**Figure 1 Flow diagram of study inclusion**

**Table 1: Patient characteristics at baseline for groups receiving SMT vs groups receiving recommended interventions *(s= 12; n=2475)***

|  |  |  |
| --- | --- | --- |
|  |  |  |
| ***Demographic data*** | SMT | Recommended interventions |
| *Age*, mean (SD) years(s=11, n=2409)  | 47 (14) | 47 (14) |
| *Sex,* n (%) female(s=11, n=2412) | 667 (57) | 684 (55) |
| *Body Mass Index,* mean (SD) (s=8, n=1434) | 27 (5) | 27 (5) |
| *Ethnicity,* n (%) white (s=5, n=861) | 409 (91) | 388 (88) |
| ***Lifestyle factors*** |  |  |
| *Physical activity,* (%) (s=6, n=824) |  |  |
| Low (1 or less than once a week)  | 115 (32) | 166 (36) |
| Medium (2-3x a week)  | 146 (40) | 166 (36) |
| High (more than 3x a week)  | 100 (28) | 131 (28) |
| *Smoking,* n (%) non-smokers(s=6, n=1173) | 451 (80) | 453 (75) |
| *Alcohol use,* n (%) | \* | \* |
| ***Socio-demographics*** |  |  |
| *Marital Status,* n (%) married; living with a partner(s=6, n=1173) | 397 (69) | 404 (68) |
| *Level of Education,* n(%) low/ middle(s=7, n=1672) | 600 (68) | 534 (68) |
| *Income,* n (%) | \* | \* |
| *Employment status,* n (%) at work(s=9, n=2126) | 818 (78) | 770 (72) |
| ***Nature and severity of LBP*** |  |  |
| *Duration of LBP,* n(%) less than 12 months(s=7, n=1252) | 121 (20) | 149 (23) |
| *Leg pain,* n(%) (s=5, n=1038) | 320 (59) | 281 (57) |
| *Previous LBP treatment received,* n (%)(s=5, n=930) | 258 (28) | 218 (23) |
| *Previous physiotherapy for low back pain received,* n (%) (s=5, n=771) | 64 (8) | 72 (9) |
| *Previous SMT for low back pain received,* n (%) (s=6, n=988) | 209 (21) | 111 (11) |
| *Used medication for low back,* n (%)(s=6, n=1018) | 200 (20) | 269 (26) |
| *Non-specific,* n (%) | \* | \* |
| ***Comorbidities*** | \* | \* |
| ***Type of treatment*** | \* | \* |
| ***Psychosocial factors*** | SMT | Control |
| *Depression,* n (%)(s=5, n=1297) | 43 (6) | 75 (13) |
| ***Treatment preference/expectations*** | \* | \* |
|  |  |  |
| ***Primary outcomes*** |  |  |
| ***Pain*** |  |  |
| *Combined pain score* *at baseline,* mean (SD), (s=12, n=2441)  | 49.5 (22.3) | 49.8 (21.6) |
| *Combined pain score at one month,* mean (SD), (s=10, n=1948)  | 34.2 (23.0) | 35.8 (23.9) |
| *Combined pain score at three months,* mean (SD), (s=9, n=1673) | 27.92 (23.0) | 32.1 (24.3) |
| *Combined pain score at six months,* mean (SD), (s=8, n=1321) | 27.35 (23.1)  | 32.3 (23.9) |
| *Combined pain score at twelve months, mean (SD), (s=10,* n=*1816)*  | 31.80 (26.8) | 33.3 (25.4) |
| ***Functional Status*** |  |  |
| *RMDQ sum score* *at baseline,* mean (SD), (s=9, n=2174)  | 9.0 (5.0) | 10.1 (5.4) |
| *RMDQ sum score at one month,*mean (SD), (s=8, n=1760)  | 5.6 (5.0) | 6.7 (5.4) |
| *RMDQ sum score* *at three months,* mean (SD), (s=8, n=1648)  | 4.8 (5.1) | 5.5 (5.3) |
| *RMDQ sum score* *at six months,*mean (SD), (s=8, n=1348) | 5.0 (5.4) | 6.3 (6.0) |
| *RMDQ sum score at twelve months,*mean (SD), (s=7, n=1575) | 5.4 (5.7) | 6.2 (5.92) |
| ***Secondary outcomes*** |  |  |
| *SF36 Physical Component Scale of SF36 at baseline,* mean (SD), (s=5, n=1362) | 40.7 (7.2) | 41.1 (7.6) |
| *SF36 Physical Component Scale of SF36 at one month,* mean (SD), (s=3, n=865) | 44.1 (7.9) | 45.7 (8.1) |
| *SF36 Physical Component Scale of SF36 at three months weeks,* mean (SD), (s=4, n=1154) | 46.7 (8.2) | 46.9 (8.5) |
| *SF36 Physical Component Scale of SF36 at six months,* mean (SD), (s=5, n=839) | 47.3 (7.8) | 47.9 (7.7) |
| *SF36 Physical Component Scale of SF36 at twelve months,* mean (SD), (s=5, n=1249) | 46.4 (8.6) | 46.8 (8.8) |
| *SF36 Mental Component Scale of SF36 at baseline,* mean (SD), (s=5, n=1362) | 43.8 (9.1) | 45.1 (9.6) |
| *SF36 Mental Component Scale of SF36 at one month*, mean (SD), (s=3, n=865) | 45.5 (8.8) | 46.9 (8.8) |
| *SF36 Mental Component Scale of SF36 at three months*, mean (SD), (s=4, n=1154) | 46.9 (9.0) | 47.3 (9.5) |
| *SF36 Mental Component Scale of SF36 at six months*, mean (SD), (s=5, n=839) | 46.9 (9.1) | 48.0 (8.9) |
| *SF36 Mental Component Scale of SF36 at twelve months, mean (SD), (s=5, n=1249)* | 45.7 (8.9) | 46.2 (10.0) |
| *Medication use at baseline,* n (% medication use) (s= 3, n=668) | 145 (22) | 216 (32) |
| *Medication use at one month*, n (% medication use) (s=3, n=646) | 84 (13) | 146 (23) |
| *Medication use at three months*, n (% medication use) (s=3, n=626) | 78 (13) | 132 (21) |
| *Medication use at six months,* n (% medication use) s=3, n=593) | 67 (11) | 143 (24) |
| *Medication use at twelve months weeks,* n (% medication use) (s=3, n==582) | 82 (14) | 141 (24) |

SD = standard deviation; s = number of studies; n = number of participants; \* combining categories was not meaningful or no data available

**Table 2**: **Main treatment effects and GRADE summary of findings for all comparisons for the primary outcomes. Regression coefficients (β) and 95% confidence intervals (CI) of the intervention effects of random-effect models adjusted for baseline using REML (one stage analysis)**

 **are presented.**

|  |  |
| --- | --- |
| Comparison 1: SMT versus recommended therapies |  |
|  |  | Time measurement | Difference in effect (β) (95% CI) | # studies | N | Quality of the evidence (and reason for downgrading) | Comments |
|  | Outcome: Pain\* |  |  |  |  |  |
|  |  | 1 month | MD -3.0, 95% CI -6.9 to 0.9 | 10 | 1922 | Moderate (inconsistency) |  |
|  |  | 3 months | MD -6.6, 95% CI -13.0 to -0.2  | 9 | 1647 | Moderate (inconsistency) |  |
|  |  | 6 months  | MD -5.6, 95% CI -9.6 to -1.5 | 8 | 1321 | Moderate (inconsistency) |  |
|  |  | 12 months | MD -2.5, 95% CI -7.1 to 2.1 | 10 | 1791  | Moderate (inconsistency) |  |
|  | Outcome: Functional status | SMD converted to a MD on the 24 point RMDQ scale |
|  |  | 1 month | SMD -0.2, 95% CI -0.4 to 0.0  | 10 | 1939 | Moderate (inconsistency) | -0.8 |
|  |  | 3 months | SMD -0.1, 95% CI -0.4 to 0.1  | 11 | 1892 | Moderate (inconsistency) | -0.6 |
|  |  | 6 months  | SMD -0.2, 95% CI -0.3 to 0.0  | 9 | 1490 | Moderate (inconsistency) | -0.8 |
|  |  | 12 months | SMD -0.1, 95% CI -0.3 to 0.1  | 10 | 1826 | Moderate (inconsistency) | -0.5 |
|  |  |  |  |  |  |  |  |
| Comparison 2: SMT versus non-recommended therapies |  |
|  | Outcome: Pain\* |  |  |  |  |  |
|  |  | 1 month | MD **-**6.6 95% CI -10. 8 to -2.3  | 5 | 755 | Moderate (inconsistency) |  |
|  |  | 3 months | Not enough data |  |  |  |  |
|  |  | 6 months  | MD -8.3, 95% CI -20.5 to 3.8 | 3 | 419 | Moderate (imprecision) |  |
|  |  | 12 months | Not enough data |  |  |  |  |
|  | Outcome: Functional status | SMD converted to a MD on the 24 point RMDQ scale |
|  |  | 1 month | SMD -0.3, 95% CI -0.6 to 0.0  | 5 | 835 | Moderate (inconsistency) | -0.6 |
|  |  | 3 months | SMD -0.0, 95% CI -0.8 to 0.7 | 2 | 375 | Moderate (inconsistency) | -0.9 ‡ |
|  |  | 6 months  | SMD -0.3, 95% CI -0.6 to -0.0 | 3 | 414 | Moderate (imprecision) | -0.9 |
|  |  | 12 months | Not enough data |  |  |  |  |
|  |  |  |  |  |  |  |  |
| Comparison 3: SMT versus sham SMT |  |
|  |  |  |  |  |  |  |  |
|  | No results only data of one study |  |  |  |  |
|  |  |  |  |  |  |  |  |
| Comparison 4: SMT + intervention vs intervention alone  |  |
|  | Outcome: Pain\* |  |  |  |  |  |  |
|  |  | 1 month | MD -7.44, 95% CI -12.7 to -2.1 | 5 | 762 | Moderate (inconsistency) |  |
|  |  | 3 months | MD -5.2, 95% CI -11.0 to 0.7 | 2 | 619 | Moderate (inconsistency) |  |
|  |  | 6 months  | MD -1.4, 95% CI -6.7 to 3.8  | 2 | 222 | Low (inconsistency, imprecision) |  |
|  |  | 12 months | MD -2.2, 95% CI -5.9 to 1.4 | 2 | 603 | Moderate (inconsistency) |  |
|  | Outcome: Functional status† |  |
|  |  | 1 month | MD -0.6, 95% CI -2.3 to 1.1 \* | 4 | 746 | Moderate (inconsistency) |  |
|  |  | 3 months | MD -1.3, 95% CI -2.6 to -0.1 \* | 3 | 681 | Moderate (inconsistency) |  |
|  |  | 6 months  | MD -1.0, 95% CI -2.1 to 0.1 \* | 2 | 218 | Low (imprecision, inconsistency) |  |
|  |  | 12 months | MD -0.9, 95% CI -1.6 to -0.2 \* | 2 | 626 | Moderate (inconsistency) |  |
|  |  |  |  |  |  |  |  |
| Comparison 5: Manipulation vs mobilization |  |
|  | Outcome: Pain |  |  |  |  |  |  |
|  |  | 1 month | MD -1.5, 95% CI -6.8 to 3.9 | 3 | 321 | Moderate (limitations) |  |
|  |  | Not enough data for other time points |  |  |  |  |
|  | Outcome: Functional status | SMD converted to a MD on the 24 point RMDQ scale |
|  |  | 1 month | SMD 0.0, 95% CI -0.0 to 0.1 | 3 | 356 | Moderate (limitations) | -0.6 |
|  |  | Not enough data for other time points |  |  |  |  |

Negative difference in effect indicates higher estimated decrease in pain or improvements in function for SMT group compared to the control

MD = mean difference of combined pain score on a 0-100 scale

SMD = standardized mean difference of combined functional status score

\* Pain measured on a 0-100 point scale

† All studies in the SMT+ intervention vs intervention alone measured Roland Morris Disability questionnaire, therefore we use a mean difference

‡ based on one small study

**Table 3: Main treatment effects and GRADE summary of findings for all secondary outcomes.**

|  |
| --- |
| Comparison 1: SMT versus recommended therapies |
|  |  | Time measurement | Difference in effect (95% CI) | # studies | N | Quality of the evidence (and reason for downgrading) |
|  | Outcome: Quality of life: Physical Component Scale of SF36 and SF12 combined |
|  |  | 1 month | MD -0.6, 95% CI -1.4 to 0.1 | 4 | 844 | High |
|  |  | 3 months | MD -0.2, 95% CI -1.0 to 0.7 | 3 | 967 | High |
|  |  | 6 months  | MD -0.3, 95% CI -1.5 to 0.91 | 4 | 688  | High |
|  |  | 12 months | MD 0.1, 95% CI -0.8 to 1.0 | 4 | 1055  | High |
|  | Outcome: Mental Component Scale of SF36 and SF12 combined |
|  |  | 1 month | MD 0.4, 95% CI -0.4 to 1.2  | 4 | 844 | High |
|  |  | 3 months | MD 0.8, 95% CI -0.0 to 1.6  | 3 | 967 | High |
|  |  | 6 months  | MD -0.1, 95% CI -1.4 to 1.2  | 4 | 688 | High |
|  |  | 12 months | MD 0.5, 95% CI -0.9to 2.0  | 4 | 1055 | High |
|  | Outcome: Recovery \*: Yes vs No |  |  |  |
|  |  | 1 month | OR 1.3, 95% CI 0.9 to 1.9  | 2 | 499 | Moderate (inconsistency) |
|  |  | 3 months | OR 1.2, 95% CI 0.8 to 1.8  | 3 | 538 | Moderate (inconsistency) |
|  |  | 6 months  | OR 1.1, 95% CI 0.8 to 1.6  | 3 | 651 | Moderate (inconsistency) |
|  |  | 12 months | OR 0.8, 95% CI 0.5 to 1.2  | 2 | 445 | Moderate (inconsistency) |
|  | Outcome: Medication Use\*: Yes vs No |
|  |  | 1 month | OR 0.7, 95% CI 0.5 to 1.0  | 3 | 646 | Moderate (inconsistency) |
|  |  | 3 months | OR 0.7, 95% CI 0.4 to 1.2  | 3 | 626 | Moderate (inconsistency) |
|  |  | 6 months  | OR 0.5, 95% CI 0.3 to 0.9  | 3 | 593 | Moderate (inconsistency)  |
|  |  | 12 months | OR 0.7, 95% CI 0.3 to 1.3  | 3 | 582 | Moderate (inconsistency) |
|  | Outcome: Return to work\*: Yes vs No |
|  |  | 1 month | Not enough data  |  |  |  |
|  |  | 3 months | OR 1.0, 95% CI 0.5 to 1.9 | 3 | 190 | Low (inconsistency, imprecision) |
|  |  | 6 months  | OR 0.6, 95% CI 0.3 to 1.3 | 3 | 189 | Low (inconsistency, imprecision) |
|  |  | 12 months | OR 1.3, 95% CI 0.6 to 2.7 | 3 | 180 | Low (inconsistency, imprecision) |
|  | Outcome: Satisfaction\*: Yes vs No |  |  |
|  |  | 1 month | OR 0. 8, 95% CI 0.4 to 1.6)  | 2 | 319 | Low (inconsistency, imprecision) |
|  |  | 3 months | OR 6.6, 95% CI 1.5 to 29.9 | 2 | 429 | Low (inconsistency, imprecision) |
|  |  | 6 months  | Not enough data |  |  |  |
|  |  | 12 months | Not enough data |  |  |  |
|  |  |  |  |  |  |  |
| Comparison 2: SMT versus non-recommended therapies |  |  |
|  | Outcome: Quality of life: Physical Component Scale of SF36 and SF12 combined |
|  |  | 1 month | MD 0.4, 95% CI -0.8 to 1.6 | 3 | 345 | Low (inconsistency, imprecision) |
|  |  | 3 months | Not enough data |  |  |  |
|  |  | 6 months | MD -0.1, 95% CI -2.5 to 2.2 | 2 | 202 | Low (inconsistency, imprecision) |
|  |  | 12 months | Not enough data |  |  |  |
|  | Outcome: Quality of life: Mental Component Scale of SF36 and SF12 combined |
|  |  | 1 month | MD 1.0, 95% CI -3.1; 5.2 | 3 | 345 | Low (inconsistency, imprecision) |
|  |  | 3 months | Not enough data |  |  |  |
|  |  | 6 months | MD 1.7, 95% CI -0.6; 4.0 | 2 | 202 | Low (inconsistency, imprecision) |
|  |  | 12 months | Not enough data |  |  |  |
|  | Other outcomes not enough data |  |  |  |
|  |  |  |  |  |  |  |
| Comparison 3: SMT versus sham SMT |
|  |  |  |  |  |  |  |
|  | No results only data of one study |  |  |  |
|  |  |  |  |  |  |  |
| Comparison 4: SMT + intervention vs intervention alone |
|  | Outcome: Quality of life: Physical Component Scale of SF36 and SF12 combined |  |
|  |  | 1 month | MD 0.1, 95% CI -1.1 to 1.5  | 3 | 708 | Moderate (inconsistency)  |
|  |  | 3 months | MD 0.3, 95% CI -0.7 to 1.3  | 2 | 619 | Moderate (inconsistency) |
|  |  | 6 months  | MD -1.4, 95% CI -2.9 to 0.1 | 2 | 221 | Low (inconsistency, imprecision) |
|  |  | 12 months | MD -2.2, 95% CI -5.9 to 1.4 | 2 | 603 | Moderate (inconsistency) |
|  | Outcome: Quality of life: Mental Component Scale of SF36 and SF12 combined |
|  |  | 1 month | MD -0.2, 95% CI -1.6 to 1.2  | 3 | 708 | Moderate (inconsistency) |
|  |  | 3 months | MD 1.9, 95% CI -0.7 to 4.5 | 2 | 619 | Moderate (inconsistency) |
|  |  | 6 months  | MD 1.8, 95% CI -0.1 to 3.7 | 2 | 221 | Low (inconsistency, imprecision) |
|  |  | 12 months | MD 1.0, 95% CI -0.3 to 2.2  | 2 | 605 | Moderate (inconsistency) |
|  | Other outcomes not enough data |  |  |  |
|  |  |  |  |  |
| Comparison 5: Manipulation vs mobilization |
|  | All outcomes not enough data |  |  |  |  |
|  |  |  |  |  |  |  |

Positive difference in effect indicates higher increased quality of health for SMT group compared to the control

MD = mean difference

OR = odds ratio

\* Recovery was classified as ‘recovered’ if the participant scored more than 50% improvement or were (much) better or had no symptoms. Medication use was classified for those using taking any using medication for LBP, while not taking any medication was classified as no medication use. Return to work was classified as participants had returned- to-work or if there were no sick days recorded. Satisfaction was classified as ‘satisfied with care’ if participants were (completely) satisfied or had scores > 75%.

**Table 4: Representativeness of the pooled effects of studies providing data for the IPD study and those not providing data. Two stage analysis; SMT vs recommended therapies**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Representativeness** | **Number of studies** | **Difference in effect (CI 95%)** | **Test of heterogeneity** |  | **Prediction Interval** |
| **Outcome** |  |  | **I2** | **P-value** |  |
| **Pain** |  | **Mean Difference**  |  |  |  |
| *Combined pain score one month* |  |  |  |  |  |
| All eligible studies | 16 | -2.4 (-4.9; 0.1) | 66% | <0.001  | -2.4 (-11.6; 6.9) |
|  |  |  |  |  |  |
| Studies providing data | 10 | -2.5 (-5.9; 0.9) | 75% | <0.001  | -2.7 (-13.8;8.8) |
| Studies not providing data | 6 | -2.2 (-6.1; 1.7) | 55% | 0.02 | -2.218 (-12.9; 8.5) |
| *Combined pain score three months* |  |  |  |  |  |
| All eligible studies | 14 | -3.1 (-7.0; 0.8) | 80% | <0.001  | -3.1 (-18.6; 12.4) |
|  |  |  |  |  |  |
| Studies providing data | 9 | -5.9 (-11.4; -0.5) | 86% | <0.001  | -5.9 (-25.0; 13.0) |
| Studies not providing data | 5 | 1.1 (-2.7; 4.9) | 29% | 0.196 | 1.1 (-7.4; 9.6) |
| *Combined pain score six months*  |  |  |  |  |  |
| All eligible studies | 13 | -4.1 (-6.7;-1.6) | 66% | <0.001  | -4.1 (-13.5; 5.2) |
|  |  |  |  |  |  |
| Studies providing data | 8 | -4.8 (-8.9; -0.6) | 72% | 0.001 | -4.8 (-17.8;8.3) |
| Studies not providing data | 5 | -3.5 (-7.0; -0.1) | 61% | 0.009 | -3.5 (-13.8; -6.4) |
|  |  |  |  |  |  |
| *Combined pain score twelve months* |  |  |  |  |  |
| All eligible studies | 12 | -1.8 (-4.8; 1.3) | 71% | <0.001  | -1.8 (-12.5; 9.0) |
|  |  |  |  |  |  |
| Studies providing data | 10 | -2.1 (-6.5; 2.2) | 79% | <0.001  | -2.1 (-16.8; 12.5) |
| Studies not providing data | 2 | -0.9 (-3.5; 1.8) | 0% | 0.6 | -0.9 (-6.7; 5.0) |
| **Functional status** |  | **Difference in Z-score**  |  |  |  |
| *Combined Functional Status* *One month*  |  |  |  |  |  |
| All eligible studies | 13 | -0.2 (-0.3; -0.0) | 49% | 0.014 | -0.2 (-0.6; 0.3) |
|  |  |  |  |  |  |
| Studies providing data | 9 | -0.3 (-0.5; -0.0) | 65% | 0.003 | -0.3 (-1.0; 0.4) |
| Studies not providing data | 4 | -0.1 (-0.2; 0.0) | 0% | 0.739 | -0.1 (-0.2; 0.1) |
| *Combined Functional Status three months*  |  |  |  |  |  |
| All eligible studies | 15 | -0.1 (-0.2; 0.1) | 75% | <0.001 | -0.1 (-0.8; 0.7) |
|  |  |  |  |  |  |
| Studies providing data | 11 | -0.2 (-0.4; 0.0) | 79% | <0.001 | -0.2 (-0.9;0.6) |
| Studies not providing data | 4 | 0.2 (-0.1; 0.4) | 45% | 0.089 | 0.2 (-0.5; 0.8) |
| *Combined Functional Status six months*  |  |  |  |  |  |
| All eligible studies | 13 | -0.1 (-0.2; 0.0) | 56% | 0.002 | -0.1 (-0.6; 0.4) |
|  |  |  |  |  |  |
| Studies providing data | 9 | -0.2 (-0.4; -0.0) | 69% | 0.001 | -0.2 (-0.9; 0.5) |
| Studies not providing data | 4 | 0.0 (-0.1; 0.1) | 0% | 0.778 | 0.0 (-0.1; 0.2) |
| *Combined Functional Status twelve months*  |  |  |  |  |  |
| All eligible studies | 13 | -0.2 (-0.3; 0.1) | 72% | <0.001 | -0.2 (-0.7; 0.4) |
|  |  |  |  |  |  |
| Studies providing data | 10 | -0.2 (-0.4; 0.1) | 79% | <0.001 | -0.2 (-0.9; 0.6) |
| Studies not providing data | 3 | -0.1 (-0.3; 0.1) | 43% | 0.132 | -0.1 (-0.7; 0.5) |

CI = conﬁdence interval; I2 = I2 statistic, which is the percentage of total variance that can be explained by heterogeneity, and 25% is considered low, 50% moderate, and 75% high heterogeneity.

**Declarations**

**Consent for publication**

Not applicable.

**Availability of data and materials**

Not applicable.

**Appendix**

**eTable 1:** PRISMA-IPD (Preferred Reporting Items for Systematic review and Meta-Analysis Individual patient data) checklist

**eTable 2:** Criteria for a judgment of ‘low risk of bias’ for the sources of bias

**eTable 3:** Descriptives of studies evaluating the effects of SMT on outcomes included in the database (n=21) in alphabetical order of first author.

**eTable 4:** Summary of risk of bias assessments among the included trials

**eTable 5**: Decision rule analysis: primary and secondary outcomes

**eTable** **6:** The GRADE approach to evidence synthesis

**eTable 7**: Patient characteristics at baseline for other comparisons at all time points

**eTable 8:** Sensitivity analyses for SMT vs recommended interventions: one stage analysis

**eTable 9:** Representativeness of the pooled effects of studies providing data for the IPD study and those not providing data for other comparisons: two stage analysis

**eTable 10**: Search strategy

**eFig. 1**: Funnel Plot: SMT vs Recommended interventions for the pain

**eFig. 2:** Funnel Plot: SMT vs Recommended interventions for the functional status

**eFig. 3:** Pain time profile

**eFig. 4**: Function time profile