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Effectiveness and cost-effectiveness of radiofrequency denervation for chronic low back pain originating from the sacroiliac joints

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ABSTRACT

Introduction Radiofrequency (RF) denervation has been used in treating mechanical low back pain (LBP) for decades. To date, the effectiveness of RF denervation has not been demonstrated unequivocally. The aim of this study was to establish whether RF denervation supplementary to a standardised exercise programme is more effective and cost-effective than the standardised exercise programme alone for patients with chronic sacroiliac joint (SI-joint) pain.

Methods This 12-month, multicentre, non-blinded randomised controlled trial (RCT) evaluated patients with suspected chronic SI-joint pain (based on at least 50% reduction of pain 30-90 minutes after a diagnostic block) unresponsive to conservative treatment. All trial participants received a standardised exercise programme. The intervention group additionally received RF denervation. The primary outcome measures were pain intensity, global perceived effect (GPE), and functional status at three months. Effectiveness was estimated using maximum likelihood estimation for longitudinal mixed-effects model and a generalized linear mixed model for the responder analysis. A cost-utility analysis focusing on quality-adjusted life years was performed using a Seemingly Unrelated Regression analysis.

Results Between January 1st 2013 and July 1st 2014, 228 patients were randomised. There was a significant difference at three months for pain (-0.71; 95%CI -1.35 to -0.06), GPE (OR 2.45; 95%CI 1.17 to 5.13) and functional status (-4.15; 95%CI -7.52 to -0.78) favouring the intervention group. These differences disappeared at 6- and 12 months follow-up. The intervention group was more costly €1933.69 (95%CI 279.64 to 3633.03) and the maximum probability of the intervention being cost-effective was low (≤0.17).

Discussion This study has shown that RF denervation added to a standardised exercise programme compared to a standardised exercise programme alone resulted in a statistically significant difference in pain reduction, functioning, and GPE in the short term for patients with chronic SI-joint pain. However, no long-term differences in effects were found, nor can the RF denervation be considered cost-effective.

INTRODUCTION

The lifetime prevalence of non-specific low back pain is estimated at 59 – 84% in industrialized countries.[1] About 10-15% of these patients will develop chronic low back pain (CLBP) (symptoms >three months). Non-specific LBP is attributable as one of the conditions leading to the highest amounts of years lived with disability worldwide[2] and is responsible for high socio-economic costs.[3-5] Effective and cost-effective treatments are needed due to the high burden to patients and society.

Non- specific LBP is defined as LBP without a clearly recognizable or specific pathology. However, it has been suggested that at least some of the non-specific LBP can be evoked by noxious stimulation of structures in the lumbar spine. Suggested sources of (chronic) LBP are the zygapophyseal joints (facet joints), the sacroiliac joint, or the intervertebral discs.[6] An estimated 10-40% of LBP patients referred to a pain clinic are diagnosed with sacroiliac joint (SI-joint) pain; confirmed by local anaesthetic blocks.[6-11] The SI-joint is densely innervated with nociceptors in both the dorsal and the ventral segment of the joint. Though controversial, it is believed that the innervation of the SI-joint predominantly stems from the dorsal rami of S1-S3, often with contributions from the dorsal rami of L4 and L5.[12-16] Consequently, it is assumed that systematic denervation of putative lateral branch nerves may be beneficial.

Lateral branch radiofrequency (RF) denervation for SI-joint pain was first described almost 15 years ago.[17-19] In daily practice, RF denervation is often provided in a multidisciplinary setting. Despite its popularity, the effectiveness and cost-effectiveness of RF denervation has not been demonstrated unequivocally in high quality randomised controlled trials (RCTs), and even less so in a multidisciplinary setting.

The aim of this study was to establish whether RF denervation supplementary to a standardised exercise programme is more effective and cost-effective than the standardised exercise programme alone: for patients with chronic SI-joint pain referred to a pain clinic.

METHODS

Study design and participants

This study is part of a larger collective initiative; the MinT study,[20] consisting of four RCTs including an economic evaluation (1:1 ratio) and a large observational study in which minimal interventional treatments (i.e. RF denervation) are being evaluated. Four RCTs are described in the study protocol: one of the four (discogenic pain) was prematurely terminated because of prolonged lack of inclusion of patients.

The study protocol was approved by the Medical Ethics Committee of the Erasmus University Medical Centre in Rotterdam (MEC 2012-079) and local research governance was obtained from the boards of all participating pain clinics. The study was registered at the Dutch Trial Register (NTR3531). All participants gave written informed consent.

This study is a multicentre, non-blinded RCT comparing RF denervation of the SI-joint in addition to a standardised exercise programme to a standardised exercise programme alone. An economic evaluation from a societal perspective was conducted alongside the trial.

Study participants were recruited in 16 multidisciplinary pain centres in the Netherlands. Participants were included if they were aged between 18-70 years with chronic SI-joint pain unresponsive to conservative treatment. To determine the presence of SI-joint pain, the participants were clinically examined and received a lateral branch blockade as a diagnostic procedure. Medical history and clinical examination followed a standard format for all participants and was undertaken by experienced clinicians. The clinical examination included SI-joint provocation tests (Compression test, Distraction test, FABER test, Gaenslen test, Thigh Thrust test, Gillette test) of which at least three had to be positive for a patient to receive a diagnostic block.[21,22]

The diagnostic blockade was performed as follows: under C-arm fluoroscopy a 25G needle was inserted 3-10mm laterally (3:00 on the right, 09:00 on the left side) of the sacral foramina S1, S2, and S3. The lateral image was checked to confirm correct depth of the needle, after which 0.5ml lidocaine (2%) was injected. The dorsal ramus of L5 was also blocked as described in the ISIS guidelines[23] using 0.5ml lidocaine (2%). No corticosteroids were administered. The diagnostic block was considered positive if the participant reported at least 50% subjective pain reduction 30-90 minutes after the block. Participants were only randomised if the diagnostic block was positive.

Exclusion criteria were: 1) severe psychiatric or psychological problems (determined with

pre-intake psychological questionnaires), 2) involvement in work related conflicts/claims 3) Body Mass Index greater than 35, 4) anticoagulant drug therapy and/or coagulopathy. Participants were required to have access to a computer with an internet connection.

Randomisation and masking

Using a power of 0.9, alpha .05 and a correlation of 0.5 for repeated measures, 85 participants per group were required to detect a mean difference of two points on the NRS for pain intensity (SD 4). We expected a potential 20% study withdrawal, so a minimum of 204 participants was needed.

Participants were randomised using a central computerized random number generator, which was accessed through a password protected website that was maintained independent from the trial. Randomisation was stratified for the participating pain clinics (n=16). Participants were randomly allocated (1:1) to receive either the minimal invasive treatment with a multidisciplinary programme (intervention group) or a multidisciplinary programme alone (control group). In this pragmatic trial, participants and caregivers were not blinded. After allocation, all participants were sequentially assigned unique numbers. The data handling, analysis and interpretation of results by the project group was done blinded to treatment allocation. Participants' expectations and treatment satisfaction were measured to evaluate a possible risk of bias due to a non-blinded treatment.

Interventions

All participants in the trial received a standardised exercise programme based on the guidelines of the Royal Dutch Society for Physical therapy.[24] The focus of the programme was quality of movement and behavioural aspects. The total duration was 8-12 hours, equally spread over three months. The study participants were referred to one of 102 participating physical therapy practices. If necessary, the participant was referred to a psychologist, were they received usual care.

The choice of technique for radiofrequent lesioning, in the intervention group was left to the experience of the treating physician, and was carried out within one week after the start of the exercise programme. Participants received either the Cooled RF technique (SInergy, Kimberly Clark Health Care, Roswell GA, USA); Bipolar Palisade Technique; or Simplicity III Probe technique (Neurotherm, St Paul MN, USA).

For the *Cooled RF technique,*[25] a P/A view of the foramina of S1, S2 and S3 was obtained under C-arm fluoroscopy. A 25G needle was placed as reference point along the inside lateral wall of each foramen, with the tip at the opening of each foramen. An Epsilon ruler (Kimberly Clark Health Care) was used together with the reference needles as landmarks for the lesions. Using the introducer, stylet and probe provided by the manufacturer RF lesions were made (at 02:30, 04:00 and 05:30 for S1 and S2 and 02:30, 04:00 for S3 on the right side, and inversely on the left) at a maximum temperature of 60°C for 2.5 minutes per lesion.

The *Palisade Technique*[26] was carried out by drawing a cranial-caudal line between the lateral aspect of the sacral foramina and the SI joint line. Under lateral fluoroscopic view 6 20G needles with 10mm active tips were placed parallel to each other, 10mm apart and perpendicular to the sacrum. Stimulations to 2.0V were done to be sure there was no motor response. Then eight bipolar lesions (90°C for 180 seconds per lesion) were made using adjacent parings of the cannulas where the maximum allowed temperature drop between cannulas was 30°C.

The *Simplicity III probe*[27] is a multi-electrode radiofrequency probe, which was inserted at the lateral, inferior border of the sacrum, 10mm below the S4 foramen under fluoroscopic view. The electrode probe was advanced in a cephalad direction along the sacrum, lateral of the foramina, medial to the sacroiliac joint and ventral to the ileum. Using A/P and lateral fluoroscopy the correct position of the electrodes was checked and the RF lesion (85°C for 90 seconds per step) was made. In all three techniques RF lesion of the ramus dorsalis of L5/S1 was carried out monopolar.[28] The lesion sites were adequately anesthetized using 10-20ml of 2% lidocaine.

The trial's treatment period was three months, in which only the participants allocated to the intervention group received a RF lesion. No co-interventions were allowed in the three-month treatment period. If in this period participants in the control group received an intervention they would be considered protocol violators. If participants in the control group had not improved after three months, they were allowed to receive other treatments including RF treatments, which was registered.

Outcomes

The three primary outcome measures were: 1) pain intensity, measured on an 11-point Numerical Rating Scale (NRS), 2) global perceived effect (GPE), measured using a 7-point Likert scale, and 3) functional status measured using the Oswestry Disability Index (ODI). Success of treatment in GPE was achieved if a patient reported "much recovery" or "complete recovery". Success of treatment for the two responder analyses in pain reduction was defined in two ways: either a ≥30% reduction of initial pain and ≥two points decrease in NRS.

Secondary outcomes where health-related quality of life (EQ-5D), patient satisfaction (7 point Likert scale), general health (Rand-36), and chronic pain experiences (MPI). Participants were followed up for 12 months, and all outcome measures were patient reported using web-based questionnaires. All questionnaires were sent at baseline and three, six and nine months after start of treatment. Pain intensity, GPE, and health-related quality of life were also assessed at three and six weeks after start of treatment. The participants' EQ-5D health states were converted into utilities using the Dutch tariff.[29] Quality Adjusted Life Years (QALYs) were calculated using linear interpolation between measurement points.

Intervention costs were estimated based on two hospitals' accounting records. Data on other healthcare use, informal care, unpaid productivity, and absenteeism due to back pain were collected using three-monthly self-reported cost questionnaires. Healthcare use included primary and secondary healthcare use as well as the use of medication. Primary and secondary healthcare was valued using Dutch standard costs.[30, 31] If unavailable, prices according to professional organizations were use. Medication use was valued using prices of the Royal Dutch Society of Pharmacy.[32] Informal care (care by volunteers e.g. family or friends) was estimated using a recommended Dutch shadow price of €13.7/hour.[31] We used the Productivity and Disease Questionnaire (PRODISQ)[33] to measure work absenteeism, which was valued in accordance with the friction cost approach (friction period=23 weeks) and using age- and gender-specific price weights.[31] Unpaid productivity loss (volunteer work, domestic and/or educational activities) was also estimated using a recommended Dutch shadow price of €13.7/hour. All costs were converted to 2014 Euros.[30]

Statistical analyses

Baseline characteristics have been presented comparing the two treatment groups. Intention-to-treat analysis was performed for each follow-up assessment. The 95% confidence intervals (CIs) were calculated for the regression coefficients and odds-ratios. The effects were estimated using a maximum likelihood estimation for longitudinal mixed-effects model; under "missing at random" assumptions for missing data in continuous outcomes. We used a generalized linear mixed model (logit link) for the post-hoc responder analysis. Using the same multilevel structure for both models. Participants marked as protocol violators and participants that received RF denervation during follow up were excluded from analysis in two separate sensitivity analyses. We used MLWin software (V2.22) for the effects models (significance P<.05).

In the cost-effectiveness analysis, missing data were imputed, using multiple imputations. The imputation model included gender, smoking, marital status, age, BMI, symptom history, education, treatment expectations, baseline costs, follow-up costs and effect measure values. Using Fully Conditional Specification and Predictive Mean Matching, 10 complete data sets were created (loss-of-efficiency<5%). Pooled estimates were calculated according to Rubin's rules.[34]

We calculated the mean between-group differences for total and disaggregated costs. We performed seemingly unrelated regression analyses, in which effect and cost differences were corrected for baseline characteristics while taking into account the possible correlation between costs and effects. An incremental cost-effectiveness ratio (ICERs) was calculated by dividing the corrected difference in total costs by the difference in QALYs. Bias corrected and accelerated (BCA) bootstrapping with 5000 replications was used to estimate the uncertainty surrounding the cost differences and ICER. A cost-effectiveness plane was constructed to graphically illustrate the uncertainty surrounding the ICER. The probability of cost-effectiveness at different values of willingness-to-pay was estimated and indicated by a cost-effectiveness acceptability curve (CEAC). In a sensitivity analysis we compared the SF-6D to the EQ-5D, the friction cost approach to the human capital approach and performed a complete-case analysis to test the robustness of the results. The economic evaluation was done using STATA (V12, Stata Corp, College Station, TX, USA).

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, interpretation of data, or writing of the paper. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Study participants
In total 7103 patients were assessed for eligibility; of whom 2381 were included in the MinT study (one of the three RCTs or observational study) between January 1st 2013 and July 1st 2014 (the inclusion period for patients in the RCTs assessing SI-joint complaints). Of these 2381 participants, 989 participants received a diagnostic SI-joint block. The block was positive in 747 participants, 228 participants met the inclusion criteria for this SI-joint RCT and were randomly assigned to the intervention (N=116) and control group (N=112) (Figure 1).
The data available (198/228) for analysis of our primary outcome was well within our power calculation margin (<20%) at three months. At 12 months we collected data from 77% of participants, there were no clear differences between participants with complete and participants with incomplete data (appendix 1). The patients with a negative diagnostic facet block continued a diagnostic trajectory or were followed-up in the observational study.
Randomisation achieved a good balance between the two groups at baseline, in terms of socio-demographic and clinical characteristics (Table 1). However, the history of the first episode of back pain complaints in the intervention group was longer (97 months) than in the control group (65 months). In the intervention group 77 participants were treated with the Palisade technique, 23 participants with Cooled RF and five with the Simplicity probe, two participants received a treatment for the facet joints and for nine participants treatment was not specified further. Seven participants in the control group received a RF lesion within the first three months and were marked as protocol violators.

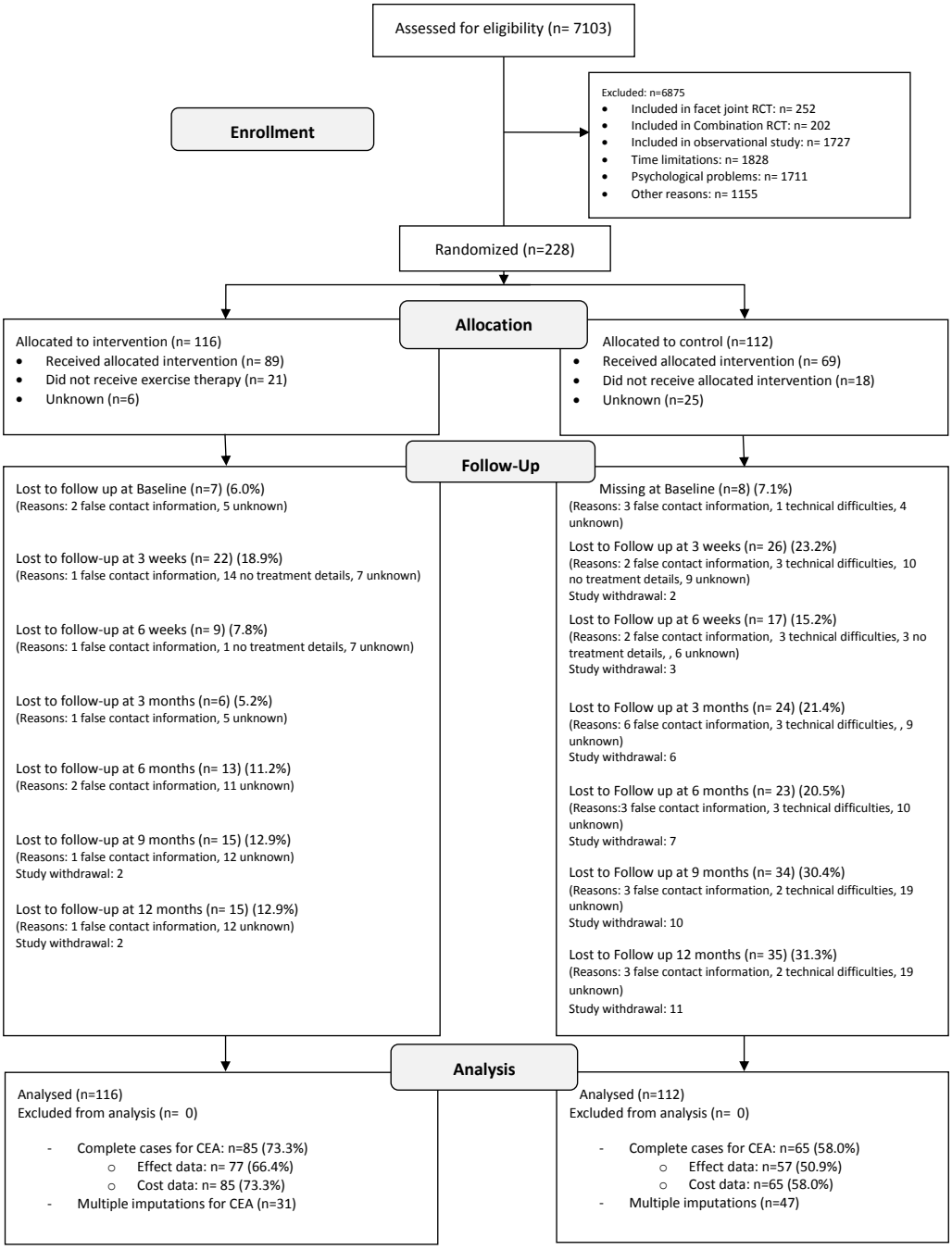


Figure 1 Flow diagram

Table 1. Baseline characteristics of participants for the intention to treat population

Characteristics	Intervention Randomised: N= 116*	Control Randomised: N= 112*
Age in years (SD)	51.58 (10.94)	51.13 (12.22)
Female (N (%))	87 (75.0%)	79 (76.0%)
BMI (SD)	26.73 (4.17)	26.76 (4.53)
Smoker (N (%))	29 (26.6%)	31 (29.8%)
Education		
• Low (N (%))	59 (54.1%)	53 (51.5%)
• Moderate (N (%))	32 (29.4%)	32 (31.1%)
• High (N (%))	18 (16.5%)	18 (17.5%)
History of back pain complaints		
• Time since first experience with low back pain in months (median (IQR))	97.33 (37.51 -228.12)	65.08 (27.08 – 144.21)
• Time since current episode with low back pain in months (median (IQR))	30.33 (12.17 – 76.03)	24.33 (12.17 – 66.58)
Married/living with a partner (N (%))	85 (78.0%)	82 (79.6%)
Expectations		
• Credibility (0-27)	21.36 (4.51)	19.88 (5.31)
• Expectancy (0-27)	18.75 (4.99)	18.23 (5.31)
Having a paid job	66 (61.1%)	50 (44.6%)
Outcomes		
Pain intensity in the past week (NRS 0-10)	7.17 (1.65)	7.06 (1.43)
Oswestry disability index (mean (SD))	38.07 (14.07)	33.70 (14.43)
Quality of life (EQ-5D)	0.50 (0.27)	0.56 (0.27)

Abbreviations: SD, Standard Deviation; N, number; BMI, Body Mass Index; EQ-5D, EuroQol-5D
** Occasional missing on baseline items, 208 participants had complete baseline dat*

Intention-to-treat analyses

Table 2 shows the primary outcomes. Pain intensity (NRS) reduced in both groups over 12 months. There was a statistically significant difference in pain reduction at three weeks (mean difference (MD) -0.96; 95%CI -1.63 to -0.29), and at three months (MD -0.71; 95%CI -1.35 to -0.06) favouring the intervention group (Table 2). However, there was no significant difference in overall effect over the 12 month follow up. There was a statistically significant difference in GPE at three weeks (Odds Ratio (OR) 3.58; 95%CI 1.45 to 8.78), six weeks (OR 5.44; 95%CI 2.27 to 13.00) and three months (OR 2.45; 95%CI 1.17 to 5.13) favouring the intervention group. There was also a difference in overall effect, over 12 months (OR 2.19; 95%CI 1.42 to 3.39) favouring the intervention. There was only a statistically significant difference in functional status (ODI) at three months (MD -4.20; 95% CI-8.39 to -0.002). We found no other differences at any other follow-up assessment in the primary outcomes. The only difference in secondary outcomes was the EQ5D utility score at three weeks (MD 0.10 95%CI 0.03 to 0.16) favouring the intervention group (Table 4).

Responder analyses

In the responder analysis (Table 3) there was a statistically significant difference at three weeks in terms of pain reduction ≥30% (OR 3.48; 95%CI 1.63 to 7.42) and ≥2 points pain reduction (OR 2.72; 95%CI 1.46 to 5.09).

Sensitivity analyses

When the seven protocol violators were excluded from the analysis, there were no changes in the interpretation of the outcomes reported (Appendix 2). After the initial treatment period of three months, 41 participants from the control group received an interventional treatment at the pain clinic (three RF Facet, five Cooled RF, 31 Palisade technique, one corticosteroid infiltration of the SI joint, one PRF of nerve root) during the 12 month follow up period. When performing an as-treated analysis, and excluding these participants from the analysis, there was no longer a significant difference in pain at three months (Appendix 3). Additionally, 23 participants in the intervention group also sought re-treatment after 3 months (5 RF Facet, 5 Cooled RF of the SI joint, 6 Palisade of the SI joint, 5 TENS, 2 PRF of the nerve root). The different treatment modalities in the intervention group are shown in Appendix 4, however these groups were too small for subgroup analysis. There was one registered complication (vasovagal reaction to Palisade intervention, during treatment).

Table 2. Treatment effects for primary outcomes based on intention-to-treat analyses, continuous

		Mean Intervention group (SD)	Mean Control group (SD)	Treatment effect (95%CI)	P value for difference	
Primary outcomes†						
NRS Pain*	Overall effect			-0.40 (-0.83 to 0.03)	0.07	
	Baseline	7.17 (1.65)	7.06 (1.43)			
	3 weeks	4.96 (2.19)	6.00 (1.89)	-0.96 (-1.63 to -0.29)	0.005	
	6 weeks	5.22 (2.16)	5.69 (1.89)	-0.53 (-1.17 to 0.10)	0.10	
	3 months	4.77 (2.46)	5.45 (2.37)	-0.71 (-1.35 to -0.06)	0.03	
	6 months	4.50 (2.47)	4.78 (2.53)	-0.12 (-0.77 to 0.53)	0.73	
	9 months	5.03 (2.45)	4.97 (2.58)	0.16 (-0.51 to 0.83)	0.64	
	12months	4.65 (2.46)	4.84 (2.38)	-0.07 (-0.74 to 0.60)	0.83	
ODI Functioning*	Overall effect			0.42 (-2.99 to 3.82)	0.81	
	Baseline	38.07 (14.07)	33.70 (14.43)			
	3 months	27.72 (17.05)	29.09 (17.09)	-4.20 (-8.39 to -0.002)	0.05	
	6 months	25.99 (15.71)	24.99 (16.59)	0.07 (-4.16 to 4.30)	0.97	
	9 months	28.40 (16.88)	23.45 (15.21)	4.45 (0.14 to 8.77)	0.04	
	12 months	27.29 (17.22)	24.49 (16.17)	2.11 (-2.25 to 6.47)	0.34	
		Success % Intervention group	**Success % Control group**	**OR (95%CI)**	**P value for difference**	**NNT**
GPE Success	Overall effect			2.19 (1.42 to 3.39)	0.0004	
	Baseline					
	3 weeks	29.80	10.20	3.58 (1.45 to 8.78)	0.01	5
	6 weeks	37.00	10.50	5.44 (2.27 to 13.00)	0.0001	4
	3 months	39.10	21.60	2.45 (1.17 to 5.13)	0.02	6
	6 months	44.70	33.00	1.56 (0.77 to 3.15)	0.21	9
	9 months	35.60	32.10	1.21 (0.58 to 2.54)	0.62	29
	12months	48.00	31.60	1.85 (0.89 to 3.85)	0.10	6

*†Values presented are model estimates of linear mixed-effects models with a random intercept, and adjusted for baseline and age, gender, BMI, education, smoking, marital status, back pain complaint history, patient expectations and baseline values. Regression coefficients can be interpreted as mean differences between interventions at a certain follow-up moment compared to baseline. Abbreviations: NRS, Numeric Rating Scale; GPE, Global Perceived Effect; ODI, Oswestry Disability Index; NNT, Numbers Needed to Treat. * Higher score indicates more severe symptoms. Range for NRS pain, 0-10; for ODI, 0-100; for GPE, 1&2 is defined as success*

Table 3. Treatment effects for primary outcomes based on intention-to-treat analyses, in terms of successful treatment

		Success % Intervention group	Success % Control group	OR (95%CI)	P value for difference	NNT
Primary outcomes						
NRS Pain success, >30% reduction	Overall effect			1.46 (1.00 to 2.13)	0.05	
	Baseline					
	3 weeks	45.6	19.3	3.48 (1.63 to 7.42)*	0.001	4
	6 weeks	41.3	27.5	1.82 (0.92 to 3.59)	0.08	7
	3 months	45.7	34.5	1.61 (0.82 to 3.16)	0.16	9
	6 months	50.5	49.4	1.03 (0.53 to 1.99)	0.94	91
	9 months	39.8	43.4	0.80 (0.40 to 1.60)	0.53	-28
	12 months	49.5	41.3	1.28 (0.64 to 2.56)	0.48	12
NRS Pain success, >2 points reduction	Overall effect			1.47 (1.00 to 2.17)	0.05	
	Baseline					
	3 weeks	61.5	36.1	2.72 (1.46 to 5.09)	0.002	4
	6 weeks	56.2	44.0	1.67 (0.94 to 2.97)	0.08	8
	3 months	58.5	47.6	1.61 (0.90 to 2.91)	0.11	9
	6 months	62.0	55.3	1.31 (0.72 to 2.39)	0.37	15
	9 months	51.5	53.9	0.91 (0.50 to 1.66)	0.76	-42
	12 months	58.2	54.7	1.10 (0.59 to 2.02)	0.77	29

Abbreviation: NRS, Numeric Rating Scale; NNT, Numbers Needed to Treat

Table 4. Treatment effects for secondary outcomes based on intention-to-treat analyses, continuous

		Mean Intervention group (SE)	Mean Control group (SE)	Treatment effect (95%CI)	P value for difference
Secondary outcomes					
EQ5D Utilities* **	Overall effect			0.02 (-0.02 to 0.06)	0.27
	Baseline	0.50 (0.27)	0.56 (0.27)		
	3 weeks	0.72 (0.18)	0.62 (0.27)	0.10 (0.03 to 0.16)*	0.002
	6 weeks	0.69 (0.22)	0.66 (0.25)	0.04 (-0.02 to 0.09)	0.22
	3 months	0.68 (0.25)	0.66 (0.26)	0.05 (-0.01 to 0.11)	0.11
	6 months	0.74 (0.19)	0.73 (0.22)	0.001 (-0.06 to 0.06)	0.98
	9 months	0.68 (0.23)	0.73 (0.21)	-0.05 (-0.11 to 0.02)	0.15
	12months	0.70 (0.23)	0.73 (0.21)	-0.02 (-0.09 to 0.04)	0.52
NRS patient satisfaction**	Overall effect			-0.21 (-0.54 to 0.13)	0.23
	Baseline	2.94 (1.39)	3.42 (1.55)		
	3 months	2.86 (1.38)	2.97 (1.43)	-0.54 (-0.96 to -0.13)	0.01
	6 months	3.05 (1.51)	3.14 (1.54)	-0.05 (-0.46 to 0.37)	0.83
	9 months	3.03 (1.45)	3.25 (1.45)	-0.06 (-0.49 to 0.36)	0.78
	12 months	2.94 (1.39)	3.42 (1.55)	-0.16 (-0.59 to 0.26)	0.45
MPI Pain severity**	Overall effect			-0.061 (-0.38 to 0.25)	0.70
	Baseline	3.99 (1.01)	3.76 (1.09)		
	3 months	2.90 (1.52)	3.17 (1.48)	-0.42 (-0.46 to -0.38)	<0.0001
	6 months	2.71 (1.44)	2.74 (1.49)	-0.071 (-0.46 to 0.33)	0.73
	9 months	3.01 (1.36)	2.76 (1.43)	0.18 (-0.23 to 0.59)	0.39
	12 months	2.87 (1.48)	2.71 (1.47)	0.128 (-0.29 to 0.54)	0.54
MPI interference**	Overall effect			-0.04 (-0.31 to 0.23)	0.77
	Baseline	3.39 (1.27)	3.05 (1.32)		
	3 months	2.94 (1.28)	2.71 (1.36)	-0.097 (-0.43 to 0.24)	0.57
	6 months	2.58 (1.27)	2.47 (1.59)	-0.093 (-0.43 to 0.24)	0.59
	9 months	2.51 (1.44)	2.35 (1.50)	-0.024 (-0.37 to 0.32)	0.89
	12 months	2.59 (1.49)	2.31 (1.49)	0.097 (-0.25 to 0.45)	0.59
MPI Life control**	Overall effect			0.072 (-0.12 to 0.27)	0.47
	Baseline	4.11 (1.05)	4.22 (0.89)		
	3 months	4.32 (1.08)	4.23 (1.09)	0.223 (-0.03 to 0.48)	0.08
	6 months	4.42 (0.91)	4.35 (1.02)	0.044 (-0.21 to 0.30)	0.74

		Mean Intervention group (SE)	Mean Control group (SE)	Treatment effect (95%CI)	P value for difference
	9 months	4.28 (1.07)	4.40 (1.15)	-0.061 (-0.32 to 0.20)	0.65
	12 months	4.39 (1.09)	4.37 (1.21)	0.059 (-0.21 to 0.32)	0.66
MPI Affective distress**	Overall effect			0.068 (-0.07 to 0.20)	0.32
	Baseline	2.75 (0.85)	2.66 (0.80)		
	3 months	2.54 (0.77)	2.44 (0.71)	0.075 (-0.12 to 0.27)	0.44
	6 months	2.54 (0.68)	2.58 (0.72)	-0.026 (-0.22 to 0.17)	0.79
	9 months	2.62 (0.88)	2.44 (0.66)	0.186 (-0.01 to 0.39)	0.07
	12 months	2.45 (0.77)	2.41 (0.65)	0.051 (-0.15 to 0.25)	0.62
MPI Support**	Overall effect			-0.002 (-0.25 to 0.24)	0.99
	Baseline	4.41 (1.19)	4.55 (0.99)		
	3 months	4.34 (1.31)	4.31 (1.30)	0.007 (-0.31 to 0.33)	0.97
	6 months	4.28 (1.20)	4.41 (1.23)	-0.09 (-0.42 to 0.24)	0.59
	9 months	4.27 (1.37)	4.31 (1.38)	-0.004 (-0.34 to 0.33)	0.98
	12 months	4.34 (1.42)	4.35 (1.35)	0.099 (-0.24 to 0.44)	0.57
RAND-36 Physical health***	Overall effect			-1.218 (-5.19 to 2.75)	0.55
	Baseline	45.50 (17.73)	48.50 (19.65)		
	3 months	53.91 (20.22)	54.37 (21.63)	2.208 (-2.82 to 7.24)	0.39
	6 months	57.04 (20.79)	59.48 (20.06)	-1.803 (-6.88 to 3.27)	0.49
	9 months	55.30 (21.18)	60.52 (19.22)	-4.348 (-9.54 to 0.85)	0.10
	12 months	56.98 (22.71)	59.80 (19.63)	-1.479 (-6.73 to 3.77)	0.58
RAND-36 mental health***	Overall effect			0.037 (-175 to 1.82)	0.97
	Baseline	76.40 (15.12)	76.76 (13.95)		
	3 months	76.87 (15.81)	76.78 (16.07)	0.791 (-2.09 to 3.67)	0.59
	6 months	62.77 (6.39)	63.03 (8.56)	-0.638 (-3.56 to 2.29)	0.67
	9 months	62.84 (7.33)	62.86 (8.36)	0.029 (-2.99 to 3.04)	0.98
	12 months	62.64 (8.34)	62.43 (8.05)	-0.059 (-3.12 to 3.01)	0.97

*Values presented are model estimates of linear mixed-effects models with a random intercept, and adjusted for baseline and age, gender, BMI, education, smoking, marital status, back pain complaint history, patient expectations and baseline values. Regression coefficients can be interpreted as mean differences between interventions at a certain follow-up moment compared to baseline. Abbreviation: EQ5D; Utility scores based on the EuroQol5D; MPI, Multidimensional Pain Inventory; RAND-36, Research and Development 36 item health survey. * Higher score indicates more severe symptoms. Range for NRS pain, 0-10; for ODI, 0-100; for GPE, 1-7; for patient satisfaction, 1-7, for MPI 0-168. *** Higher score indicates more quality of life. Range for EQ5D utility: 0-1; for RAND36 0-100*

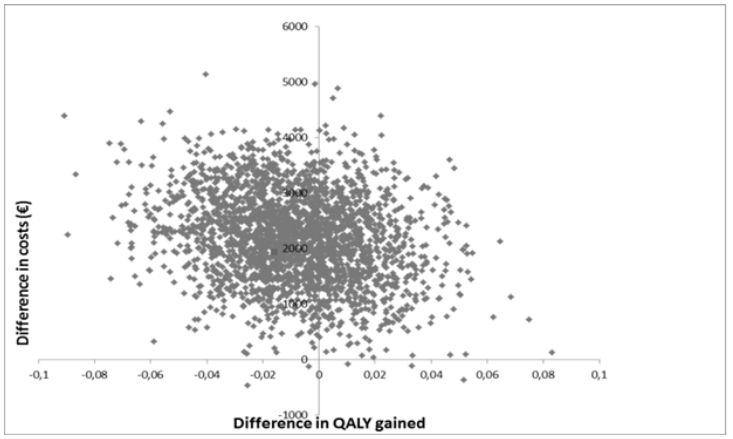
Cost-utility analyses

Societal costs were higher in the intervention group than in the control group, with an adjusted mean cost difference of €1933.69 (95%CI 279.64 to 3633.03) (Table 5). One QALY lost was associated with a societal cost of €120,914.00 (ICER -120914) (Table 6), with 75% of the CE pairs located in the north-west quadrant, indicating that the intervention was more costly and less effective than the control condition. This large ICER was due to the small effect on QALYs (MD -0.02; 95%CI -0.07 to 0.03). The sensitivity analyses, to test the robustness of these findings, did not yield different results. The CEAC (Figure 2) indicates that the probability of the intervention being cost-effective in comparison with the control condition was low for all willingness to pay values (≤0.17).

Table 5. Mean costs per participant in the intervention and control group, and mean cost differences between both groups during the 12-month follow-up period from a societal perspective

Cost category	Intervention group n=116; mean (SEM)	Control group n=112; mean (SEM)	Mean cost difference crude (95%CI)	Mean cost difference adjusted (95%CI)
Intervention	799 (0)	0 (0)	NA	NA
Primary healthcare	1446.15 (116.10)	1093.95 (128.77)	352.20 (-5.99 to 675.82)	414.49 (49.01 to 728.07)
Secondary healthcare	701.35 (95.08)	784.48 (146.69)	-83.13 (-492.31 to 219.52)	-44.53 (-353.13 to 220.42)
Medication	350.98 (46.67)	196.28 (50.10)	154.71 (16.66 to 280.64)	156.26 (4.85 to 300.06)
Informal care	1141.56 (325.77)	797.21 (187.81)	344.36 (-227.12 to 1427.55)	300.29 (-221.99 to 1355.86)
Absenteeism	1433.75 (416.57)	939.81 (332.76)	493.95 (-425.01 to 1608.74)	563.19 (-314.76 to 1620.67)
Unpaid productivity	1242.83 (216.06)	1463.86 (304.31)	-221.03 (-950.74 to 440.26)	-255.00 (-937.87 to 387.96)
Total	**7115.62 (667.41)**	**5275.59 (644.56)**	**1840.05 (99.62 to 3645.18)***	**1933.69 (279.64 to 3633.03)***

*Abbreviations: n, number; SEM, Standard Error of the Mean; CI, Confidence Interval; NA, Not Applicable; SD, Standard Deviation. Note: Costs are expressed in 2014 Euros *p<0.05*



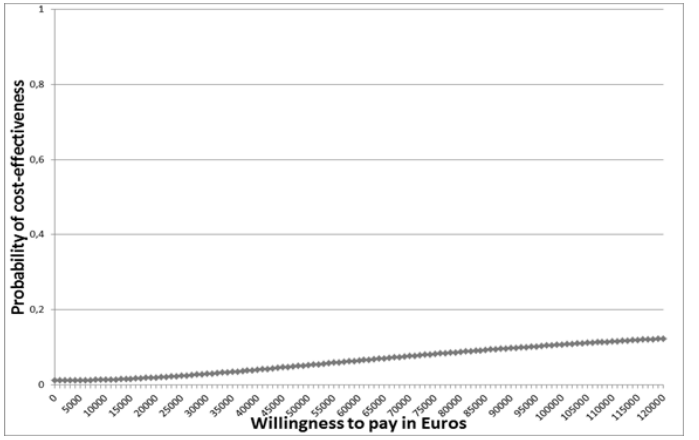


Figure 2. Cost-effectiveness planes indicating the distribution of incremental cost-effect pairs around its four quadrants (1) and cost-effectiveness acceptability curves indicating the probability of adding minimal interventional treatments in the pain programme being cost-effective in comparison with usual care for different values (€) of willingness-to-pay (2) for QALYS (EQ5D)

Table 6. Differences in pooled mean costs and effects (95% Confidence intervals), incremental cost-effectiveness ratios, and the distribution of incremental cost-effect pairs around the quadrants of the cost-effectiveness planes

Analysis	Sample size		Outcome	ΔC (95% CI)	ΔE (95% CI)	ICER	Distribution CE-plane (%)			
	Int.	Control		€	Point	€/point	NE	SE	SW	NW
Main analysis – Imputed dataset	116	112	QALY EQ5D (0-1)	1933.69 (348.14 to 3649.14)	-0.02 (-0.07 to 0.03)	-120914	23.9	0.7	0.4	75.0
SA1 – complete cases	84	62	QALY EQ5D (0-1)	2417.28 (710.69 to 4344.19)	-0.02 (-0.07 to 0.03)	-122910	21.4	0.1	0.1	78.4
SA2 - HCA	116	112	QALY EQ5D (0-1)	1935.47 (349.70 to 3650.97)	-0.02 (-0.07 to 0.03)	-121025	23.9	0.6	0.5	75.0
SA3 – SF6D	116	112	QALY SF6D (0-1)	1933.69 (348.14 to 3649.14)	-0.02 (-0.04 to 0.01)	-123694	7.4	0.2	0.9	91.5

Abbreviations:; CI: Confidence Interval; ICER: Incremental Cost-Effectiveness Ratio; CE-lane: Cost-Effectiveness plane; SA: Sensitivity Analysis; HCA: Human Capital Approach. Note: Costs are expressed in 2014 Euros

DISCUSSION

In this study we compared the value of RF denervation in addition to a standardised exercise programme to a standardised exercise programme alone for patients with SI-joint pain. We found a statistically significant difference in the primary outcomes three months after start of the intervention, in favour of RF denervation added to a standardised exercise programme compared to a standardised programme alone in patients with chronic SI-joint pain. There were no differences between the intervention group and control group at long-term follow-up. The cost-effectiveness analysis showed that the maximum probability of RF denervation added to a standardized exercise programme being cost-effective for QALYs in comparison with a standardised exercise programme alone was low (≤0.17).

This is the largest trial assessing the effectiveness of RF denervation in the SI-joint to date, with a notably longer follow-up than previous published studies. Additionally, this is the only trial comparing RF treatments embedded in a standardised exercise programme to a standardised exercise programme alone. The aim of this study was to provide more insight in whether RF denervation is an effective and cost-effective treatment for SI-joint pain.

There were some possible limitations to our study. We took a pragmatic approach to show the effectiveness of RF treatments in a daily practice setting due to the wide availability of the interventional treatments studied, and the fact that we chose to evaluate the cost-effectiveness. As a result blinding was not possible. We found no difference in participant satisfaction nor was there a notable difference in participants' expectations. Therefore, we believe that the lack of blinding did not introduce a risk of bias. We assessed different treatment modalities (Palisade technique, cooled RF, Simplicity III) in the intervention group, and although the groups are too small for subgroup analysis we do not expect much difference in outcomes per treatment modality.

Only two RCTs comparing SI-joint lateral branch denervation to placebo have been undertaken prior to the MinT study. These smaller studies did not unequivocally show the efficacy of SI-joint RF denervation.[25,35] There have been no previous studies evaluating the cost-effectiveness of RF treatments of the SI-joint. Another possible limitation of our study is that we identified participants with SI-joint pain using a single anaesthetic block, which was positive when there is a 50% pain reduction. Even though there is literature supporting double blocks to eliminate high false-positive rates,[36] other studies found

no difference in treatment effect between the use of one or two blocks.[37] Similarly, there is discussion as to whether a 50% pain reduction or an 80% reduction should be used as threshold for a positive block, but there seems to be no difference between these two thresholds and RF denervation outcomes.[37] A limitation in the assessment of cost-effectiveness is the possible influence of recall bias due to the use of retrospective questionnaires. However, with an interval of three months, we tried to minimalize this. Additionally, inherent to all cost-effectiveness studies is the fact that the results may not be universally applicable due to differences in healthcare systems across countries.[38] Finally, there is a somewhat higher drop out in the control group, however we do not believe this drop out to have biased our results since there are no differences in baseline characteristics between the complete cases and the participants who were lost to follow up.

Both the intervention group and the control group showed an improvement in mean pain intensity during the 12 months follow-up, however some pain remained (intervention 4.65, control 4.84). Even though there was no significant difference between groups in the long-term and RF denervation was not more cost-effective, we believe this trial could serve as a tool for clinicians to involve the patient in making a decision on their treatment options. Patients can be informed that conservative treatment could also provide an improvement in the long term without the need for RF denervation. However, better patient selection, improvement in the treatment techniques and additional outcome measures are topics for future research and might yield a greater difference in effect. In our observational study, part of the MinT study, we have collected vast data to identify subgroups and evaluate the diagnostic process. However, future research is still needed identify whether this treatment is a valuable supplement to conservative treatment in the long term.

This study has shown that RF denervation added to a standardised exercise programme compared to a standardised exercise programme alone resulted in a statistically significant difference in pain reduction, functioning and GPE in the short term for patients with chronic SI-joint pain. However, no long-term differences in effects were found, nor can the RF denervation be considered cost-effective.

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Appendix 1. Baseline characteristics of participants that were lost to follow compared to all participants values.

Characteristics	Intervention Randomised: N= 116 Complete baseline: N=107	Intervention- Complete Effects N= 77 Complete baseline: N=76	Intervention Incomplete Effects N=39 Complete baseline: N=31	Control Randomised: N= 112 Complete baseline: N=100	Control Complete Effects N=57 Complete baseline: N=57	Control Incomplete Effects N=55 Complete baseline: N=42
Age in years (SD)	51.58 (10.94)	53.10 (10.46)	48.56 (11.37)	51.13 (12.22)	53.33 (11.62)	48.83 (12.52)
Female (N (%))	87 (75.0%)	63 (81.8%)	24 (75.0%)	79 (76.0%)	42 (73.7%)	37 (78.7%)
BMI (SD)	26.73 (4.17)	26.79 (4.16)	26.57 (4.25)	26.76 (4.53)	26.89 (4.70)	26.61 (4.36)
Smoker (N (%))	29 (26.6%)	19 (24.7%)	10 (31.3%)	31 (29.8%)	18 (31.6%)	13 (27.7%)
Education						
• Low (N (%))	59 (54.1%)	45 (58.4%)	14 (43.8%)	53 (51.5%)	30 (52.6%)	23 (50.0%)
• Moderate (N (%))	32 (29.4%)	20 (26.0%)	12 (37.5%)	32 (31.1%)	21 (36.8%)	11 (23.9%)
• High (N (%))	18 (16.5%)	12 (15.6%)	6 (18.8%)	18 (17.5%)	6 (10.5%)	12 (26.1%)
History of back pain complaints						
• Time since first experience with low back pain in months (median (IQR))	97.33 (37.51 - 228.12)	109.50 (41.02 - 243.33)	79.08 (36.50 - 164.43)	65.08 (27.08 - 144.21)	60.83 (27.83 - 121.67)	103.33 (24.33 - 219.00)
• Time since current episode with low back pain in months (median (IQR))	30.33 (12.17 - 76.03)	26.33 (10.00 - 79.08)	34.75 (13.52 - 77.55)	24.33 (12.17 - 66.58)	20.17 (9.50 - 53.17)	36.50 (16.17 - 73.00)
Married/living with a partner (N (%))	85 (78.0%)	64 (83.1%)	21 (65.6%)	82 (79.6%)	49 (86.0%)	33 (71.7%)
Expectations						
• Credibility (0-27)	21.36 (4.51)	21.18 (4.51)	21.77 (4.56)	19.88 (5.31)	20.05 (5.60)	19.64 (4.94)
• Expectancy (0-27)	18.75 (4.99)	18.86 (4.82)	18.48 (5.47)	18.23 (5.31)	18.51 (5.09)	17.88 (5.64)
Outcomes						
Pain intensity in the past week (NRS 0-10)	7.17 (1.65)	7.09 (1.78)	7.34 (1.310)	7.06 (1.43)	7.12 (1.68)	6.98 (1.035)
Oswestry disability index (mean (SD))	38.07 (14.07)	38.26 (14.97)	37.63 (11.81)	33.70 (14.43)	34.46 (14.23)	32.70 (14.79)
Quality of life (EQ-5D)	0.50 (0.27)	0.50 (0.28)	0.47 (0.26)	0.56 (0.27)	0.54 (0.27)	0.60 (0.26)

Abbreviations: SD, Standard Deviation; IQE, Inter Quartile Range; N, number; BMI, Body Mass Index; EQ-5D, EuroQol-5D

Appendix 2. Treatment effects for primary outcomes based on as-treated analyses, without 7 protocol violators

		Mean Intervention group (SD	Mean Control group (SD)	Treatment effect (95%CI)	P value for difference
Primary outcomes					
NRS Pain*	Overall effect			-0.41 (-0.85 to 0.02)	0.06
	Baseline	7.17 (1.65)	7.05 (1.43)		
	3 weeks	4.96 (2.19)	5.93 (1.90)	-0.92 (-1.59 to -0.24)	0.01
	6 weeks	5.22 (2.16)	5.70 (1.86)	-0.50 (-1.15 to 0.14)	0.13
	3 months	4.77 (2.46)	5.44 (2.97)	-0.73 (-1.39 to -0.07)	0.03
	6 months	4.50 (2.47)	4.90 (2.46)	-0.28 (-0.94 to 0.38)	0.40
	9 months	5.03 (2.45)	5.01 (2.63)	0.13 (-0.56 to 0.81)	0.72
	12 months	4.65 (2.46)	4.73 (2.42)	0.03 (-0.66 to 0.72)	0.93
ODI Functioning*	Overall effect			-0.31 (-3.79 to 3.17)	0.86
	Baseline	38.07 (14.07)	33.79 (14.58)		
	3 months	27.72 (17.05)	29.46 (17.19)	-4.99 (-9.27 to -0.70)	0.02
	6 months	25.98 (15.71)	25.80 (16.55)	-0.95 (-5.26 to 3.36)	0.67
	9 months	28.40 (16.88)	23.83 (15.34)	3.88 (-0.53 to 8.28)	0.08
	12 months	27.29 (17.22)	24.72 (16.51)	1.71 (-2.75 to 6.46)	0.45

		Success % Intervention group	Success % Control group	OR (95%CI)	P value for difference	NNT
GPE (Success)*	Overall effect			2.291 (1.47 to 3.58)	0.0003	
	3 weeks	29.80	9.80	3.873 (1.51 to 9.22)	0.0048	5
	6 weeks	37.00	10.10	5.818 (2..4 to 14.45)	0.0001	4
	3 months	39.10	20.70	2.614 (1.22 to 5.63)	0.01	5
	6 months	44.70	31.30	1.679 (0.82 to 3.45)	0.16	7
	9 months	35.60	31.50	1.241 (0.58 to 2.66)	0.58	24
	12 months	48.00	32.90	1.759 (0.83 to 3.73)	0.14	7

Values presented are model estimates of linear mixed-effects models with a random intercept, and adjusted for baseline and age, gender, BMI, education, smoking, marital status, back pain complaint history, patient expectations and baseline values. Regression coefficients can be interpreted as mean differences between interventions at a certain follow-up moment compared to baseline.Abbreviations: NRS, Numeric Rating Scale; GPE, Global Perceived Effect; ODI, Oswestry Disability Index; NNT, Numbers Needed to Treat

** Higher score indicates more severe symptoms. Range for NRS pain, 0-10; for ODI, 0-100; for GPE, 1&2 is defined as success*

Appendix 3. Treatment effects for primary outcomes based on intention-to-treat analyses adjusted for treatment after 3 months, continuous

		Mean Intervention group (SD	Mean Control group (SD)	Treatment effect (95%CI)	P value for difference
Primary outcomes					
NRS Pain (SE)	Overall effect			-0.19 (-0.68 to 0.30)	0.44
	Baseline	7.17 (1.65)	6.73 (1.46)		
	3 weeks	4.96 (2.19)	5.62 (1.90)	-0.57 (-1.33 to 0.19)	0.14
	6 weeks	5.22 (2.16)	5.37 (1.86)	-0.20 (-0.93 to 0.52)	0.58
	3 months	4.77 (2.46)	4.78 (2.46)	-0.07 (-0.82 to 0.69)	0.86
	6 months	4.50 (2.47)	4.70 (2.52)	-0.11 (-0.86 to 0.65)	0.79
	9 months	5.03 (2.45)	5.24 (2.56)	-0.17 (-0.95 to 0.62)	0.67
	12 months	4.65 (2.46)	4.53 (2.19)	0.15 (-0.64 to 0.95)	0.71
ODI Functioning (SE)	Overall effect			2.26 (-1.83 to 6.35)	0.28
	Baseline	38.07 (14.07)	31.81 (14.07)		
	3 months	27.72 (17.05)	24.81 (15.44)	0.03 (-4.95 to 5.00)	0.99
	6 months	25.98 (15.71)	23.24 (15.70)	1.12 (-3.86 to 6.10)	0.66
	9 months	28.40 (16.88)	22.10 (16.05)	4.82 (-0.30 to 9.94)	0.06
	12 months	27.26 (17.22)	21.07 (14.28)	3.64 (-1.52 to 8.81)	0.17

		Success % Intervention group	Success % Control group	OR (95%CI)	P value for difference	NNT
GPE (Success)	Overall effect			2,15 (1.29 to 3.58)	0.003	
	3 weeks	29.80	10.50	3,37 (1.74 to 9.67)	0.024	5
	6 weeks	37.00	10.00	5,02 (1.80 to 14.03)	0.002	4
	3 months	39.10	28.80	1,66 (0.72 to 3.88)	0.23	10
	6 months	44.70	32.70	1,61 (0.70 to 3.68)	0.26	8
	9 months	35.60	28.90	1,51 (0.61 to 3.75)	0.37	15
	12 months	48.00	32.60	1,82 (0.75 to 4.39)	0.18	6

Values presented are model estimates of linear mixed-effects models with a random intercept, and adjusted for baseline and age, gender, BMI, education, smoking, marital status, back pain complaint history, patient expectations and baseline values. Regression coefficients can be interpreted as mean differences between interventions at a certain follow-up moment compared to baseline.Abbreviations: NRS, Numeric Rating Scale; GPE, Global Perceived Effect; ODI, Oswestry Disability Index; NNT, Numbers Needed to Treat Higher score indicates more severe symptoms. Range for NRS pain, 0-10; for ODI, 0-100; for GPE, 1&2 is defined as success

Appendix 4. Pain reduction per treatment modality

		Cooled RF (n=23)	Simplicity (n=5)	Palisade (n=77)
NRS Pain (SD)	Baseline	6.95 (1.96)	6.40 (3.65)	7.26 (1.45)
	3 weeks	5.16 (2.34)	6.67 (2.89)	4.80 (2.14)
	6 weeks	4.15 (2.25)	6.00 (2.16)	5.38 (2.12)
	3 months	4.14 (2.66)	5.00 (2.55)	4.89 (2.44)
	6 months	4.10 (2.53)	4.25 (2.22)	4.44 (2.51)
	9 months	4.76 (2.83)	5.75 (0.96)	5.06 (2.45)
	12 months	4.45 (2.44)	4.50 (3.32)	4.62 (2.53)

Values presented are model estimates of linear mixed-effects models with a random intercept, and adjusted for baseline and age, gender, BMI, education, smoking, marital status, back pain complaint history, patient expectations and baseline values. Regression coefficients can be interpreted as mean differences between interventions at a certain follow-up moment compared to baseline.
Abbreviations: NRS, Numeric Rating Scale
Higher score indicates more severe symptoms. Range for NRS pain, 0-10

Appendix 5. Treatment effects for primary outcomes based on intention-to-treat analyses Complete Case Analysis

		Mean Intervention group (SD)	Mean Control group (SD)	Treatment effect (95%CI)	P value for difference
Primary outcomes					
NRS Pain	Overall effect			-0.29 (-0.84 to 0.25)	0.29
	Baseline	7.07	7.12		
	3 weeks	5.00	6.14	-1.00 (-1.80 to -0.20)	0.01
	6 weeks	5.09	5.95	-0.74 (-1.54 to 0.06)	0.07
	3 months	4.63	5.43	-0.70 (-1.50 to 0.10)	0.09
	6 months	4.44	4.37	0.18 (-0.62 to 0.98)	0.66
	9 months	5.05	4.75	0.42 (-0.38 to 1.22)	0.31
	12 months	4.65	4.70	0.06 (-0.74 to 0.86)	0.88
ODI Functioning	Overall effect			-0.31 (3.47 to 2.85)	0.53
	Baseline	37.95 (15.75)	34.46 (14.23)		
	3 months	27.12 (18.30)	30.46 (18.56)	-5.17 (-9.28 to -1.06)	0.07
	6 months	12.37 (11.84)	10.42 (10.53)	0.45 (-3.87 to 4.36)	0.47
	9 months	14.72 (13.28)	10.18 (9.73)	2.84 (-1.27 to 6.95)	0.03
	12 months	13.92 (13.09)	11.26 (11.39)	0.84 (-3.28 to 4.95)	0.30

		Success % Intervention group	Success % Control group	OR (95%CI)	P value for difference	NNT
GPE (Success)	Overall effect			1.87 (1.12 to 3.12)	0.017	
	3 weeks	28.00	12.30	2.85 (1.00 to 8.11)	0.049	6
	6 weeks	38.70	8.80	6.86 (2.21 to 21.24)	0.001	3
	3 months	41.30	24.60	2.20 (0.91 to 5.33)	0.08	6
	6 months	46.70	40.40	1.29 (0.56 to 2.96)	0.55	16
	9 months	36.00	35.10	1.04 (0.44 to 2.42)	0.94	111
	12 months	48.00	36.80	1.59 (0.69 to 3.66)	0.28	9

Values presented are model estimates of linear mixed-effects models with a random intercept, and adjusted for baseline and age, gender, BMI, education, smoking, marital status, back pain complaint history, patient expectations and baseline values. Regression coefficients can be interpreted as mean differences between interventions at a certain follow-up moment compared to baseline.
Abbreviations: NRS, Numeric Rating Scale; GPE, Global Perceived Effect; ODI, Oswestry Disability Index; NNT, Numbers Needed to Treat
Higher score indicates more severe symptoms. Range for NRS pain, 0-10; for ODI, 0-100; for GPE, 1&2 is defined as success