment and opinion regarding further management and suitability for more invasive treatments. The trial will investigate the clinical effectiveness and cost-effectiveness of this stratified care model.

2. Aims and Objectives

The overall aim of the SCOPiC trial is to investigate whether the management of primary care patients with sciatica and suspected sciatica can be improved through stratified care. The specific objectives are:

Primary objective: To compare the clinical effectiveness of stratified care compared to usual, non-stratified care, in terms of patient-reported time to resolution of symptoms, for adults consulting in primary care with sciatica and suspected sciatica.

Secondary objectives:

- To compare the clinical effectiveness of stratified care compared to usual, non-stratified care, on a range of important secondary outcomes, including function, pain, quality of life, work loss, healthcare use and patient satisfaction
- To compare the cost-effectiveness of stratified care compared to non-stratified care over 12 months
- To investigate the impact of stratified care on service delivery, specifically proportions of patients receiving sciatica group-appropriate referrals and treatments
- To determine, and understand, the acceptability of the fast-track pathway to patients and clinicians

3. Design

This is a multi-centre pragmatic, assessor-blind, open-label two-arm, parallel randomised controlled superiority trial comparing stratified care versus usual, non-stratified care, with internal pilot and concurrent health economic evaluation and linked qualitative interviews. Allocation ratio is 1:1 which is achieved through stratified block randomisation (using random permuted blocks of size 2, 4 and 6) – including 'Centre' and 'sciatica subgroup' (1, 2, 3), as stratifying variables.

The interventions are described fully in section 4 of the Study Protocol. In brief, in the stratified treatment group: patients in group 1 (if they score 3 or less on the STarTBack screening tool) will receive brief education and self-management support in up to two treatment visits, patients in group 2 (STarTBack score of 4 or more overall but with 3 or less on the psychosocial subscale, and 3 or fewer clinical indicators; or STarTBack psychosocial subscale score of 4 or more, but 2 or fewer clinical indicators) will receive a course of evidence-based physiotherapy care, and patients in group 3 (score 4 or more in the STarTBack psychosocial subscale and 3 or more clinical indicators; or score 4 or more on the STarTBack tool and are positive on all 4 clinical indicators) will have a fast-track referral (including MRI scan) to spinal specialist assessment and opinion regarding further management and suitability for more invasive treatments. The control arm of the SCOPiC trial (usual, non-stratified care) is based on current usual primary care under the management of physiotherapists in the SCOPiC community clinic (no reference STarTBack tool score and clinical indicator-led guidance will be available to physiotherapists managing patients in this arm). The 'Research hypothesis': the null hypothesis is that outcome will be no different between the two study groups; the alternative hypothesis is that there will be a difference in outcome.

4. Randomisation

Eligible patients who consent to take part will be randomised to one of the two trial arms using a 1:1 web-based randomisation service ensuring allocation concealment, operated by the clinic administrator. Individual patients will be randomised, stratified by treatment site and sciatica group, using random permuted blocks of varying size (2, 4 and 6), to either stratified care or usual, non-stratified care. Thus, three Centres and 3 sciatica groups equates to 9 stratified cells upon which patients will be randomised in block sequences – with random selection from the following blocks: AB, BA, AABB, ABAB, ABBA, BAAB, BABA, BBAA, AAABBB, AABABB, AABBAB, AABBBA, ABAABB, ABABAB, ABABBA, ABBAAB, ABBABA, ABBBAA, BAAABB, BAABAB, BAABBA, BABAAB, BABABA, BABBAA, BBAAAB, BBAABA, BBABAA, BBBAAA.

The clinic administrator will use the web-based randomisation method (with a back-up process to telephone the Keele Clinical Trials Unit (CTU) randomisation service in the event of web access failure), provide information about treatment site (Centre 1, 2 or 3) and patient sciatica group (1, 2, 3), find out the random allocation for each participant and continue with patient's care pathway (stratified or usual care) as per protocol.

5. Sample size

The sample size is 470 participants in total, in order to compare stratified care to usual, non-stratified care, for superiority of care management. The primary outcome of interest in the SCOPiC trial is time to resolution of symptoms (defined as patient self-report of being 'completely recovered' or 'much better' compared to baseline (from the 6-point ordinal 'global perceived change' scale (GPC)). In our previous trial of stratified care for LBP (STarTBack trial) (Hill et al 2011), nearly 60% of patients in total had a clinically important improvement on the primary outcome measure (GPC) at 4 and/or 12 months follow up; the absolute difference at 4 months was 11%. If proportional hazards are to be assumed (i.e. in this case assumed relative rate of 'resolution'), this difference would equate to a hazard ratio (HR) in the interval 1.4-1.5. Allowing for 20% dropout, a sample size of 470 (235 per treatment group) is required to detect a HR between 1.4-1.5 with 80-90% power (given a two-tailed significance level of 5%) assuming a rate of resolution in excess of 60% and intra-class correlation for therapist effect less than 0.01 (based on estimates from STarTBack and other primary care trials (Hill et al 2011, Adams et al 2004) and allowing for a coefficient of variation in therapist cluster size of 0.65 (Eldridge et al 2006); specifically:

- a HR of 1.4 in median survival times with 90% power (if all patients in the trial are recovered by 12 months follow up and ICC for therapist effect is <0.001) [least conservative]
- a HR of 1.5 in median survival times with 80% power (if 60-65% of patients in the trial are recovered by 12 months follow up and ICC for therapist effect is 0.01) [most conservative]

Note, a HR above 1 (and correspondingly lower 'survival' function) in this context is a positive result in contrast to traditional survival analysis of mortality.

This sample size will also provide more than 80% power to detect a 'small' to 'moderate' standardised mean difference (effect size) of 0.35 (Cohen, 1988) between the two study arms in our key secondary outcome at 12 months follow-up (activity limitation measured using the sciatica version of the RMDQ) allowing for 1% therapist effect.

In an internal pilot, at 8 months from the start of recruitment (just over one third of the anticipated total recruitment period) we will assess recruitment, follow-up, completeness of response, and rate of resolution of symptoms.

6. Data verification

Data checking will be carried out on all variables to identify data entry errors and missing data. Any identified errors will be cross-checked against returned questionnaires and outstanding issues resolved by consensus opinion within the study team. All manually entered data will be verified

through a random 10% double-entry validation process (across all returned baseline and follow up questionnaires); the data entry will be considered valid if complete agreement of data entry is verified across 90% or more of the (randomly-chosen) test questionnaires and if any errors are spread across several variables (as opposed to being present on certain variables). In the case of consistent errors limited to one or few variables, the team will investigate and put in place an appropriate strategy for data entry for the variable(s) in question. If more than 10% of questionnaires have one or more data entry errors then necessary training and re-entry of data will be carried out (and further verification checks put in place). All discrepancies will be investigated and corrected ahead of final analysis.

For the primary outcome (perceived change scale) all data from the SMS-responses are electronically transmitted to the secure patient database. All back-up telephone responses are manually entered into the patient database by a single blind-assessor.

7. Blinding of analysis

For the Statisticians and Health Economists involved with the data analysis, the plan along with all monitoring reports and the interim analysis that occur during the implementation of the trial through to final analysis of the trial dataset will be carried out blind to treatment allocation. Treatment allocation is stored in a secure computer-server location which can only be accessed by authorised individuals outside of the 'analysis' team. In the event of any necessary emergency unblinding the trial statisticians will remain blind to treatment allocation (if required an independent statistician will be used to assist with any unblinded data handling). Trial statistician(s) will work with a dummy coded variable for treatment allocation until the dataset has been analysed (at least for the primary evaluation and key secondary analyses) and authorisation is provided by independent members of the Trial Steering Committee and Data Monitoring Committee to reveal group membership. However, as the SCOPiC trial in not investigating new treatments it is not envisaged that there will be any need for unblinding.

8. Interim analysis

In an internal pilot, we will assess recruitment and follow-up rates over the first 8 months of recruitment adjusting for initial staggered recruitment and set-up of GP practices and participating NHS sites. The internal pilot will also provide information on the following key aspects: success of GP practice recruitment, set-up and retention (ability to identify, recruit and maintain approximately 30 GP Practices (providing a combined population of approximately 150.000) anticipated to fulfil the sample size requirement of the main trial); success of physiotherapy site recruitment, training and engagement (ability to recruit and engage 2 Centres); adherence to the treatment protocols

(assessment of number of patients in the intervention arm that have treatment aligned with sciatica group on the algorithm); suitability of the patient selection criteria (by checking numbers that are entered into the study in contrast to numbers that are deemed ineligible according to the various criteria – numbers (%) of patients screened who do not fulfil eligibility criteria will be listed against each of the ineligibility criteria); proportion of participants allocated to each of the three stratified care groups (1, 2, 3); time to fast-track MRI and specialist opinion for those in sciatica group 3 (time in days from first clinic visit to time of consultation with the specialist), the event rate of the primary outcome (how many patients (% of patients) report being 'completely recovered' or 'much better' within the 4-month (truncated) window of follow up specific to the pilot) and rate of missing data for the primary outcome up to 4 months follow-up for all participants (stratified and usual care arms) recruited within the 8-month pilot phase. The interim data on event rate of the primary outcome (recovery), up to 4 months follow-up for all pilot participants (stratified and usual care arms) recruited within the 8-month pilot phase, will be used to re-assess the sample size/power calculation of the trial (as previously outlined). Rate of missing data for the primary outcome will also be checked in the pilot phase for all participants.

The considered criteria for re-evaluating and adjusting methods for recruitment and follow-up optimisation, based on this internal pilot will be if, from the start of patient recruitment:-

(i) Observed recruitment rate falls short of 70% of that anticipated i.e. less than 90 recruited over the first 8 month period (130 would be expected over the first 8 month period across Centres taking into account staggered GP recruitment and set-up).

(ii) Overall loss to follow up (dropouts i.e. withdrawals, deaths, departures) in the primary outcome measure (SMS) is in excess of 25% after taking into account sufficient lag time in response. To account for 'lag time', data collected for the first 7 months will be analysed as this time frame includes time for reminders (amounting to 4 weeks) to those not responding initially.

No formal interim analysis of patients' clinical outcomes is proposed for the internal pilot.

The Data Monitoring Committee (DMC) will review the data on recruitment and follow-up from the internal pilot (follow-up rates from primary outcome data collection by SMS/ phone and response rates to the 4 month postal questionnaire) and make recommendations to the Trial Steering Committee (TSC) and the Trial Funders in respect of re-evaluating and adjusting methods for recruitment and follow-up optimisation for the remaining timeline.

9. Study population

A CONSORT-style flowchart will illustrate uptake and patient progression through the trial from initial screening for eligibility to completion of the final primary outcome assessment. This will include:-

- numbers invited for screening;
- numbers (percent of invited) screened;
    - numbers (percent of number screened) who were eligible;
    - numbers (percent of number screened, with reasons) for ineligibility;
    - numbers (percent of number screened) not providing consent to study;
        - numbers randomised to the two trial arms;
            - numbers (percent of patients randomised) who received treatment (as per protocol) by treatment arm;
            - numbers (percent of patients randomised) actively withdrawing from follow up by treatment arm (including count of reasons for withdrawal) by week/month of follow up;
            - numbers (percent of patients randomised) who are successfully followed for the primary outcome (time to resolution of symptoms) and include various assumptions around 'loss-to-follow up' (missing) data (detailed in section 15 and 17).

The numbers included in the final analysis for the primary endpoint analysis will be all those who were randomised (according to intention to treat) with sensitivity analyses exploring the robustness of estimates to varying statistical assumptions and data missingness.

10. Compliance and protocol violations

All physiotherapists who deliver care to patients in the intervention arm of the SCOPiC trial will record treatment in a standardised format on CRFs in order to fully record the detail of the interventions provided. Thus we will document the types of treatments received and the number of treatment sessions. Each intervention will adhere to the specific treatment protocol (for sciatica groups 1, 2 and 3, as described in the study protocol) and any protocol deviations will be reported and recorded.

The physiotherapists treating patients in sciatica groups 1 and 2 will be responsible for providing good clinical governance to their patients and will be permitted to overrule the stratification algorithm recommendation for matched treatment if they strongly believe there is clear clinical evidence that the matched treatment recommended for a patient is inappropriate. As in our previous studies (e.g. STarTBack trial), such protocol deviations are expected to be rare and will always be discussed with the treating physiotherapist's spinal specialist mentor and the trial PI, and documented.

11. Interventions received

As mentioned in the section above, all physiotherapists delivering care to patients in the stratified care arm of trial, will record types of treatments on CRFs, including duration and number of sessions received. Each intervention will adhere to the specific protocol with supporting documentation developed for the trial and any protocol deviations will be reported and recorded. Details of the care patients receive in the 'fast-tracked' pathway and timeframe of any interventions delivered (such as surgical or injection procedures) will be collected by populating CRFs with the relevant information from the clinical letters generated in the interface clinics and/or secondary care for each patient as this is normal clinical practice. Similarly, all physiotherapists who deliver care to patients in the control arm of the SCOPiC trial will also record treatment on a CRF. This will include, date of start and completion of treatment, number of treatments received and types of physiotherapy interventions and/or onwards referrals to specialist services.

Following the 12 months of follow-up, reviews of patients' medical records for information on the sciatica treatments they have accessed will also be undertaken by members of the trial team for completeness.

Information on treatment received will also be collected via the postal questionnaires at 4 and 12 months.

The details of the treating physiotherapists will be collected on the CRFs – this information will be used to take account of potential therapist effects in the statistical analysis.

12. Baseline characteristics

Patients will be described by treatment group with respect to baseline socio-demographic and health-related characteristics (including randomisation stratification variables). Numerical variables will be summarised according to their mean values (standard deviation) or median (interquartile range) – depending on skewness of the distribution. Summary of categorical variables will be presented as frequency counts and percentages (calculated using the number of patients for whom data is available as the denominator). Tests of statistical significance of baseline balance/imbalance will not be undertaken.

13. Endpoints for analysis

Full detail on outcomes for the study is detailed in section 8 of the Study Protocol.

The primary outcome measure is time to first resolution of symptoms of sciatica, measured on a 6-point ordered categorical scale: 'completely recovered', 'much better', 'better', 'same/ no change', 'worse' and 'much worse' – the anchor being against the patients' baseline symptoms when they attended the SCOPiC research clinic ("Compared to how you were at the SCOPiC clinic X weeks/months ago, how are your back and leg symptoms today?"). The primary definition of patient-reported resolution of symptoms is defined as a response of either 'completely recovered' or 'much better', collected using regular SMS messages (with the alternative of brief phone calls for those where text messaging is not possible or missed). Data collection for the primary outcome will occur weekly starting on the first Sunday following a participant's assessment at the SCOPiC research clinic, for the first 16 weeks for all participants, and thereafter monthly up to week 48, or until stable resolution of symptoms (defined as: two consecutive responses of 'completely recovered' or 'much better'). Secondary definitions of good outcome comprise: (i) two consecutive recordings of 'completely recovered' or 'much better' ('stable resolution'); (ii) 'improvement' (as opposed to 'resolution') through response of 'completely recovered', 'much better' or 'better' (through single response (or two consecutive responses to denote 'stable improvement'). A comprehensive reminder approach is in place for non-responders in order to minimise missing data – for details see Study Protocol.

Secondary health outcome measures and resource use data are collected via the postal questionnaires at 4 and 12 months follow up. These are listed in full in section 8.2 and Table 1 of the Study Protocol. For health outcome measures scores will be generated from available standard (validated) algorithms.

14. Levels of confidence and p-values

All applicable statistical tests will be performed using a two-sided 5% significance level. All confidence intervals of primary and secondary outcomes will be presented at the same level of 95% two-sided. There will be no adjustment for multiplicity since there is one primary endpoint evaluation. Interpretation around any statistical significance of secondary outcomes will consider the limitation of multiple testing. We will report the number of observations used in each analysis.

15. Missing data

The number of missing data for the primary outcome measure of perceived change will be reported by study group. Primary data will be utilised to the point of 'resolution of symptoms' ('completely recovered' or 'much better') or censoring. Participants with no available outcome data will be right-censored at week 1, and withdrawals / dropouts will be right-censored on the day they last provided

data. In the primary analysis, if any primary outcome data is missing before a recording of 'resolution of symptoms' we will assume that 'resolution' has not occurred.

To assess degree of missingness of primary data we will calculate two statistics, stratified by trial arm. First, the percent of complete cases (those providing full data up to the point of resolution of symptoms or end of follow-up period) will be reported. Second, we will derive the completeness (C-) ratio (expressed as a percentage): the total observed person-time follow-up relative to the potential person-time follow-up in a study (Clarke and Altman, Lancet 2002). Both statistics will be assessed against baseline characteristics to check on pattern of missingness.

16. Primary analysis

The primary analysis will compare time to self-reported resolution between stratified care and usual, non-stratified care, on an intention-to-treat basis (i.e. analysed as randomised). A Kaplan-Meier survival analysis will estimate the time from randomisation until first resolution of symptoms. Patients who drop out of the study through active withdrawal will be censored at the time interval this occurs (by contrast, patients lost to follow up at any time point are continued to be followed up until they actively withdraw). This will provide us with the data for comparing the relative mean and median survival times of the two trial arms. A Cox proportional hazards regression analysis will compare time to resolution between arms by calculation of a HR of rates of resolution along with 95% confidence interval estimates (and corresponding p-value) adjusted for Centre, sciatica group (stratifying variables) and pain duration. The treatment variable will be coded as 0=non-stratified care; 1=stratified care. The primary outcome will be classified as: 0= no resolution of symptoms ('better', 'no change', 'worse' or 'much worse'); 1= resolution of symptoms ('completely recovered' or 'much better'). The HR will be presented along with a 95% confidence interval for the HR; a p-value<0.05 (two-tailed) based on the Wald test statistic will signify rejection of the null hypothesis of no difference in recovery time between the two groups. A statistically significant p-value with HR>1 would indicate statistically significant shorter time to recovery for the intervention compared to the control group; a statistically significant p-value with HR<1 would indicate a (statistical) significantly longer time to recovery for the intervention compared to the control.

The primary analysis and sensitivity analyses will be double-analysed by two statisticians working independently (from the source data) following the final agreed analysis plan. Any differences will be resolved through consensus agreement; in the event of any continued disagreement a third independent (blind) statistician will review the two sets of analyses and make judgement as to the most appropriate set of results.

Analyses will be conducted using Stata, R and M-Plus. In Stata (version 13) the *stcox* command fits, via maximum likelihood, a proportional Cox hazards frailty model by specifying the *shared (cluster)* option, with the physiotherapist being our cluster variable (to adjust for the therapist effect). Though commonly the semi-parametric Cox-model is generally preferred in medical research, alternative parametric proportional hazards models have been proposed, for example using Weibull, exponential and lognormal distributions (Royston and Lambert, 2011; Pourhoseingholi et al., 2007); these can be used within a mixed-model via the *stmixed* command, and will be scrutinised alongside the Cox model (as previously detailed).

17. Sensitivity analyses (of the primary endpoint)

A number of sensitivity analyses will be carried out to test the rigour and robustness of the primary outcome evaluation through evaluation of:

- Alternative assumptions regarding missing data – for the primary evaluation, missing data is assumed to be synonymous with non-recovery. The primary evaluation is based on 'recovery' at the first point of a positive response, but if any missing data immediately precede this response then all these observations are assumed to be indicative of 'non-recovery' – an additional sensitivity analysis will set the time interval of recovery as the mean time between the last patient's response (indicating 'non-resolution') and the time at which 'resolution' is first classified. A more extreme sensitivity analysis will take the contrary view on missingness to equate to, and imputed as, a 'resolved' case.
- Alternative assumption regarding interval-censoring– since we only know the interval of time within which the resolution occurred and not the exact time (especially after the first 16 weeks when outcome data is collected monthly), a further sensitivity analysis will use methods that allow for interval censoring. This will be achieved through non-parametric maximum likelihood estimation (e.g. using the icfit function in package interval or the Icens package in R).
- Alternative definitions of good outcome - we will use separate secondary classifications based on 'stable resolution'; 'improvement', and 'stable improvement' (as described previously).
- Analysis of subgroups of participants that: (i) complete follow up – i.e. not including censoring, and (ii) receive appropriate matched treatment – as per treatment protocol (this will need to follow the unblinding of the trial statisticians to treatment allocation). Protocol deviations for the patients allocated to the intervention arm will be defined as: (i) patients allocated to sciatica group 1 but receive more than two treatment sessions with the physiotherapist, (ii) patients allocated to sciatica group 2 but receive less than three treatment sessions, (iii)

patients allocated to sciatica group 3 but are not seen by spinal specialist, and (iv) patients allocated to groups 1 or 2 but are referred to spinal specialist services and imaging investigation.

18. Subgroup Analyses

A small number of re-analyses of the primary endpoint analysis of time to resolution (as described above under Primary Analysis and Sensitivity Analyses) will be carried out to include testing the effectiveness of stratified care for those with/without suspected disc-related radiculopathy as determined by clinical assessment in the SCOPiC clinic visit, and for patients in each sciatica group (1, 2, 3). Descriptive statistical summaries will be provided through mean/median time to resolution per treatment group per patient subgroup. Tests of statistical significance will be through evaluation of 95% interval estimates / p-values for the interaction term for the product of subgroup variable by treatment group within the Cox regression model adjusting for Centre, sciatica group (stratifying variables) and pain duration.

19. Secondary outcomes analysis

We will analyse between-group differences in secondary outcomes at 4 and 12 months and provide point and 95% interval estimates from longitudinal linear- and logistic- mixed regression models as appropriate to the outcome data being analysed (linear- for numerical measures and logistic- for categorical measures) adjusting for Centre, sciatica group (stratifying variables) and pain duration. Time-by-group interactions will be included as well as time-by-(baseline) covariates to account for potential attrition bias. Descriptive summary of mean scores for the two study groups and difference in mean scores (numerical outcomes) and frequency counts (percentages) along with odds ratios (categorical outcomes) will be presented – between-group comparisons being presented in the form of point and 95% interval estimates, alongside p-values for the test of statistical association. Main analysis will be by intention-to-treat.

20. Process outcomes analysis

This will involve cross-tabulating sciatica groups by different healthcare resource utilisation such as physiotherapy, GP consultations, secondary care consultations and treatments. For example, patients in group 1 are expected to have no more than two physiotherapy sessions in the intervention arm of the trial and we anticipate this low level attendance to occur more frequently in those participants randomised to stratified care than those randomised to usual care who proceed to access

physiotherapy services. Secondary care specialist opinion is expected to occur more frequently and earlier for participants in stratified care than usual care, for patients who are in sciatica group 3. We will examine and report the number and percentage of participants who proceeded to secondary care treatments, and the types of interventions they received, in both treatment arms – and stratified by sciatic group. Analysis will include descriptive summary and formal comparison through Mann-Whitney rank test as appropriate. For the patients randomised to usual care arm, the GPs opinion on their preferred approach of managing such patients (i.e. keeping patient under GP care, referring patient to physiotherapy, or referring patient to specialist spinal services), when available, will be descriptively compared to what actually happens to these patients at the research clinic as recorded on the CRFs.

We will also examine whether there are any differences in sciatica group stratification among the three recruitment centres by cross-tabulating the sciatica group by recruitment centre. If there are any systematic differences in the sciatica group allocation among the recruitment centres then we will examine the association between the sciatica stratification and: (i) socioeconomic status of the participants from each centre (based on the National Statistics Socio-economic Classification derived from the job title), and (ii) area level deprivation of the participants in each centre, to describe the socio-demographic profiles of the patient sciatica groups.

21. Assumption checking

The Cox regression model assumption of proportional hazards will be examined in two ways: (i) firstly, through graphical review of the survival curves – if the survival curves are observed to cross this would indicate non-proportionality; (ii) through inclusion of a time-group interaction in the regression model with statistical significance of this term signifying important deviation from the assumption of proportional hazards. If either of the two examinations shows violation of the proportional hazards assumption then alternative statistical testing will be performed using an unadjusted log rank test.

For the linear models we will examine inverse normal plots to check for normality (in the event of any reasonable violation we will use a suitable data-transformation function). Potential covariance structures will be explored for goodness-of-fit of mixed models through comparing likelihood and Bayesian Information Criteria (BIC).

22. Health economic analysis

The within-trial health economic analysis will determine the cost-effectiveness of a stratified care model for sciatica in primary care compared with usual, non-stratified care. A cost-consequence analysis will initially be reported, describing all the important results relating to costs and outcomes. Subsequently, an incremental cost-utility analysis will be undertaken using patient responses to the EQ-5D-5L questionnaire to calculate the cost per additional quality-adjusted life year (QALY) gained.

The analysis will be performed according to the intention-to-treat principle, with the multiple imputation technique adopted to address missing EQ-5D-5L and cost data. All estimates will be presented as means with bootstrapped 95% confidence intervals. Patient responses to the EQ-5D-5L questionnaire will be converted to tariff values using the UK Crosswalk value set, and QALYs over the 12 month time period will be calculated for each study participant, using the area under the curve method. The base-case analysis will adopt a health care perspective, incorporating UK National Health Service (NHS) and private sciatica-related healthcare resources utilised during the 12-month follow-up period. However, analysis from a wider societal perspective will also be undertaken, to explore the impact on the results when productivity costs are taken into account. Additional exploratory analyses will consider the cost-effectiveness for the sciatica groups (1, 2, 3) separately, a strategy previously used in stratified care for LBP. Deterministic and probabilistic sensitivity analyses will be conducted to test the robustness of the base-case results and overall uncertainty in the trial cost and outcome data respectively. This will include for example a complete case analysis as an alternative to using an imputed data set, and any assumptions made in the data collection and analysis methods.

Uncertainty in the trial data will be explored by undertaking bootstrapping using STATA to produce 5000 bootstrap replications of cost-QALY difference pairs. Cost-utility planes and acceptability curves will be derived in order to provide a graphical display (plane) and quantification (curve) of the level of uncertainty around incremental cost-effectiveness ratios (ICERs). The cost-effectives acceptability curves will be used to show the probability that the stratified care model is cost-effective against threshold values for cost-effectiveness.

23. Adverse events and serious adverse events

The number of adverse / serious adverse events and degree of severity of such events are likely to be low given the health condition and nature of the intervention in question. Frequency counts (and as a percentage of the total patients treated) who suffer adverse events in each study group will be recorded. This will be recorded in total and also stratified according to whether the events are serious/not serious and expected/unexpected.

A list of potential adverse events (AEs) and serious adverse events (SAEs) is presented in the Study Protocol. The SCOPiC trial is investigating the effectiveness of new care pathways (stratified care) for sciatica and not new treatments for the condition. The treatments themselves are all part of routine clinical practice and it is therefore unlikely that there will be SAEs that are related to the trial intervention.

Occurrence of AEs/SAEs will be reported by participating physiotherapists and other clinicians, and also by patient self-report in their 4 and 12 month postal questionnaires.

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