Supplementary material 1

MEDLINE search strategy

1. spinal cord stimulat*.ti,ab,kw.
2. dorsal column stimulat*.ti,ab,kw.
3. epidural stimulat*.ti,ab,kw.
4. exp Spinal cord stimulation/
5. 1 or 2 or 3 or 4
6. (Diabetic adj2 neuropath*).ti,ab,kw.
7. (diabetic adj2 polyneuropath*).ti,ab,kw.
8. exp Diabetic Neuropathies/
9. 6 or 7 or 8
10. 5 and 9
11. randomized controlled trial.pt.
12. controlled clinical trial.pt.
13. randomized.ab.
14. placebo.ti,ab.
15. drug therapy.fs.
16. randomly.ab.
17. trial.ab.
18. groups.ab.
19. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. exp animals/
21. humans/
22. 20 not 21
23. 19 not 22
24. clinical trial, phase iii/
25. ("phase 3" or "phase3" or "phase III" or P3 or "PIII").ti,ab,kw.
26. 24 or 25
27. 23 or 26
28. 10 and 27

Notes:

1. Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format
2. Addition of #24 and #25 to RCT filter as recommended in Cooper C, Varley-Campbell J, Carter P. Established search filters may miss studies when identifying randomized controlled trials. J Clin Epidemiol 2019;112:12-19.

Supplementary material 2

The RoB 2.0 tool (individually randomized, cross-over trials)

Study details

Reference	de Vos 2014

Study design

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Spinal cord stimulation Comparator: Best medical therapy

Specify which outcome is being assessed for risk of bias	Proportion of patients with at least a 50% reduction in pain Pain intensity Health-related quality of life
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Patients with at least a 50% reduction in pain (table 2) Pain intensity (table 2) Health-related quality of life (table 2)

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions

☐ failures in implementing the intervention that could have affected the outcome

☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

X Journal article(s) with results of the trial
☐ Trial protocol
☐ Statistical analysis plan (SAP)
X Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
X Personal communication with trialist
☐ Personal communication with the sponsor

1.1 Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Described as randomisation performed by an independent third party but no information provided about the sequence generation process. Only additional information is that stratified block randomisation is used which almost certainly indicates it is computer randomisation. No information provided on how allocation sequence was performed.	PY
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Baseline characteristics were relatively well balanced between the 2 groups, the main exceptions being a somewhat higher age and lower pain score in the control group. However, none of the differences between the groups was significant.	N
Risk-of-bias judgement		Low

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Open label trial	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	No mentions made regarding deviations from the intended intervention	N
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	ITT analysis using last observation carried forward for missing data	PY
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Low

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	No information is provided in the manuscript about extent of missing data. Access to individual patient data from the trial analysis allows to make this judgement. We have access to IPD for all randomised participants, as well as data imputed for participants with missing data so we could replicate the complete case and last observation carried forward analysis.	Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	The methods to measure the outcomes were appropriate.	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Open label trial. Study author mentioned the outcome assessors were aware of the treatments being received by participants.	Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Assessment of pain is subjective and therefore knowledge of treatment being received could influence outcome assessment. It is plausible that knowledge and beliefs of beneficial effect from the intervention could have influenced the outcomes.	PY
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		PY
Risk-of-bias judgement		High

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Unclear if a pre-specified analysis plan was finalised before data were available for analysis.	NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from…		
5.2. … multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	All eligible reported results for the outcome domains correspond to all intended outcome measurements.	N
5.3 … multiple eligible analyses of the data?		N
Risk-of-bias judgement		Some concerns

Overall risk of bias

Risk-of-bias judgement		High

Study details

Reference	Slangen 2014

Study design

X Individually-randomized parallel-group trial

☐ Cluster-randomized parallel-group trial

☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Spinal cord stimulation Comparator: Best medical therapy

Specify which outcome is being assessed for risk of bias	Proportion of patients with at least a 50% reduction in pain Pain intensity Health-related quality of life
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Patients with at least a 50% reduction in pain (table 2) Pain intensity (table 2) Health-related quality of life (table 2)

Is the review team's aim for this result…?

X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions

☐ failures in implementing the intervention that could have affected the outcome

☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

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☐ Trial protocol
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☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
☐ "Grey literature" (e.g. unpublished thesis)
☐ Conference abstract(s) about the trial
☐ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐ Research ethics application
☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
X Personal communication with trialist
☐ Personal communication with the sponsor

1.2 Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Described as computerised randomisation. No information provided on how allocation sequence was performed.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Baseline characteristics were relatively well balanced between the 2 groups.	N
Risk-of-bias judgement		Low

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	Open label trial	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	No mentions made regarding deviations from the intended intervention	N
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	ITT analysis.	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Low

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Outcome data were available for 19 patients (86.4%) in the SCS group and 14 patients in the BMT group (100%) at 6 months.	Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	The methods to measure the outcomes were appropriate.	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Open label trial. Study author mentioned the outcome assessors were aware of the treatments being received by participants.	Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Assessment of pain is subjective and therefore knowledge of treatment being received could influence outcome assessment. It is plausible that knowledge and beliefs of beneficial effect from the intervention could have influenced the outcomes.	PY
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		PY
Risk-of-bias judgement		High

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Unclear if a pre-specified analysis plan was finalised before data were available for analysis.	NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from…		
5.2. … multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	All eligible reported results for the outcome domains correspond to all intended outcome measurements.	N
5.3 … multiple eligible analyses of the data?		N
Risk-of-bias judgement		Some concerns

Overall risk of bias

Risk-of-bias judgement		High

Supplementary material 3

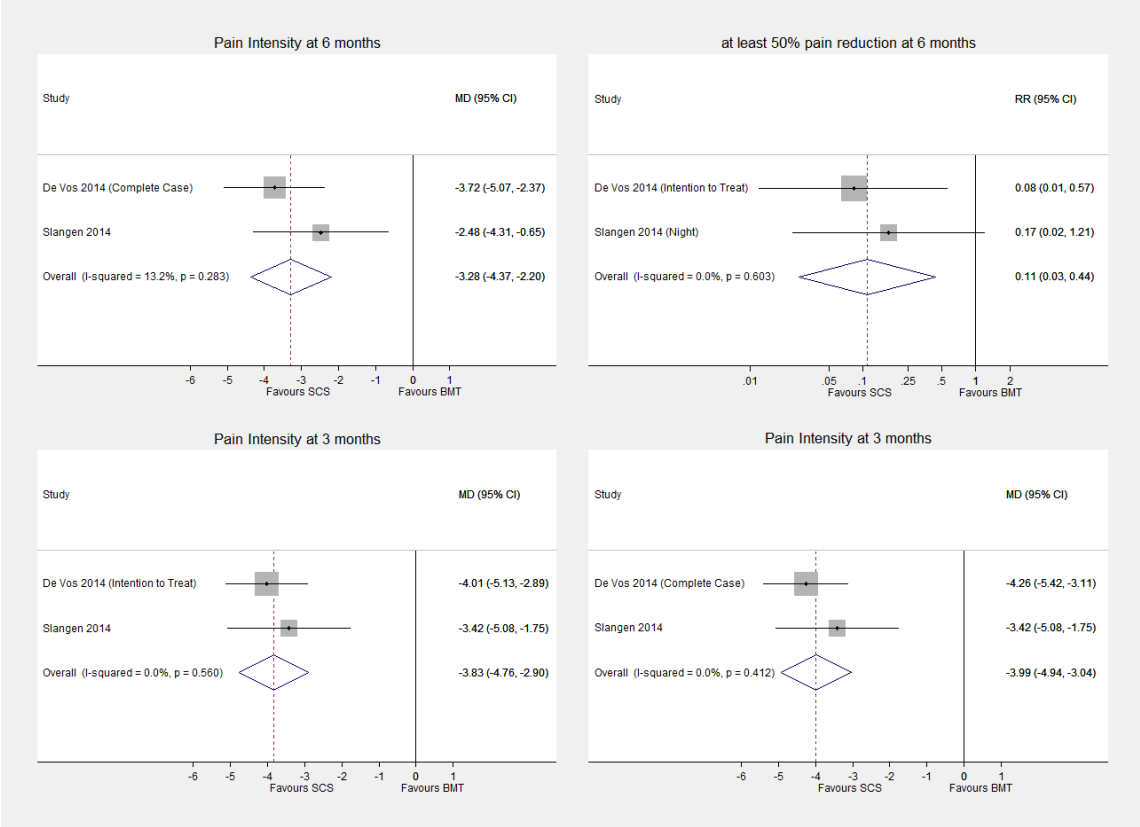

Figure S1. Additional fixed effects meta-analyses of pain intensity at 3 months, sensitivity analysis with de Vos 2014 complete case data and sensitivity analysis with Slangen 2014 night pain scores

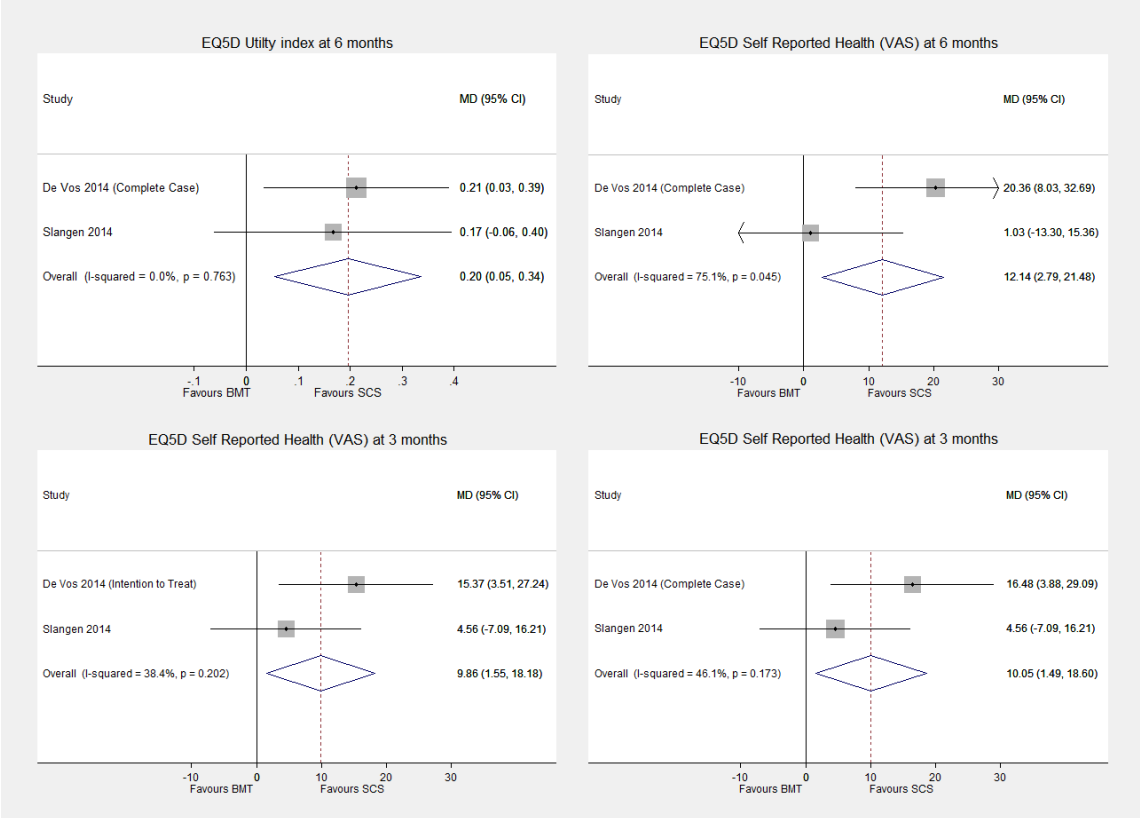

Figure S2. Additional fixed effects meta-analyses of EQ-5D at 3 months and sensitivity analysis with de Vos 2014 complete case data

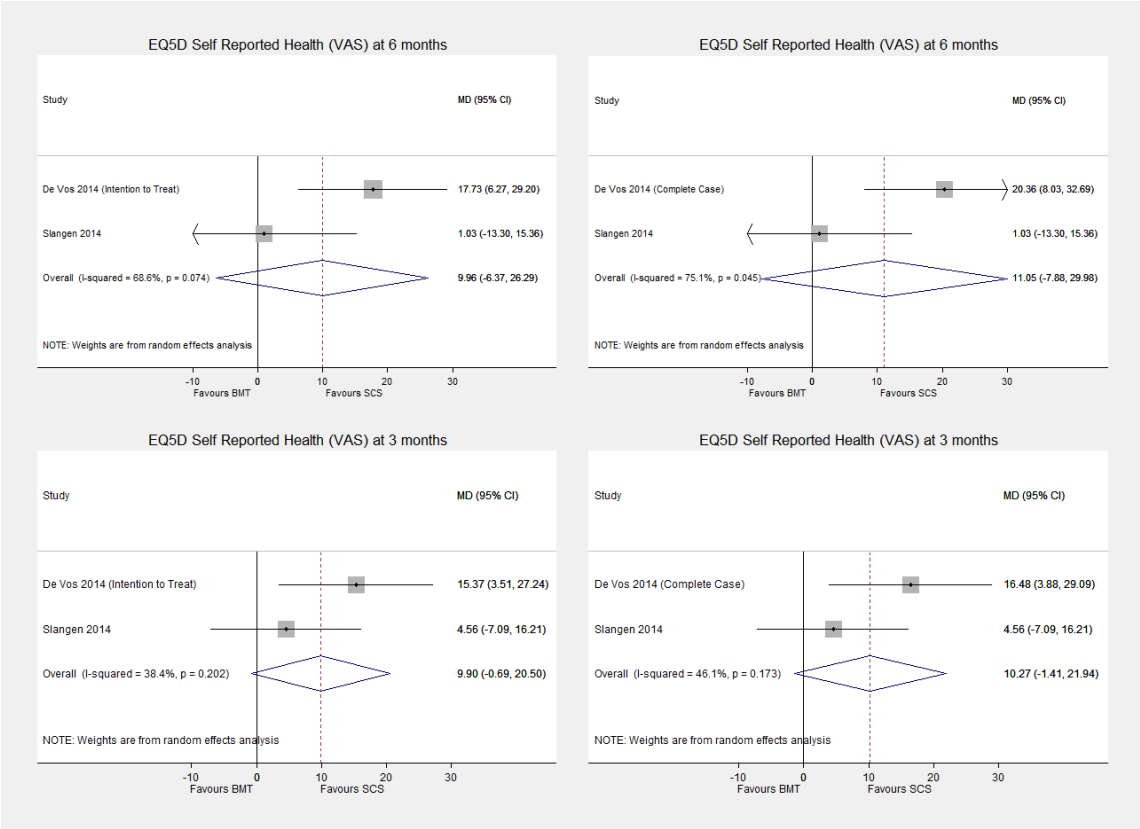

Figure S3. Random-effects meta-analyses of EQ-5D self-reported health at 3 months and 6 months