SUPPLEMENTARY MATERIAL

Supplementary table 1. Clinical effectiveness – primary complete case analysis of primary and secondary outcomes at 3-months follow up

	TG		NTG		Between group difference	
	Baseline Mean (SD) or n/N	Follow up Mean (SD) or n/N	Baseline Mean (SD) or n/N	Follow up Mean (SD) or n/N	Mean difference or Odds ratio (95% CI)	P-value
Primary outcome						
Pain NRS: clinic	7.5 (1.1)	4.0 (2.0)	7.5 (1.1)	4.9 (2.5)	0.7 (-0.3 to 1.8)	0.17
Secondary outcomes						
Pain NRS: 4 day	7.3 (1.1)	3.9 (2.2)	7.4 (0.9)	5.0 (2.2)	0.8 (-0.2 to 1.8)	0.13
Pain relief ≥50%		17/37 (46%)	-	15/48 (31%)	0.6 (0.2 to 1.8)	0.42
Pain relief ≥30%		27/37 (74%)	-	23/48 (48%)	0.3 (0.1 to 0.9)	0.02
EQ-5D-5L	0.32 (0.22)	0.59 (0.19)	0.30 (0.24)	0.52 (0.27)	-0.06 (-0.17 to 0.04)	0.23
PGIC	-	36/37 (97%)	-	41/48 (85%)	0.1 (0.1 to 0.9)	0.04
ODI	56.1 (13.6)	37.2 (18.9)	57.6 (14.9)	43.1 (21.7)	2.8 (-4.1 to 9.8)	0.42

Supplementary table 2. Impact of different imputation methods – between group difference (95% CI), P-value (all N=105)

	Multiple imputation	LOCF	LOCF + best case	LOCF + worst case
6-months follow up				
NRS clinic	0.0 (-1.0 to 1.1), 0.98	-0.7 (-1.6 to 0.3), 0.17	-0.3 (-1.1 to 0.6), 0.53	-1.1 (-2.2 to 0.4), 0.06
NRS 4-day	0.2 (-0.8 to 0.2), 0.69	-0.2 (-1.2 to 0.8), 0.69	0.2 (-0.8 to 1.1), 0.74	-0.6 (-1.6 to 0.5), 0.29
≥50% pain relief	1.2 (0.4 to 1.6), 0.71	1.6 (0.7 to 3.8), 0.25	1.6 (0.7 to 3.8), 0.25	1.6 (0.7 to 3.9), 0.25
≥30% pain relief	1.4 (0.4 to 3.4), 0.50	1.9 (0.8 to 4.3), 0.12	0.8 (0.4 to 1.8), 0.59	1.9 (0.8 to 4.3), 0.12
EQ-5D	0.01 (-0.12 to 0.10), 0.86	0.04 (-0.06 to 0.13), 0.43	-0.02 (-0.10 to 0.09), 0.67	-0.06 (-0.16 to 0.04), 0.23
PGIC	0.87 (0.3 to 2.1), 0.67	Not applicable	0.1 (0.0 to 1.2), 0.08*	2.2 (0.8 to 5.8), 0.13
ODI	0.3 (-1.2 to 7.8), 0.94	-2.0 (-8.7 to 4.6), 0.54	1.7 (-5.8 to 9.2), 0.65	-0.3 (-6.1 to 5.3), 0.92
3-months follow up				
NRS clinic	0.6 (-0.4 to 1.7), 0.23	-0.2 (-1.1 to 0.8), 0.70	-0.4 (-0.5 to 1.2), 0.37	-0.6 (-1.7 to 0.5), 0.28
NRS 4-day	1.0 (-0.1 to 2.0), 0.06	0.0 (-0.8 to 0.9), 0.91	0.5 (-0.3 to 1.3), 0.24	-0.3 (-1.3 to 0.8), 0.61
≥50% pain relief	0.5 (0.3 to 1.7), 0.41	1.0 (0.4 to 2.4), 0.95	1.0 (0.4 to 2.4), 0.95	1.0 (0.9 to 1.0), 1.00
≥30% pain relief	0.3 (0.2 to 0.9), 0.03	0.8 (0.4 to 1.8), 0.67	0.8 (0.4 to 1.9), 0.59	0.8 (0.4 to 1.9), 0.67
EQ-5D	-0.04 (-0.14 to 0.66), 0.48	0.02 (-0.07 to 0.11), 0.68	-0.06 (-0.16 to 0.04), 0.23	-0.04 (-0.09 to 0.01), 0.10
PGIC	0.1 (0.1 to 1.0), 0.05	Not applicable	0.1 (0.0 to 1.0), 0.05	2.3 (0.9 to 5.8), 0.08
ODI	1.6 (-5.2 to 8.5), 0.63	-1.9 (-7.9 to 4.2), 0.54	2.8, (-4.1 to 9.7), 0.43	-0.9 (-7.5 to 0.55), 0.77

PGIC: best case – if missing assume satisfied; worst case – if missing assume dissatisfied

Supplementary table 3. Subgroup analyses for primary outcome at 6-months follow up - Interaction test coefficient (95% CI), P-value

	Site	Gender	age	Presence of FBSS	Type of stimulation*
NRS clinic	0.7 (-0.5 to 1.9), 0.25	1.4 (-0.6 to 3.5), 0.17	0.1 (-3.1 to 3.3), 0.96	-0.2 (-2.3 to 1.9), 0.85	0.2 (-0.8 to 1.2), 0.70

* conventional vs HF vs burst

Supplementary table 4. Medication use

	TG	NTG
Continued medication	50/54	49/51
Stopped medication	3/54	1/51
Missing data	1/54	1/51

Supplementary table 5. Diagnostic performance of test screen – worst case scenario

3-months follow up			
	Pain relief ≥50%	**Pain relief <50%**	**Totals**
Trial screen positive	17	20	37
Trial screen negative	5	0	5
Totals	22	20	42
Sensitivity (%)	77 (95% CI: 55 to 92)		
Specificity (%)	0 (95% CI: 0 to 17)		
Positive Likelihood Ratio	0.77 (95% CI: 0.62 to 0.97)		
Negative Likelihood Ratio	Not calculable		
Positive Predictive Value (%)	46 (95% CI: 40 to 51)		
Negative Predictive Value (%)	Not calculable		
6-months follow up			
	Pain relief ≥50%	**Pain relief <50%**	**Totals**
Trial screen positive	15	24	39
Trial screen negative	3	2	5
Totals	18	26	44
Sensitivity (%)	83 (95% CI: 59 to 96)		
Specificity (%)	8 (95% CI: 1 to 25)		
Positive Likelihood Ratio	0.90 (0.71 to 1.14)		
Negative Likelihood Ratio	2.17 (0.40 to 11.69)		
Positive Predictive Value (%)	38 (95% CI: 33 to 44)		
Negative Predictive Value (%)	40 (95% CI: 11 to 78)		

Supplementary table 6. Diagnostic performance of test screen – best case scenario

3-months follow up			
	Pain relief ≥50%	**Pain relief <50%**	**Totals**
Trial screen positive	17	20	37
Trial screen negative	0	5	5
Totals	15	25	42
Sensitivity (%)	100 (95% CI: 80 to 100)		
Specificity (%)	20 (95% CI: 7 to 41)		
Positive Likelihood Ratio	1.25 (95% CI: 1.03 to 1.52)		
Negative Likelihood Ratio	0.00		
Positive Predictive Value (%)	46 (95% CI: 41 to 51)		
Negative Predictive Value (%)	100		
6-months follow up			
	Pain relief ≥50%	**Pain relief <50%**	**Totals**
Trial screen positive	15	24	39
Trial screen negative	0	5	5
Totals	15	29	44
Sensitivity (%)	100 (95% CI: 78 to 100)		
Specificity (%)	17 (95% CI: 6 to 36)		
Positive Likelihood Ratio	1.17 (1.00 to 1.36)		
Negative Likelihood Ratio	0.00		
Positive Predictive Value (%)	38 (95% CI: 35 to 42)		
Negative Predictive Value (%)	100		

Supplementary table 7. Adverse events and serious adverse events (6 months follow-up)

	TG (n=54) **n patients (%)/n events**	**NTG (n=51)** **n patients (%)/n events**
Serious Adverse Event	1 (2)/1	0 (0)/0
Infected haematoma in implantable pulse generator pocket	1 (2)/1	0 (0)/0
Adverse Event	8 (15)/10	8 (16)/10
Superficial wound infection responding to antibiotics, implant saved	2 (4)/2	0 (0)/0
Deep infection not responding to antibiotics, implant explanted	0 (0)/0	0 (0)/0
IPG or anchor site pain requiring re-operation	1 (2)/1	0 (0)/0
New neurological change thought to be due to implanted epidural electrodes	1 (2)/1	1 (2)/1
Lead migration or breakage requiring re-operation	1 (2)/2	0 (0)/0
Moderate to severe pain reported over the implant sites	1 (2)/1	1 (2)/1
Other (non-device related AEs)	3 (6)/3	6 (11)/8

Supplementary table 8. Adverse events and serious adverse events (3-month follow-up)

	TG (n=54) **n patients (%)/n events**	**NTG (n=51)** **n patients (%)/n events**
Serious Adverse Event	1 (2)	0 (0) /0
Infected haematoma in implantable pulse generator pocket	1 (2)	0 (0.0) / 0
Adverse Event	5 (9)/ 5	3 (5.9) / 4
Superficial wound infection responding to antibiotics, implant saved	2 (4)/2	0 (0)/0
Deep infection not responding to antibiotics, implant explanted	0 (0)/0	0 (0)/0
IPG or anchor site pain requiring re-operation	0 (0)/0	0 (0)/0
New neurological change thought to be due to implanted epidural electrodes	0 (0)/0	0 (0)/0
Lead migration or breakage requiring re-operation	0 (0)/0	0 (0)/0
Moderate to severe pain reported over the implant sites	1 (2)/1	0 (0)/0
Other (non-device related AEs)	2 (4)/2	3 (6)/4

Supplementary material: economic evaluation

Perspective
Base-case analyses were conducted from the NHS perspective, with additional analyses presented from a societal perspective.

Time horizon
The within-trial analysis compared costs and consequences over the six-months follow-up period of the TRIAL-STIM Study.

Discount rates for costs and benefits
No discount rate was required for the within-trial analysis since the time horizon is only six-months (i.e. less than one year).

Resource use
For each patient enrolled in the trial, the case report form (CRF) registered clinical data and resource events at specific measurement points including the day of the intervention, three and six-months follow-up. Relevant resource events for each patient were extracted from the CRF. These included appointments with healthcare professionals, procedures performed, investigations, inpatient hospitalisations, treatment given, management of adverse events and work absenteeism related with the chronic pain condition.
In addition to the questions about appointments with healthcare professionals in the previous 3 months, the CRF includes a section on non-medicinal pain treatments. These data were excluded from the cost-consequence and cost-effectiveness analyses, as it was felt these were likely to be duplicates of the patient reported 'other healthcare professionals', and therefore there was a risk of double counting of resource use.
Supplementary table 9 lists the resource use for patients who received the allocated intervention. The table includes patients who were lost to follow-up and may therefore represent an underestimate of the actual resource use consumption.

Supplementary table 9. Resource use by item in 6-month follow-up period

Resource	TG (N=47)	NTG (N=49)
Intervention costs		
Screening trial	47	0
Device implant	42	49
Failed screening trial	5	0
Visits to healthcare professionals (non-pain related): Total (mean per patient)		
GP	103 (2.19)	110 (2.34)
Nurse (GP practice)	21 (0.45)	47 (1)
Specialist doctor	39 (0.83)	61 (1.30)
Specialist nurse	28 (0.60)	30 (0.64)
Physiotherapist	71 (1.51)	50 (1.06)
A&E	7 (0.15)	9 (0.19)
Other HC	3 (0.06)	14 (0.30)
Visits to healthcare professionals (pain related): Total (mean per patient)		
GP	34 (0.72)	47 (1)
Nurse (GP practice)	0 (0)	2 (0.04)
Specialist doctor	19 (0.40)	28 (0.60)
Specialist nurse	13 (0.28)	17 (0.36)
Physiotherapists	45 (0.96)	23 (0.49)
A&E visits	2 (0.04)	3 (0.06)
Other HC	1 (0.02)	7 (0.15)

AEs by category		
SAEs (including explanting device)	2	0
Re-implantation	1 [c]	0
Superficial wound infection responding to antibiotics, implant saved	2	1 [a]
New neurological change thought to be due to implanted epidural electrodes	1	1
Moderate to severe pain reported over the implant sites	2	3
Other	1	0
Unscheduled visits [b]		
Reprogrammed	0	2
Surgical procedure (SCS) [c]	0	1
Other	2	1
Work absence (days)		
Full-time	104	151
Part-time	123	4

[a] One patient has been re-categorised to this category as upon further inspection was not explanted, although had a 4 day hospital stay and antibiotics upon discharge
[b] At any point within -months follow-up, multiple visits per patient possible
[c] One patient in this category but whilst listed for explant the explant did not take place therefore no cost has been allocated

Adverse events
Each adverse event that occurred during the trial was categorised according to its relationship to the study. In the base case within-trial economic analysis only those adverse events recorded as having a "possible", "probable" or "definite" relationship to the study were included. Eleven treatment-related AEs were recorded along with 2 serious AEs. Both SAEs occurred in patients in the TG group.

Supplementary table 10. Serious adverse events and assumed resource use

Serious AE	Details	Resource use
Infected haematoma in implantable pulse generator pocket	Explant detailed in notes	A& E admission Hospitalisation for infection Explant
Infection	No further details	A& E admission Hospitalisation for infection Explant Re-implant

Details of an additional patient who was hospitalised were included within the costing exercise. For all other AEs it is assumed that hospitalisations did not occur beyond a visit to A&E and follow-up antibiotics for 2 weeks for patients with an AE categorised as "Superficial wound infection responding to antibiotics, implant saved".

Unscheduled visits
During the trial period, a record was made of any unscheduled visits to a healthcare professional made by the patients. A total of 6 unscheduled visits were recorded. The action taken was categorised and the results by treatment group are shown in supplementary table 9.

Medication for pain
The medications used by the patients for pain were recorded at the start of the trial, with any changes to the use of pain medications recorded during the trial. The medications included were categorised as anti-inflammatories, anticonvulsants, antidepressants, opioids and any other medications that were described as prescribed for pain in the dataset. Each drug has been costed for the duration of use over the trial period. The trial protocol specified to only stop or reduce the dose of pain medications if requested by the patient.

Work absence
The perspective of the base case within-trial economic analysis is that of the NHS. However, as part of the resource use questionnaire provided to the patients, data were collected on work absenteeism over the trial period. Incorporating these data into the economic analysis extends the perspective to include some societal aspects. In the analysis only patients who described their work status as currently working at each time point are included.

Patients who are retired or are unable to work due to their pain, for example do not generate any costs. Patients who were part-time were assumed to earn half of the national average monthly earnings, estimated as half of the estimate day rate.

Supplementary table 11. Work-status

Time point	Work status	TG	NTG
Baseline	Working full-time	14	18
	Working part-time by choice	1	2
	Working part-time due to pain	9	2
	Does not work due to pain	21	20
	Does not work due to choice or other reasons	1	1
	Student	0	0
	Part-time student	0	0
	Retired	8	8
	Total (N)	**54**	**51**
6-months	Working full-time	13	17
	Working part-time by choice	2	2
	Working part-time due to pain	3	2
	Does not work due to pain	10	17
	Does not work due to choice or other reasons	2	1
	Student	1	0
	Part-time student	0	0
	Retired	8	9
	Total (N)	**39**	**48**

Time in surgery

As NHS Reference Costs include the costs of theatre time in their estimates, adding additional costs based on time in surgery would double-count this element of resource use. Therefore, no costs have been added to the time in surgery field. The results include complete cases only.

Supplementary table 12. Time in surgery

	TG (N=35)	NTG (N=46)	Between group unadjusted difference	Between group adjusted difference[a]
	Mean (SD)	Mean (SD)	Mean (95% CI)	Mean (95% CI)
Time in surgery (minutes)	124.31 (39.74)	91.48 (25.68)	32.86 (18.33 to 47.34)	36.66 (25.42 to 47.90)

[a] Adjusted for baseline EQ-5D index score, site, sex, age, failed back surgery syndrome

Valuation of resource use

Intervention costs have been taken from standard national costs. Secondary care data were valued using the National Reference Costs from the Department of Health.[1] Primary and community based health services were valued using National Reference Costs from the Personal Social Services Research Unit.[2] Productivity costs were valued considering national average weekly earnings[3] from the patient's perspective using the human capital approach. Cost components were added up to derive total patient level costs.

The costs assumed for each resource use item along with a description and the source of the costs are shown in supplementary table 13.

Supplementary table 13. Costs per resource use item

Resource use	Cost	Details	Source
Intervention and device costs			
Screening trial	£ 2,632.83	Insertion of Neurostimulator Electrodes for Pain Management	NHS Reference Costs (2017-2018)[1] HRG: AB14Z
Device implantation	£ 5,035.93	Insertion of Neurostimulator for Pain Management	NHS Reference Costs (2017-2018) [1] HRG: AB12Z
Non-rechargeable SCS device	£ 10,972.97	Device cost – non-rechargeable	Taylor et al [4] inflated to 2017/18 using HCSC index
Screening trial failure	£ 2,346.03	Screening trial removal of electrodes	Taylor et al [4] inflated to 2017/18 using HCSC index
Visits to healthcare professionals (non-pain related)			
Nurse (GP practice)	£ 14.00	Assume 20 minute appointment at £42 per hour	PSSRU 2018 [2]
GP	£ 37.40	per 9.22 minute consultation (patient contact)	PSSRU 2018 [2]
Specialist doctor	£ 134.89	consultant-led, spinal surgery service; non-admitted face to face follow-up	NHS Reference Costs (2017-2018) [1] HRG: WF01A 108
Specialist nurse	£ 81.28	non-consultant-led, WF01A 108 spinal surgery service; non-admitted face to face follow-up	NHS Reference Costs (2017-2018) [1] HRG: WF01A 108
Physiotherapist	£ 52.07	non-consultant-led, WF01A 650 physiotherapy; non-admitted face to face follow-up	NHS Reference Costs (2017-2018) [1] HRG: WF01A 650
A&E	£ 160.32	All admissions average Accident & Emergency	NHS Reference Costs (2017-2018) [1]
Other healthcare	£ 52.07	Assume same as physio	NHS Reference Costs (2017-2018) [1] HRG: WF01A 650
Visits to healthcare professionals (pain related)			
Nurse (GP practice)	£ 14.00	Assume same as non-pain visits	PSSRU 2018 [2]
GP	£ 37.40	Same as non-pain visits	PSSRU 2018 [2]
Specialist doctor	£ 146.74	consultant-led, pain; non-admitted face to face follow-up	NHS Reference Costs (2017-2018) [1] HRG: WF01A 191
Specialist nurse	£ 102.99	non-consultant-led, pain; non-admitted face to face follow-up	NHS Reference Costs (2017-2018) [1] HRG: WF01A 191

Physiotherapists	£ 52.07	non-consultant-led, physiotherapy; non-admitted face to face follow-up	NHS Reference Costs (2017-2018) [1] HRG: WF01A 650
A&E	£ 160.32	All admissions average Accident & Emergency	NHS Reference Costs (2017-2018) [1]
Other healthcare	£ 52.07	Assume same as physio	
Adverse events			
SCS device explant	£ 2,104.38	Electrode removal – inflated to 2017/18 prices using HCSC inflation index	Simpson et al [5]
Hospitalisation for infection	£ 8,621.60	Spinal Infection with Interventions, with CC Score 0-5	NHS Reference Costs (2017-2018) [1] HRG: HC31J
Non-hospitalisation AEs	£ 160.32	Assumed same as A&E visit	
2 weeks oral flucloxacillin qd	£ 5.56	28 tab pack 500mg x 2 (£2.28 per pack)	NHS Drug Tariff
Unscheduled visits, by action			
Reprogrammed	£ 134.89	Assumed to require a spinal surgery follow-up consultant visit	NHS Reference Costs (2017-2018) [1]
Surgical procedure (SCS)	£ 2,104.38	Explant – inflated to 2017/18 prices	Simpson et al [5]
Other	£ 134.89	Assumed to require a spinal surgery follow-up consultant visit	NHS Reference Costs (2017-2018) [1]
Work absence			
Earnings per week	£ 507.00	National average weekly earnings	ONS (2019) [3]
Part-time weekly earnings	£ 353.50	Half on the national average weekly earnings	Assumption

Costs

Supplementary table 14. Unadjusted costs at 6 months follow-up between treatment groups

	TG (N=47)		NTG (N=49)		Between group unadjusted differences
	Mean (SD)	Median	Mean (SD)	Median	Mean
Intervention and device costs					
Screening trials	2,632.83 (0)	2,632.83			2,632.83
Failed screening trials	249.58 (731.17)				249.58
Device implantations	14,305.83 (4,989.34)	16,008.90	16,008.90 (0)	16,008.90	-1,703.08
Visits to healthcare professionals (non-pain related)					
GP	81.96 (102.76)	74.8	83.96 (83.12)	37.4	2.00
Nurse (GP practice)	6.26 (12.32)	0	13.43 (21.94)	0	-7.17
Specialist doctor	111.93 (135.82)	0	167.92 (263.43)	134.89	-55.99
Specialist nurse	48.42 (80.68)	0	49.76 (87.50)	0	-1.34
Physiotherapist	78.66 (234.34)	0	53.13 (185.16)	0	25.52
A&E	23.88 (74.59)	0	29.45 (70.75)	0	-5.57
Other HC	3.32 (12.87)	0	14.88 (48.70)	0	-11.55
Visits to healthcare professionals (pain related)					
GP	27.06 (66.04)	0	35.87 (66.54)	0	-8.82
Nurse (GP practice)	0	0	0.57 (2.80)	0	-0.57
Specialist doctor	54.53 (87.42)	0	77.08 (143.07)	0	-22.55
Specialist nurse	22.48 (55.44)	0	28.20 (58.78)	0	-5.72
Physiotherapists	49.85 (153.53)	0	24.44 (90.88)	0	25.41
A&E	6.82 (46.77)	0	9.82 (38.83)	0	-3.00
Other HC	1.11 (7.609)	0	7.44 (33.61)	0	-6.33
Adverse events					
AEs	20.70 (64.42)	0	192.42 (1,254.23)		-171.72
SAEs	592.90 (412.89)	0	0	0	592.90
Unscheduled visits					
Reprogrammed	0 (0)	0	5.51 (26.97)	0	-5.51
Surgical procedure (SCS)	0 (0)	0	2.75 (19.27)	0	-2.75
Other	5.74 (39.35)	0	2.75 (19.27)	0	2.99
Medications					
Pain medications	493.09 (896.40)	214.12	680.91 (2,040.71)	218.10	-187.82
Concomitant medications for pain	10.18 (54.15)	0	9.73 (39.49)	0	0.45
Work absence	357.06 (1116.75)	0	316.62 (1,261.34)	0	40.44

Supplementary table 15 shows that TG incurred more costs than NTG. The total costs were estimated after multiple imputation using propensity mean matching. The difference was estimated using a generalized linear model to account for the distribution of the cost data. As shown in supplementary table 16, NTG remains less costly even once the impact of work absence is incorporated. The cost difference may also be larger if the additional surgery time required for patients undergoing a screening trial (as shown in supplementary table 12) could be appropriately included in the costs.

Supplementary table 15. Total costs at 6 months excluding work absence

	TG (N=54)	NTG (N=51)	Between group unadjusted difference	Between group adjusted difference[a]
	Mean (SD)	Mean (SD)	Mean (95% CI)	Mean (95% CI)
Total costs	19,073.38 (683.84)	17,487.90 (337.31)	1,585.26 (98.24 to 3,198.02)	1,341.22 (-34.26 to 2,832,85)

[a] Adjusted for baseline EQ-5D index score, site, sex, age, failed back surgery syndrome

Supplementary table 16. Total costs at 6 months including work absence

	TG (N=54)	NTG (N=51)	Between group unadjusted difference	Between group adjusted difference
	Mean (SD)	Mean (SD)	Mean (95% CI)	Mean (95% CI)
Total costs	19,491.98 (680.62)	17,813.10 (378.05)	1,678.22 (163.53 to 3,320.55)	1,471.08 (67.09 to 2,993.40)

[a] Adjusted for baseline EQ-5D index score, site, sex, age, failed back surgery syndrome

Effects

The primary within-trial outcome measure for the economic evaluation was health-related quality of life assessed at baseline, three and six-months follow-up using the EQ-5D-5L questionnaire. In line with NICE's position statement, base-case analyses were conducted using the crosswalk value sets for the EQ-5D-5L (NICE 2018).[6] Baseline EQ-5D index data was missing for one patient. There were 20 missing EQ-5D index scores at 3 months, and 19 missing values at 6 months. These analyses exclude patients with missing values at each time point.

Supplementary table 17. EQ-5D index scores at baseline, 3- and 6- months

EQ-5D index score [a]	TG	N	NTG	N	Between group unadjusted difference	Between group adjusted difference [b]
	Mean (SD)		Mean (SD)		Mean (95% CI)	Mean (95% CI)
Baseline (N=104)	0.323 (0.224)	53	0.302 (0.243)	51	-	-
3-months (N=85)	0.588 (0.196)	37	0.510 (0.276)	48	0.077 (-0.029 to 0.183)	0.062 (-0.040 to 0.164)
6-months (N=86)	0.569 (0.238)	39	0.529 (0.275)	47	0.039 (-0.072 to 0.151)	0.019 (-0.089 to 0.128)

[a] EQ-5D-5L cross-walked to EQ-5D-3L index scores
[b] Adjusted for baseline EQ-5D index score, site, sex, age, failed back surgery syndrome

Supplementary table 18. EQ-5D scores for patient with complete EQ-5D profiles

EQ-5D index score [a]	TG (N=35)	NTG (N=46)	Between group unadjusted difference	Between group adjusted difference [b]
	Mean (SD)	Mean (SD)	Mean (95% CI)	Mean (95% CI)
Baseline	0.322 (0.224)	0.313 (0.235)	-	-
3-months	0.599 (0.191)	0.529 (0.265)	0.069 (-0.036 to 0.175)	0.063 (-0.037 to 0.164)
6-months	0.567 (0.234)	0.524 (0.275)	0.044 (-0.071 to 0.159)	0.021 (-0.092 to 0.134)

[a] EQ-5D-5L cross-walked to EQ-5D-3L index scores
[b] Adjusted for baseline EQ-5D index score, site, sex, age, failed back surgery syndrome

Quality-adjusted life years are calculated by estimating the health-related quality of life of any given health state and multiplying in by the time spent in that health state. The measurement of quality-adjusted life years (QALYs) at six-month follow-up is used for the within-trial cost-utility analysis. QALYs have been calculated using the area under the curve approach, with regression-based adjustment for baseline EQ-5D index score. Supplementary table 19 shows the estimated QALYs for each group after multiple imputation, using propensity mean matching, of missing data.

Supplementary table 19. QALYs at 6 months follow-up using multiple imputation

QALYs	TG (N=54)	NTG (N=51)	Between group unadjusted difference	Between group adjusted difference[a]
	Mean (SD)	Mean (SD)	Mean (95% CI)	Mean (95% CI)
N=105	0.256 (0.124)	0.232 (0.161)	0.024 (-0.016 to 0.063)	0.017 (-0.015 to 0.049)

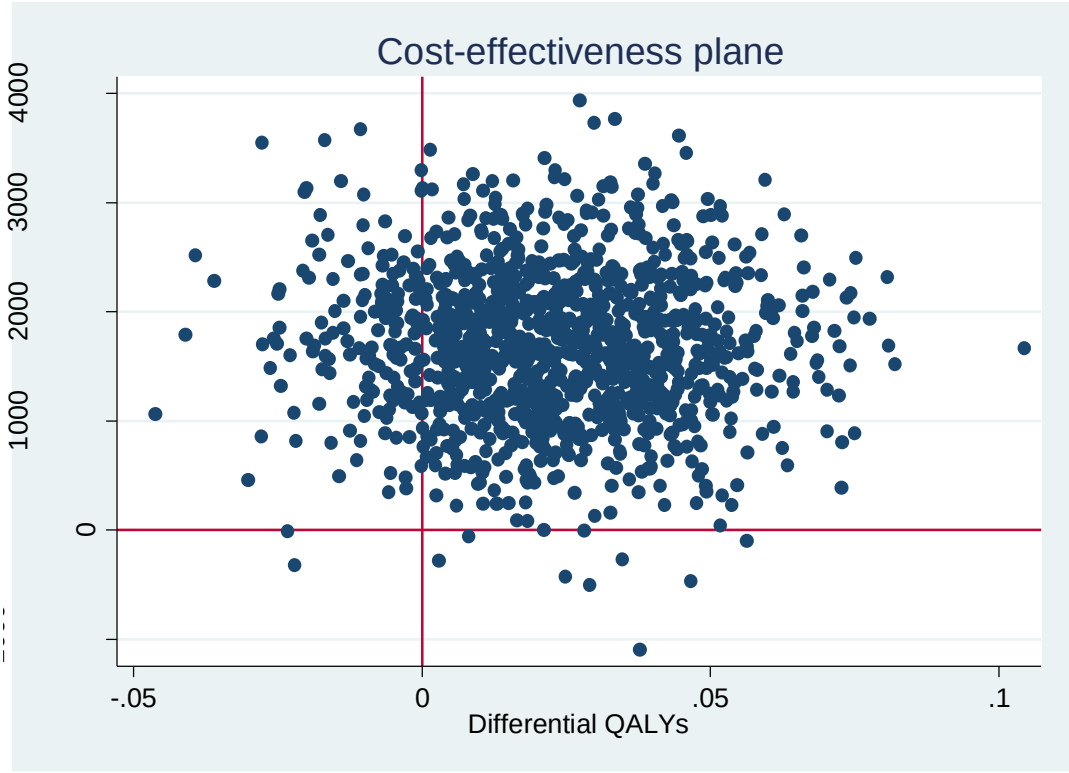
[a] Adjusted for baseline EQ-5D index score, site, sex, age, failed back surgery syndrome

Incremental analysis

The difference in costs between the treatment groups is divided by the difference in QALYs to generate an incremental cost-effectiveness ratio (ICER).

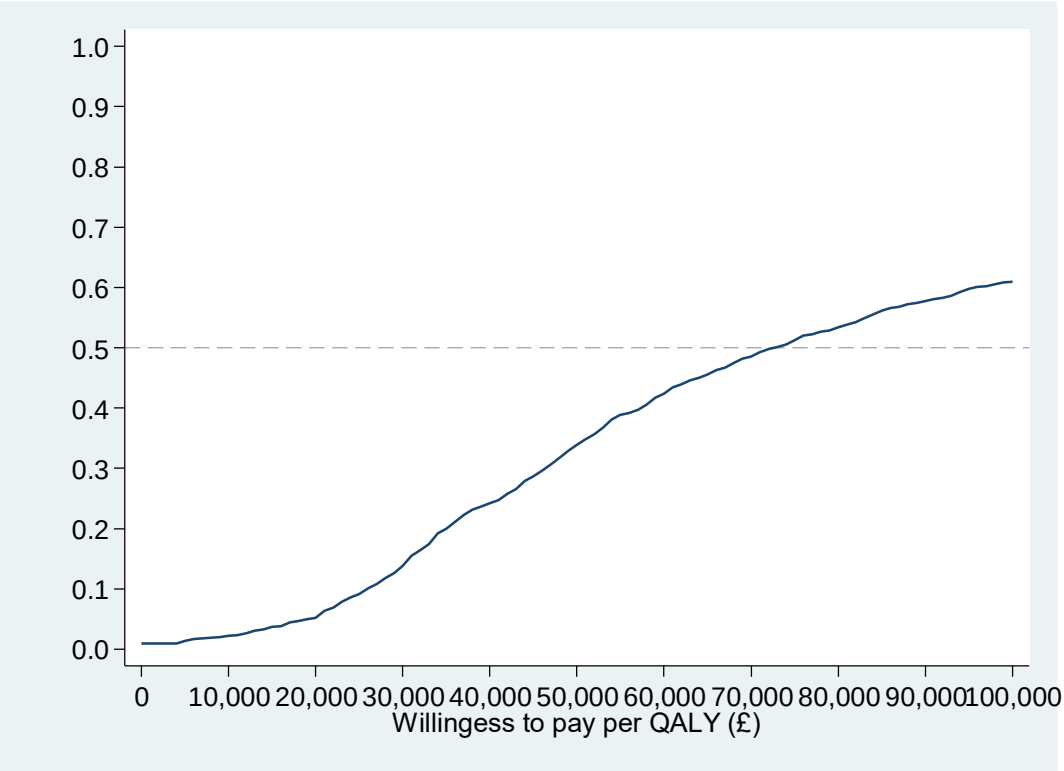
From an NHS perspective, a trial screening strategy generates more QALYs but at an increased cost, thus producing an ICER of £66,041 per additional QALY gained (unadjusted) and an ICER of £78,895 per additional QALY gained when adjusted for pre-specified stratification variables. Inclusion of work absence (i.e. societal perspective) generates an ICER of £69,925 per additional QALY gained (unadjusted) and £86,534 per additional QALY gained when adjusted for pre-specified stratification variables.

The cost effectiveness plane shows the results of each of 10,000 bootstrap estimates (supplementary figure 1). The majority of the estimates lie in the north-east quadrant meaning a positive ICER.



Supplementary figure 1. Cost-effectiveness plane

The cost-effectiveness acceptability curve (CEAC) demonstrates the probability that a screening trial would be cost-effective at different cost per QALY thresholds (supplementary figure 2). The probability of a screening trial being cost-effective at £20,000 per QALY, the lower portion of the threshold commonly adopted in decisions made by NICE, is only 9.2%. The probability of a screening trial being cost-effective at £30,000 per QALY, the upper threshold commonly adopted in decisions made by NICE, is only 13.8%.



Supplementary figure 2. Cost-effectiveness acceptability curve indicating the probability of a screening trial strategy being cost-effective for a range of thresholds (cost/QALY)

Scenario analysis

Each of the following scenarios are conducted on the ITT population derived from the dataset after multiple imputation with propensity mean matching.

The EQ-5D-5L tool was used to measure health-related quality of life in the trial. The values used in the base case results are those when the estimates are cross-walked to the EQ-5D-3L value set, as recommended by NICE.[6] A scenario analysis has been conducted with the health-related quality of life estimates from the EQ-5D-5L value set for England.[7]

Supplementary table 20. QALYs at 6 months follow-up using EQ-5D-5L value set

QALYs	TG (N=35)	NTG (N=46)	Between group unadjusted difference	Between group adjusted difference[a]
	Mean (SD)	Mean (SD)	Mean (95% CI)	Mean (95% CI)
N=81	0.203 (0.120)	0.202 (0.202)	-0.0004 (-0.053 to 0.052)	-0.007 (-0.023 to 0.010)

[a] Adjusted for baseline EQ-5D index score, site, sex, age, failed back surgery syndrome

Using the EQ-5D-5L value set results in the no trial screen arm dominating the trial screen arm as the trial screen arm generates fewer QALYs at an increased cost.

Another scenario analysis based on quality of life was conducted. The QALYs for the screening trial group were increased and decreased by 10% to explore the impact on the ICER. Using the base case adjusted cost difference of £1,341.22 and a decrease in the QALYs of 10% results in an implant only strategy being dominant over a screening trial strategy (i.e. less costs and more benefits). Using the base case adjusted cost difference and an increase in the QALYs of 10% generates an ICER of £31,191.16 per additional QALY gained.

Supplementary table 21. Scenario analysis - variation of QALYs by 10% in screening trial strategy

QALYs N=105	TG (N=54)	NTG (N=51)	Between group unadjusted difference	Between group adjusted difference[a]
	Mean (SD)	Mean (SD)	Mean (95% CI)	Mean (95% CI)
90% of SCS trial total QALYs	0.230 (0.011)	0.232 (0.161)	-0.002 (-0.040 to 0.036)	-0.008 (-0.039 to 0.023)
110% of SCS trial total QALYs	0.281 (0.017)	0.232 (0.161)	0.049 (0.008 to 0.091)	0.043 (0.009 to 0.076)

[a] Adjusted for baseline EQ-5D index score, site, sex, age, failed back surgery syndrome

The influence of the device costs, as the largest individual costs and therefore likely to have an impact on the overall ICER, was also explored. The costs of a screening trial, screening trial failure and the cost of implantation were increased and decreased by 10% each.

Supplementary table 22. Scenario analysis - variation by 10% of costs of a screening trial, screening trial failure and the cost of implantation

Device costs N=105	TG (N=54)	NTG (N=51)	Between group unadjusted difference	Between group adjusted difference[a]
	Mean (SE)	Mean (SE)	Mean (95% CI)	Mean (95% CI)
90% of screening trial cost	18,810.10 (683.84)	17,487.90 (337.31)	1,321.98 (-160.22 to 2930.96)	1,092.494 (-277.12 to 579.15)
110% of screening trial cost	19,336.67 (683.84)	17,487.90 (337.31)	1,848.55 (256.68 to 3465.15)	1,590.399 (209.05 to 3087.05)
90% of screening failure cost	19,051.66 (691.48)	17,487.90 (337.31)	1,563.54 (64.18 to 3190.98)	1,317.18 (-70.46 to 2823.39)
110% of screening failure cost	19,095.11 (676.23)	17,487.90 (337.31)	1,606.99 (132.21 to 3205.20)	1,365.25 (1.84 to 2842.46)
90% of implantation cost	18,077.69 (648.65)	16,390.60 (337.31)	1,686.85 (257.59 to 3238.82)	1,441.798 (127.18 to 2868.49)
110% of implantation cost	20,069.08 (719.95)	18,585.19 (337.31)	1,483.67 (-63.94 to 3160.60)	1,240.56 (-198.46 to 2800.30)

[a] Adjusted for baseline EQ-5D index score, site, sex, age, failed back surgery syndrome

When the base case adjusted QALY difference of 0.017 used, the ICERs under the device costs scenarios, are shown in the table below.

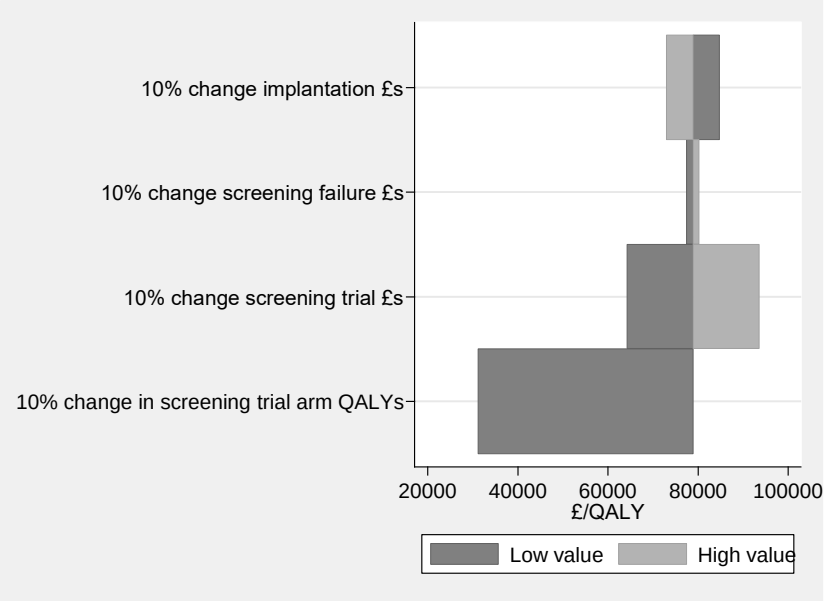
Supplementary table 23. ICERs considering variation in costs

Device costs	N=105
	ICER
90% of screening trial cost	£64,264.35
110% of screening trial cost	£93,552.88
90% of screening failure cost	£77,481.18
110% of screening failure cost	£80,308.82
90% of implantation cost	£84,811.65
110% of implantation cost	£72,974.18

Supplementary figure 3 demonstrates the impact on the ICER of four of the five scenario analyses conducted. As the use of the EQ-5D-5L value set generates only one new set of results, and as this results in a dominant ICER as the QALYs generated by the trial screen arm are (slightly) higher at a lower cost, this result is omitted from the Tornado diagram. When the total QALYs generated from the screening trial arm is increased by 10%, the ICER falls to approximately £30k, however when the total QALYs generated by the screening trial arm is reduced by 10%, the no trial screen arm dominates the screening trial arm as it generates more benefits at a lower cost. The dominant result is not shown in the diagram below.

The cost of the screening trial has the largest impact on the ICER when varying the costs of a screening trial, screening trial failure and the cost of implantation. This is to be expected as these costs are only relevant to the

screening trial arm and therefore make a difference to the incremental costs. However, the quality of life difference has the biggest influence on the cost-effectiveness of the screening trial.



Supplementary figure 3. Tornado diagram

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