#### Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

**eTable 1.** Risk of Bias Summary from Randomized Controlled Trials for Non-pharmacological Postoperative Pain Management after Total Knee Arthroplasty.

| Study                        | Random sequence generation | Allocation concealment | Incomplete<br>outcome data | Selective outcome reporting | Other sources of bias | Blinding |
|------------------------------|----------------------------|------------------------|----------------------------|-----------------------------|-----------------------|----------|
| Adravanti et al.<br>(2013)   | Low                        | High                   | Unclear                    | High                        | Low                   | High     |
| Albrecht et al.<br>(2008)    | Unclear                    | Unclear                | Low                        | Unclear                     | Unclear               | High     |
| Beauprè et al.<br>(2001)     | Unclear                    | Unclear                | Low                        | Unclear                     | Low                   | High     |
| Bennett et al.<br>(2005)     | Low                        | Low                    | Low                        | High                        | Low                   | High     |
| Borckardt et al. (2013)      | Low                        | Low                    | Low                        | Unclear                     | Low                   | High     |
| Bruun-Olsen et<br>al. (2009) | High                       | Low                    | Low                        | Low                         | Unclear               | High     |
| Calatayud et al.<br>(2016)   | Low                        | Low                    | Low                        | Low                         | Unclear               | High     |
| Chen et al.<br>(2013)        | High                       | High                   | Unclear                    | Unclear                     | Low                   | High     |
| Chen et al.<br>(2015)        | Unclear                    | Unclear                | Low                        | Unclear                     | Unclear               | High     |
| Colwell et al.<br>(1992)     | Unclear                    | Unclear                | Low                        | High                        | Low                   | High     |
| Denis et al.<br>(2006)       | Low                        | Low                    | Low                        | Low                         | Low                   | High     |
| Gibbons et al.<br>(2001)     | Unclear                    | Unclear                | Low                        | High                        | Low                   | High     |

| Gstoettner et al. | Low      | Low       | Unclear  | Low       | Low       | High      |
|-------------------|----------|-----------|----------|-----------|-----------|-----------|
| (2011)            |          |           |          |           |           |           |
| Harms et al.      | Unclear  | Unclear   | Unclear  | High      | Low       | High      |
| (1991)            |          |           |          | <u> </u>  |           | <u> </u>  |
| lvey et al.       | Low      | Low       | Unclear  | Unclear   | Unclear   | Low       |
| (1994)            |          |           |          |           |           |           |
| Kim et al.        | Low      | Unclear   | Unclear  | Low       | Unclear   | High      |
| (2009)            |          |           |          |           |           | -         |
| Kullenberg et al. | Unclear  | Unclear   | Low      | High      | Low       | High      |
| (2006)            |          |           |          |           |           |           |
| Lensson et al     | Low      | Low       |          | Low       | Low       | High      |
| (2002)            | LOW      | LOW       |          | EOW       | LOW       | riigii    |
| (2003)            | 1        | 1         | 1.       | 1.12 - 1. | 1         | 1.12 - 1- |
| Lenssen et al.    | LOW      | LOW       | LOW      | High      | LOW       | High      |
| (2008)            |          |           |          |           |           |           |
| Levy et al.       | Unclear  | Unclear   | Unclear  | High      | Low       | Unclear   |
| (1993)            |          |           |          |           |           |           |
| MacDonald et      | Low      | Low       | Unclear  | High      | Low       | High      |
| al. (2000)        |          |           |          | 0         |           | U U       |
| Maniar et al.     | Hiah     | low       | Unclear  | Low       | Hiah      | High      |
| (2012)            |          | 2011      | erioloai | 2011      | · ···g··· |           |
| May at al         | Lincloar | Low       | Low      | High      |           | High      |
| (1000)            | Unclear  | LOW       | LOW      | riigii    | LOW       | riigii    |
| (1999)            |          | 1.12 - 1- | 1        |           | 1.        | 1.12 - 1- |
| McKay et al.      | Unclear  | High      | LOW      | Unclear   | LOW       | High      |
| (2012)            |          |           |          |           |           |           |
| McInnes et al.    | High     | Low       | Low      | Low       | Unclear   | High      |
| (1992)            |          |           |          |           |           |           |
| Mikashima et al.  | Low      | Low       | Low      | Unclear   | Unclear   | Unclear   |
| (2012)            |          |           |          |           |           |           |
| Montgomery et     | High     | Unclear   | Low      | Unclear   | Low       | High      |
| al (1006)         | i ngin   | Griotea   |          | Choical   |           | i ngi i   |
| Maratti at al     | Low      | Low       | Lliab    | High      | Undoor    | Lliab     |
|                   | LOW      | LOW       | пıyn     | пуп       | Unclear   | пığıı     |
| (2012)            |          |           |          |           |           |           |

| Morsi E. (2002)            | High    | High    | Low     | High    | Low     | High    |
|----------------------------|---------|---------|---------|---------|---------|---------|
| Pope et al.<br>(1997)      | Unclear | Unclear | Low     | Unclear | Unclear | High    |
| Radkowski et al.<br>(2007) | Low     | Unclear | Low     | High    | Low     | Low     |
| Sahin et al.<br>(2006)     | High    | Unclear | Low     | Low     | Unclear | High    |
| Smith et al.<br>(2002)     | High    | Unclear | Low     | Unclear | Unclear | High    |
| Su et al. (2012)           | Unclear | Unclear | Low     | Unclear | Low     | High    |
| Thienpont et al.<br>(2014) | Low     | Low     | Low     | Low     | Unclear | Unclear |
| Tsang et al.<br>(2007)     | Low     | Low     | Low     | High    | Unclear | Unclear |
| Tzeng et al.<br>(2015)     | Unclear | Low     | Unclear | Unclear | Low     | High    |
| Walker et al.<br>(1991)    | Unclear | Unclear | Low     | Unclear | Low     | Unclear |
| Webb et al.<br>(1998)      | Unclear | Unclear | Low     | Unclear | Low     | Unclear |

eTable 2. GRADE of Evidence Assessment for Non-pharmacological Postoperative Pain Management after Total Knee Arthroplasty.

| Study Outcome         | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | GRADE           |
|-----------------------|--------------|---------------|--------------|-------------|------------------|-----------------|
| Pain relief – VAS     |              |               |              |             |                  |                 |
| CPM                   | Very Serious | Not Serious   | Not Serious  | Serious     | Not Serious      | ⊕<br>Very Low   |
| Cryotherapy           | Very Serious | Serious       | Not Serious  | Not Serious | Serious          | ⊕<br>Very Low   |
| Electrotherapy        | Very Serious | Serious       | Not Serious  | Not Serious | Serious          | ⊕<br>Very Low   |
| Acupuncture           | Serious      | Serious       | Not Serious  | Not Serious | Not Serious      | ⊕⊕<br>Low       |
| Pain relief – WOMAC   |              |               |              |             |                  |                 |
| СРМ                   | Very Serious | Not Serious   | Not Serious  | Not Serious | Not Serious      | ⊕⊕<br>Low       |
| Preoperative exercise | Serious      | Serious       | Not Serious  | Not Serious | Not Serious      | ⊕⊕<br>Low       |
| Opioid consumption    |              |               |              |             |                  |                 |
| СРМ                   | Serious      | Serious       | Not Serious  | Serious     | Not Serious      | ⊕<br>Very Low   |
| Cryotherapy           | Serious      | Serious       | Not Serious  | Not Serious | Serious          | ⊕<br>Very Low   |
| Electrotherapy        | Serious      | Not Serious   | Not Serious  | Not Serious | Not Serious      | ⊕⊕⊕<br>Moderate |

| Acupuncture       | Serious      | Serious     | Not Serious | Not Serious | Not Serious | ⊕⊕<br>Low       |
|-------------------|--------------|-------------|-------------|-------------|-------------|-----------------|
| NSAID consumption |              |             |             |             |             |                 |
| Cryotherapy       | Very Serious | Serious     | Not Serious | Serious     | Not Serious | ⊕<br>Very Low   |
| Time to first PCA |              |             |             |             |             |                 |
| Acupuncture       | Serious      | Not Serious | Not Serious | Not Serious | Not Serious | ⊕⊕⊕<br>Moderate |

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eTable 3. Summary of Key Review Findings for Non-pharmacological Postoperative Pain Management after Total Knee Arthroplasty.

| Study                 | Duration of intervention           | Outcome<br>measure<br>timepoints | Primary<br>outcome<br>measure    | Secondary<br>outcome<br>measure   | Main<br>findings/Conclusi<br>on   | Conflict of<br>interest/funding<br>disclosure   |
|-----------------------|------------------------------------|----------------------------------|----------------------------------|---|---|---|
| Continuous passive    | motion (CPM)                       | -                                |                                  |   |   |   |
| Beauprè et al. (2001) | 3 days<br>postoperative<br>ly (PO) | 3 and 6<br>months PO             | Knee<br>extension<br>and flexion | WOMAC<br>(Pain,<br>Stiffness,<br>Function),<br>SF36   | Self-reported pain,<br>function, or overall<br>quality of life was<br>not different at<br>either of the<br>postoperative<br>measurement<br>times.                                   | Study funded by a grant<br>from the Health Services<br>Research and Innovation<br>Fund, Canada.   |
| Bennett et al. (2005) | 6 days PO                          | 3 months, 1<br>year PO           | Range of<br>Motion<br>(ROM)      | Length of<br>stay (LOS),<br>Pain,<br>Wound<br>healing,<br>Perceived<br>Health<br>Status<br>Measure<br>SF-12 | Statistically<br>significant<br>differences in mean<br>pain scores<br>between groups.<br>The differences are<br>not clinically<br>significant (≤1 point<br>on a 10-point<br>scale). | Funds received in partial or<br>total support of the research<br>material described in this<br>article from the Alfred Grant,<br>Australia. |

| Brunn-Olsen et al.<br>(2009) | 6 to 12–14<br>weeks PO   | 14 weeks, 9<br>months PO                      | Pain (VAS<br>scale)   | ROM  | CPM was not found<br>to have an<br>additional short-<br>time effect<br>compared with<br>physiotherapy.<br>After three months<br>pain relief was<br>obtained.   | A grant for the study was<br>received from the<br>Norwegian Foundation of<br>Postgraduate<br>Physiotherapists.<br>Conflict of interest not<br>stated. |
|------------------------------|--------------------------|---|---|--|--|---|
| Chen et al. (2013)           | 3 days PO                | 2 weeks, 6<br>weeks,<br>3month, 6<br>month PO | ROM   | Pain                                       | No significant<br>difference   | Project funded by the<br>National Health Research<br>Institute, Taiwan.   |
| Colwell et al. (1992)        | 3 days PO                | 1, 2 and 3<br>days PO                         | ROM   | Analgesia<br>use                           | CPM reduces<br>opioid consumption<br>and LOS.  | Not stated.   |
| Denis et al. (2006)          | 9 days PO                | Discharge                                     | ROM<br>(flexion,<br>extension,<br>Timed up<br>and go test<br>- TUG) | WOMAC<br>(Pain,<br>Stiffness,<br>Function) | The results do not<br>support the addition<br>of CPM<br>applications to<br>conventional<br>physical therapy.<br>CPM did not show<br>to further reduce<br>knee impairments<br>or disability or the<br>length of the<br>hospital stay. | Not stated.   |
| Harms et al. (1991)          | 6hr/day for 1<br>week PO | Discharge                                     | Pain (VAS<br>scale)   | ROM, LOS                                   | No significant<br>differences found in<br>VAS scores   | Not stated.   |

| Kim et al. (2009)          | 20<br>minutes/day,<br>from day 2 to<br>day 14 PO | Flexion<br>contracture<br>and<br>maximum<br>flexion: day<br>7 after TKA,<br>day 14. 6<br>weeks, 3<br>months and<br>6 months.<br>Level of pain<br>during ROM<br>exercise:<br>day 7 and<br>day 14. | Flexion<br>contracture,<br>maximum<br>flexion              | AKS knee<br>score, AKS<br>function<br>score,<br>WOMAC<br>pain,<br>WOMAC<br>stiffness,<br>WOMAC<br>function | Regular passive<br>ROM exercise does<br>not offer additional<br>clinical benefits to<br>the patients after<br>TKA | Not stated.   |
|----------------------------|--|--|--|--|---|---|
| Lenssen et al. (2003)      | 4 days PO  | 4days  | Pain (VAS<br>scale)  | ROM  | No significant<br>differences found in<br>VAS scores  | Not stated.   |
| Lenssen et al. (2008)      | 4 hours/day<br>for 4 days PO                     | 17 day, 6<br>weeks, 3<br>months  | Function<br>and pain<br>(WOMAC<br>scale),<br>ROM           | Medication<br>Use,<br>Satisfaction   | No significant<br>differences found in<br>WOMAC scores  | The authors declare that they have no competing interests.  |
| MacDonald et al.<br>(2000) | 6 weeks PO                                       | 6, 12, 26<br>weeks, and<br>1 year PO   | Function<br>(KSS scale)                                    | ROM, Pain  | No significant<br>differences found in<br>VAS scores  | Not stated  |
| Maniar et al. (2012)       | Day 1 and 3<br>PO                                | 3, 5, 14±2,<br>42±5, 90±10   | Pain-VAS,<br>ROM, TUG,<br>swelling<br>and wound<br>healing | WOMAC,<br>SF-12  | No significant<br>differences found in<br>VAS scores  | The Conflict of Interest<br>disclosure related to this<br>article available at<br>doi:10.1016/j.arth.2011.04.0<br>09. |
| May et al. (1999)          | 1 week PO  | 1 month  | ROM, VAS,  | LOS  | No differences at   | Not stated.   |

|                             |  |                                     | KSS                               |   | VAS outcome  |  |
|-----------------------------|--|-------------------------------------|-----------------------------------|---|--|--|
| McInnes et al. (1992)       | Starting<br>within 24<br>hours from<br>surgery | 7 days, 6<br>weeks                  | Cost                              | Pain (VAS<br>scale),<br>swelling,<br>ROM              | No significant<br>differences found in<br>VAS scores   | Study supported by National Institutes of Health.  |
| Montgomery et al.<br>(1996) | 3 hours 3<br>times daily, 7<br>days a week     | 1, 3, 5 days<br>PO                  | Pain (VAS<br>scale)               | Mid-patellar<br>effusion,<br>Knee<br>flection,<br>ROM | Postoperative pain<br>levels and LOS<br>similar in the two<br>groups.  | Not stated.  |
| Pope et al. (1997)          | 1 week PO                                      | Up to 1 year<br>PO                  | ROM                               | Blood loss,<br>analgesia<br>use                       | Clinical<br>disadvantages in<br>the short term in<br>CPM groups with<br>no worthwhile<br>improvement in the<br>range of movement<br>or function. | No benefits in any form<br>received from a commercial<br>party.  |
| Sahin et al. (2006)         | 1 week PO                                      | 2 weeks, 6<br>weeks, 6<br>months PO | ROM, Pain<br>(VAS scale)          | Swelling,<br>KSS score                                | No significant<br>differences found in<br>VAS scores in CPM<br>groups  | Not stated.  |
| Walker et al. (1991)        | From day 3<br>PO until<br>discharge            | 1 month, 12<br>months.              | Manipulatio,<br>adverse<br>events | ROM, pain<br>(VAS scale),<br>LOS                      | CPM showed a<br>significant reduction<br>in analgesia<br>consumption   | Supported by a grant from<br>the National Institutes of<br>Health, General Clinical<br>Research Center Branch.<br>Division of Research<br>Resources. |
| Preoperative exercise       |  |                                     |                                   |   |  |  |

| Calatayud et al.<br>(2016)  | 3 days/week<br>for 8 weeks<br>before<br>surgery | 8 weeks<br>before<br>surgery (T1),<br>after 8<br>weeks of<br>training (T2),<br>1 month<br>after TKA<br>(T3) and<br>finally 3<br>months after<br>TKA (T4) | WOMAC<br>functional<br>and pain<br>scale | SF-36<br>scale, pain<br>VAS scale,<br>TUG   | The present study<br>supports the use of<br>preoperative<br>training in end-<br>stage OA patients<br>to improve early<br>postoperative<br>outcomes.   | The authors did not<br>receive financial support for<br>this study, and there are no<br>known conflicts of interest<br>associated with this<br>publication that could have<br>influenced its outcome. |
|-----------------------------|---|--|--|---|---|---|
| Gstoettner et al.<br>(2011) | 1 day/week<br>for 6 weeks<br>before<br>surgery. | 6 weeks pre-<br>operatively;<br>6 weeks PO   | Balance,<br>gait speed,<br>and function  | WOMAC<br>pain and<br>stiffness<br>subscales,<br>KSS scale   | There was a<br>significant<br>improvement in<br>KSS, WOMAC pain<br>and stiffness within<br>both groups after<br>TKA. No difference<br>in clinical outcome<br>was observed<br>between the two<br>groups. | Not stated.   |
| МсКау et al. (2012)         | 3 days/week<br>for 6 weeks<br>before<br>surgery | Baseline<br>testing 6<br>weeks (±3<br>days) before<br>surgery.<br>Before TKA,<br>at 6 and 12<br>weeks after<br>TKA,                                      | Isometric<br>quadriceps<br>strength.     | Mobility,<br>pain, self-<br>reported<br>function,<br>health-<br>related<br>quality of<br>life, and<br>arthritis self- | Reduction of pain<br>within the groups,<br>but there is not a<br>direct comparison<br>between them.<br>Perceived<br>functional ability<br>shows an inverse<br>relationship to pain,                     | Not stated.   |

|                        |   | participants<br>completed<br>the<br>questionnair<br>e battery<br>and physical<br>testing.   |            | efficacy.   | but no information<br>on significance.  |             |
|------------------------|---|---|------------|---|---|-------------|
| Cryotherapy            |   |   |            |   |   |             |
| Albrecht et al. (2008) | 2 days PO   | 1 week PO   | VAS Scale  | Blood loss,<br>ROM,<br>Adverse<br>effects                       | Significant<br>reduction in VAS<br>for CT group   | Not stated. |
| Gibbons et al. (2001)  | 6 hours/day<br>throughout<br>the hospital<br>stay | Blood loss:<br>during the<br>procedure.<br>Amount of<br>morphine<br>received:<br>over the 48<br>h<br>The amount<br>of oral<br>analgesia:<br>up to the 10-<br>day stage.<br>Pain scores<br>recorded on<br>alternate<br>days after a<br>period of<br>physiotherap<br>y at the end | Blood loss | ROM, pain<br>scores,<br>analgesia,<br>LOS,<br>complication<br>s | No difference was<br>found between the<br>2 groups except for<br>less blood loss in<br>the surgical drains<br>in the cold<br>compression group. | Not stated. |

|                             |             | of the<br>afternoon.<br>The range of<br>movement:<br>10 days<br>after TKA.    |            |   |   |   |
|-----------------------------|-------------|---|------------|---|---|---|
| lvey et al. (1994)          | 72 hours PO | Number of<br>attempts:<br>every hour<br>PO<br>Amount of<br>morphine:<br>daily | Pain       | Number of<br>Patient-<br>controlled<br>analgesia<br>(PCA)<br>attempts | Different<br>temperature did not<br>show any<br>significant<br>differences in pain<br>improvement after<br>surgery, and in the<br>amount of injected<br>morphine. | Not stated.   |
| Kullenberg et al.<br>(2006) | 3 days PO   | Up to 3<br>weeks PO   | ROM        | Pain, LOS,<br>Hemoglobin<br>loss                                      | Cold compression<br>therapy improves<br>control of pain and<br>might lead to<br>improvement in<br>ROM and reduce<br>the length of<br>hospital stay.               | No benefits or funds were<br>received in support of the<br>study. |
| Levy et al. (1993)          | 4 days PO   | Up to 2<br>weeks PO   | Blood loss | Pain, ROM   | Significant lower<br>blood loss and<br>morphine<br>consumption in the<br>intervention group;<br>Significant   | Not stated.   |

|                            |  |                                     |                              |   | improvement in<br>ROM at 7 and 14<br>days from surgery.   |             |
|----------------------------|--|-------------------------------------|------------------------------|---|---|-------------|
| Morsi E. (2002)            | 2 weeks PO   | Up to 6<br>weeks after<br>discharge | Analgesic<br>consumptio<br>n | Pain score,<br>ROM                        | Continuous-flow<br>cold therapy is<br>advantageous<br>after TKA. It<br>showed to provide<br>better results in all<br>the areas<br>compared.   | Not stated. |
| Radkowski et al.<br>(2007) | Postsurgical<br>period until<br>discharge  | 2 weeks PO                          | Adverse<br>events            | Pain,<br>Analgesia,<br>Blood loss,<br>ROM | Postoperative<br>narcotic<br>consumption,<br>postoperative<br>drainage, self-<br>reported knee<br>function, and range<br>of motion were not<br>affected by the<br>different<br>cryotherapy<br>temperatures. | Not stated. |
| Smith et al. (2002)        | Treatment 1<br>for 24 hours<br>after surgery;<br>treatment 2<br>for 6 hours;<br>and then<br>cryo-pad | Day 1-3 PO                          | Function,<br>swelling        | Pain,<br>Analgesia                        | Not significant<br>differences in pain<br>improvement   | Not stated. |

| Su et al. (2012)           | Inpatient<br>stay: 2 hours<br>on plus 1<br>hour off for a<br>minimum of 4<br>cycles per<br>day.<br>After<br>discharge: 1<br>hour on plus<br>30 minutes<br>off for a<br>minimum of 4<br>cycles per<br>day. | Pre-<br>operative, 2<br>weeks, 6<br>weeks PO             | ROM and function   | Pain (VAS<br>scale) and<br>morphine<br>consumptio<br>n         | No improvement in<br>ROM and pain<br>perception.<br>Significant<br>decrease in pain<br>medication<br>consumption and<br>higher satisfaction. | Not stated.   |
|----------------------------|---|--|--|--|--|---|
| Thienpont et al.<br>(2014) | Postsurgical<br>period  | Day 2, 6<br>weeks PO                                     | Pain (VAS<br>scale), and<br>analgesics<br>consumptio<br>n. | ROM,<br>swelling,<br>and blood<br>loss.                        | Advanced<br>cryotherapy with a<br>continuous cooling<br>for a prolonged<br>period did not<br>provide an earlier<br>recovery.                 | The authors report no<br>conflict of interest. All<br>conflict of interest forms are<br>on file with the publication. |
| Webb et al. (1998)         | 48 hours PO   | Pre-<br>operative, 5<br>days, 6<br>weeks, 3<br>months PO | Blood loss   | Pain scores,<br>pain<br>medication<br>consumptio<br>n, and ROM | Cryo/cuff showed<br>improvement in<br>postoperative blood<br>loss and pain but<br>did not influence<br>swelling and return<br>to motion      | Not stated  |

| Walker et al. (1991)       | From day 3<br>PO until<br>discharge   | Discharge, 3<br>months                                     | Manipulatio,<br>adverse<br>events | ROM, pain<br>(VAS scale),<br>LOS  | Cryotherapy<br>showed a<br>significant reduction<br>in analgesia<br>request.  | Supported by a grant from<br>the National Institutes of<br>Health, General Clinical<br>Research Center Branch.<br>Division of Research<br>Resources. |
|----------------------------|---|--|-----------------------------------|---|---|--|
| Electrotherapy             |   |  |                                   |   |   |  |
| Adravanti et al.<br>(2013) | 2 months PO   | 1 month, 2<br>months, 6<br>months, 3<br>years PO           | Pain (VAS<br>scale)               | KSS<br>function<br>score, SF36<br>score, Knee<br>swelling                               | PEMFs showed<br>significant<br>differences in pain<br>improvement and in<br>functional scores in<br>all timepoints. | One of the authors is<br>employee of the device<br>manufacturer.   |
| Borckardt et al.<br>(2013) | 80<br>minutes/day<br>in<br>postoperative<br>period  | 48 hours PO  | Opioid<br>Consumptio<br>n         | Pain (BPI<br>and VAS<br>scales)   | TENS may be able<br>to reduce post-TKA<br>opioid<br>requirements.   | Not stated.  |
| Moretti et al. (2012)      | Treatment<br>began within<br>seven days<br>from TKA,<br>and consisted<br>of 4-hour<br>sessions/day<br>for 60 days<br>PO | Pre-<br>operatively,<br>and at 1, 2,<br>6, 12<br>months PO | Pain (VAS<br>scale)               | Knee<br>Society<br>Score; SF-<br>36; Joint<br>swelling<br>score;<br>Functional<br>score | PEMFs showed<br>significant<br>differences in pain<br>improvement and in<br>functional scores in<br>all timepoints. | Two of the authors are<br>employees of the device<br>manufacturer.   |
| Walker et al. (1991)       | From day 3<br>PO until<br>discharge   | 3 day PO,<br>discharge                                     | Manipulatio,<br>adverse<br>events | ROM, pain<br>(VAS scale),<br>LOS  | TENS did not show<br>a significant<br>difference in<br>analgesia<br>consumption.                                    | Supported by a grant from<br>the National Institutes of<br>Health, General Clinical<br>Research Center Branch.<br>Division of Research               |

Resources.

| Acupuncture                |  |  |   |   |  |  |
|----------------------------|--|--|---|---|--|--|
| Chen et al. (2015)         | 20<br>minutes/day<br>in the<br>postoperative<br>period | 2, 4, 8, 12,<br>24, 36, 48<br>hours PO | Opioid<br>consumptio<br>n   | Time to the<br>first PCA<br>request;<br>pain<br>intensity | Acupuncture<br>showed significant<br>pain improvement<br>and opioid<br>consumption.  | The authors declare that they have no competing interests.       |
| Mikashima et al.<br>(2012) | 3 times/week<br>from day 7<br>until day 21<br>PO       | 6, 14, 21<br>days PO                   | VAS pain<br>score   | Swelling;<br>time to<br>achieve<br>preoperative<br>ROM    | Acupuncture<br>showed significant<br>improvement in<br>pain, reduction of<br>swelling around the<br>knee and early<br>recovery of ROM.       | Not stated.  |
| Tsang et al. (2007)        | Postsurgical<br>period                                 | 4-8, 11-15<br>days PO                  | Pain at rest<br>and at<br>maximum<br>after<br>exercise<br>(VAS<br>scale). | ROM, TUG.   | Acupuncture did<br>not show significant<br>improvement in<br>pain, reduction of<br>swelling around the<br>knee and early<br>recovery of ROM. | The authors declare that<br>they have no competing<br>interests. |

| Tzeng et al. (2015) | 48 hours PO | 48 hours PO | Time for<br>first PCA<br>request | N/A | Acupuncture<br>showed significant<br>longer time to the<br>first demand for<br>Patient-controlled<br>Analgesia. | Supported by China Medical<br>University under the Aim for<br>Top University Plan of the<br>Ministry of Education,<br>Taiwan and by the Taiwan<br>Ministry of Health and<br>Welfare Clinical Trial and<br>Research Center of<br>Excellence. The authors<br>declare that they have no<br>competing interests. |
|---------------------|-------------|-------------|----------------------------------|-----|---|--|
|---------------------|-------------|-------------|----------------------------------|-----|---|--|





#### eFigure 2. Pain relief: Cryotherapy

|                                   | Cry         | Cryotherapy Control |         |           |                     |                    |        | Mean Difference      | Mean Difference                     |
|-----------------------------------|-------------|---------------------|---------|-----------|---------------------|--------------------|--------|----------------------|-------------------------------------|
| Study or Subgroup                 | Mean        | SD                  | Total   | Mean      | SD                  | Total              | Weight | IV, Random, 95% CI   | IV, Random, 95% Cl                  |
| 12.2.1 Cryotherapy                | - postope   | rative da           | ay 1    |           |                     |                    |        |                      |                                     |
| Albrecht 1997                     | 6           | 3.16                | 32      | 7         | 3.16                | 16                 | 4.0%   | -1.00 [-2.90, 0.90]  | <b>+</b> _                          |
| Albrecht 1997                     | 2.65        | 5.11                | 35      | 7         | 5.11                | 15                 | 2.0%   | -4.35 [-7.44, -1.26] |                                     |
| Gibbons 2001                      | 6.7         | 3.101               | 30      | 6.2       | 3.101               | 30                 | 5.0%   | 0.50 [-1.07, 2.07]   | _ <del></del>                       |
| Kullenberg 2006                   | 2.1         | 4.55                | 43      | 2.2       | 1                   | 40                 | 5.6%   | -0.10 [-1.49, 1.29]  |                                     |
| Levy 1993                         | 7.4         | 2.7                 | 40      | 7.8       | 2.7                 | 40                 | 6.4%   | -0.40 [-1.58, 0.78]  |                                     |
| Morsi 2002                        | 4           | 0                   | 30      | 6.9       | 0                   | 30                 |        | Not estimable        |                                     |
| Radkowski 2007                    | 6           | 2.72                | 28      | 5.5       | 2.72                | 36                 | 5.8%   | 0.50 [-0.84, 1.84]   | _ <b>+-</b> _                       |
| Smith 2002                        | 4.3         | 1.8                 | 44      | 4.2       | 2                   | 40                 | 8.0%   | 0.10 [-0.72, 0.92]   | +                                   |
| Subtotal (95% CI)                 |             |                     | 282     |           |                     | 247                | 36.8%  | -0.21 [-0.89, 0.48]  | <b>+</b>                            |
| Heterogeneity: Tau <sup>2</sup> : | = 0.32; CI  | hi² = 9.93          | 3, df = | 6 (P = 0  | l.13); <b>l</b> ² ∈ | = 40%              |        |                      |                                     |
| Test for overall effect           | t: Z = 0.59 | (P = 0.5            | 5)      |           |                     |                    |        |                      |                                     |
| 12.2.2 Cryotherapy                | - postope   | rative da           | av 2    |           |                     |                    |        |                      |                                     |
| Albrecht 1997                     | 512         | 4 5 4               | 32      | 65        | 4 5 4               | 16                 | 2.5%   | -1 38 -4 10 1 341    |                                     |
| Albrecht 1997                     | 2.34        | 4.94                | 36      | 6.5       | 4.94                | 15                 | 2.3%   | -4.16[-7.12]-1.20]   |                                     |
| Lew 1993                          | 59          | 24                  | 40      | 73        | 1.00                | 40                 | 7 7 %  | -1 40 [-2 28 -0 52]  |                                     |
| Morsi 2002                        | 5.5         | 2.4                 | 30      | 9         | 1.0                 | 30                 | 1.1.70 | Not estimable        |                                     |
| Smith 2002                        | 4.3         | 2                   | 44      | 48        | 1 9                 | 40                 | 79%    | -0.50[-1.33_0.33]    |                                     |
| Thiennont 2014                    | 4           | 3                   | 50      | 3.5       | 5                   | 50                 | 4.8%   | 0.50[-1.12, 2.12]    | _ <b>_</b>                          |
| Subtotal (95% CI)                 |             | 0                   | 231     | 0.0       |                     | 191                | 25.1%  | -1.00 [-2.01, 0.02]  | •                                   |
| Heterogeneity: Tau <sup>2</sup> : | = 0.69: CI  | hi² = 9.80          | ). df = | 4 (P = 0  |                     | = 59%              |        |                      | -                                   |
| Test for overall effect           | : Z = 1.93  | (P = 0.0            | 5)      |           |                     |                    |        |                      |                                     |
| 12.2.3 Cryotherapy                | - postope   | rative da           | av 3    |           |                     |                    |        |                      |                                     |
| Gibbons 2001                      | 3.8         | 2 41                | 30      | 4.2       | 2 41                | 30                 | 63%    | -0.40 [-1.62 0.82]   |                                     |
| Kullenberg 2006                   | 0.0         | 4 09                | 43      | 1.2       | 3.19                | 40                 | 5.0%   | -0.40[-1.97, 1.17]   | <b>_</b>                            |
| Lew 1993                          | 5.6         | 1.6                 | 40      | 6.9       | 1.9                 | 40                 | 8.2%   | -1.30 [-2.070.53]    | -                                   |
| Morsi 2002                        | 5           | 2.73                | 30      | 7         | 2.63                | 30                 | 5.7%   | -2.00 [-3.36, -0.64] | _ <b>—</b>                          |
| Radkowski 2007                    | 7.1         | 2.75                | 28      | 6.3       | 3.75                | 36                 | 4.9%   | 0.80 [-0.79, 2.39]   | _ <del></del>                       |
| Smith 2002                        | 4.2         | 1.8                 | 44      | 3.5       | 1.9                 | 40                 | 8.1%   | 0.70 (-0.09, 1.49)   |                                     |
| Subtotal (95% CI)                 |             |                     | 215     |           |                     | 216                | 38.1%  | -0.44 [-1.37, 0.49]  | ◆                                   |
| Heterogeneity: Tau <sup>2</sup> : | = 0.97; CI  | hi² = 20.1          | 4, df=  | = 5 (P =  | 0.001);             | l² = 75°           | %      |                      |                                     |
| Test for overall effect           | t: Z = 0.94 | (P = 0.3            | 5)      |           |                     |                    |        |                      |                                     |
| Total (95% CI)                    |             |                     | 728     |           |                     | 654                | 100.0% | -0.51 [-1.00, -0.02] | •                                   |
| Heterogeneity: Tau <sup>2</sup> : | = 0.61: CI  | hi² = 44.2          | 24. df= | = 17 (P = | = 0.000             | 3);   <b>2</b> = 6 | 62%    | - / -                |                                     |
| Test for overall effect           | Z = 2.06    | (P = 0 0            | 4)      |           |                     | -,                 |        |                      | -10 -5 0 5 10                       |
| To at fair and another at         | ~           |                     |         | <         | 0.00                | 17 00              | ,      |                      | Favours Cryotherapy Favours control |

Test for subgroup differences:  $Chi^2 = 1.59$ , df = 2 (P = 0.45),  $I^2 = 0\%$ 

#### eFigure 3. Pain relief: Continuous Passive Motion (CPM)

|  |           | СРМ                 |                  | С         | ontrol  |                        |        | Mean Difference      | Mean Difference             |  |  |  |
|--|-----------|---------------------|------------------|-----------|---------|------------------------|--------|----------------------|-----------------------------|--|--|--|
| Study or Subgroup                            | Mean      | SD                  | Total            | Mean      | SD      | Total                  | Weight | IV, Random, 95% CI   | IV, Random, 95% CI          |  |  |  |
| 12.1.1 CPM vs. control                       | ol - 1 we | ek                  |                  |           |         |                        |        |                      |                             |  |  |  |
| Bennet 2005                                  | 3.6       | 3                   | 47               | 3.1       | 2.9     | 52                     | 4.6%   | 0.50 [-0.66, 1.66]   |                             |  |  |  |
| Bennet 2005                                  | 2.6       | 2.9                 | 48               | 3.1       | 2.9     | 52                     | 4.8%   | -0.50 [-1.64, 0.64]  |                             |  |  |  |
| Bruun-Olsen 2009                             | 4         | 2.3                 | 30               | 4         | 2.1     | 33                     | 5.1%   | 0.00 [-1.09, 1.09]   |                             |  |  |  |
| Lenssen 2003                                 | 2.6       | 1.8                 | 20               | 4.7       | 2.6     | 19                     | 3.5%   | -2.10 [-3.51, -0.69] |                             |  |  |  |
| MacDonald 2000                               | 5.1       | 1.3                 | 40               | 5.2       | 1.2     | 40                     | 10.5%  | -0.10 [-0.65, 0.45]  |                             |  |  |  |
| May 1999                                     | 1.5       | 1.6                 | 7                | 2.1       | 2.4     | 7                      | 1.7%   | -0.60 [-2.74, 1.54]  |                             |  |  |  |
| McInnes 1992                                 | 2.8       | 2.05                | 47               | 3.6       | 2.05    | 45                     | 7.1%   | -0.80 [-1.64, 0.04]  |                             |  |  |  |
| Montgomery 1996                              | 5         | 2.5                 | 28               | 5         | 1.5     | 32                     | 5.3%   | 0.00 [-1.06, 1.06]   |                             |  |  |  |
| Sahin 2006                                   | 3.85      | 1.29                | 14               | 3.5       | 1.34    | 14                     | 5.9%   | 0.35 [-0.62, 1.32]   |                             |  |  |  |
| Subtotal (95% CI)                            |           |                     | 281              |           |         | 294                    | 48.6%  | -0.27 [-0.70, 0.16]  | ◆                           |  |  |  |
| Heterogeneity: Tau² =                        | 0.14; C   | hi² = 1             | 2.30, dt         | f= 8 (P : | = 0.14) | ); I <sup>z</sup> = 38 | 5%     |                      |                             |  |  |  |
| Test for overall effect: Z = 1.24 (P = 0.21) |           |                     |                  |           |         |                        |        |                      |                             |  |  |  |
| 40.4.0.000                                   |           |                     |                  |           |         |                        |        |                      |                             |  |  |  |
| 12.1.2 CPM vs. control                       | ol - 2 we | eks                 |                  |           |         |                        |        |                      |                             |  |  |  |
| Chen 2013                                    | 5.12      | 1.39                | 68               | 4.77      | 1.56    | 39                     | 9.9%   | 0.35 [-0.24, 0.94]   | <b>—</b>                    |  |  |  |
| Lenssen 2003                                 | 2.3       | 2.6                 | 20               | 4.5       | 2.4     | 18                     | 2.9%   | -2.20 [-3.79, -0.61] |                             |  |  |  |
| Subtotal (95% CI)                            |           |                     | 88               |           |         | 57                     | 12.8%  | -0.81 [-3.30, 1.68]  |                             |  |  |  |
| Heterogeneity: Tau <sup>2</sup> =            | 2.88; C   | hi <sup>2</sup> = 8 | .68, df=         | = 1 (P =  | 0.003;  | ); I <sup>z</sup> = 88 | 8%     |                      |                             |  |  |  |
| l est for overall effect:                    | Z = 0.64  | F (H = I            | J.52)            |           |         |                        |        |                      |                             |  |  |  |
| 12.1.3 CPM vs. contro                        | ol - 3 ma | onths               |                  |           |         |                        |        |                      |                             |  |  |  |
| Bruun-Olsen 2009                             | 29        | 22                  | 30               | 19        | 1.5     | 33                     | 6.2%   | 1 00 00 06 1 941     |                             |  |  |  |
| Chen 2013                                    | 3.22      | 1 28                | 68               | 3.05      | 1.54    | 39                     | 10.2%  | 0 17 [-0 40 0 74]    | _ <b>_</b>                  |  |  |  |
| Subtotal (95% CI)                            | 0.22      | 1.20                | 98               | 0.00      | 1.01    | 72                     | 16.4%  | 0.50 [-0.30, 1.29]   | -                           |  |  |  |
| Heterogeneity: Tau <sup>2</sup> =            | 0.19: C   | hi <b>²</b> = 2     | .19. df=         | = 1 (P =  | 0.14):  | $ ^{2} = 54^{\circ}$   | %      |                      | -                           |  |  |  |
| Test for overall effect:                     | Z = 1.23  |                     | 1.22)            |           | 0.1.171 |                        |        |                      |                             |  |  |  |
|  |           |                     | ,                |           |         |                        |        |                      |                             |  |  |  |
| 12.1.4 CPM vs. control                       | ol - 6 mo | onths               |                  |           |         |                        |        |                      |                             |  |  |  |
| Chen 2013                                    | 0.37      | 0.6                 | 68               | 0.21      | 0.47    | 39                     | 15.2%  | 0.16 [-0.05, 0.37]   | -                           |  |  |  |
| Sahin 2006                                   | 1.21      | 1.12                | 14               | 1.14      | 1.16    | 14                     | 7.0%   | 0.07 [-0.77, 0.91]   |                             |  |  |  |
| Subtotal (95% CI)                            |           |                     | 82               |           |         | 53                     | 22.2%  | 0.15 [-0.04, 0.35]   | ♦                           |  |  |  |
| Heterogeneity: Tau² =                        | 0.00; C   | hi² = 0             | .04, df=         | = 1 (P =  | 0.84);  | l <sup>z</sup> = 0%    | ,      |                      |                             |  |  |  |
| Test for overall effect:                     | Z = 1.52  | 2 (P = 0            | ).13)            |           |         |                        |        |                      |                             |  |  |  |
| Total (05% CI)                               |           |                     | 540              |           |         | 476                    | 100.0% | 0.05[0.35_0.25]      |                             |  |  |  |
| Hotorogonoity Tou? -                         | 0.14:0    | hiz - O             | 049<br>042 4     | - 11/1    |         | 470                    | 500.0% | -0.00 [-0.00, 0.20]  | <b>T</b>                    |  |  |  |
| Teat for everall effects                     | 7 - 0.22  | nr= z<br>) / = - (  | 9.12,01<br>1.745 | i = 14 (F | - = 0.0 | 1), 12 = 3             | 5270   |                      | -4 -2 0 2 4                 |  |  |  |
| Test for overall effect.                     | ∠ = 0.33  | ) (F = l            | J.74)<br>- 4 CC  | df = 2.4  | n_ 0.2  | 0) 17                  | 25.70  |                      | Favours CPM Favours control |  |  |  |
| Test for subgroup diff                       | erences   | . Uni≛              | = 4.06,          | ur = 3 (i | P = 0.2 | u), in=                | 33.1%  |                      |                             |  |  |  |

#### eFigure 4. Pain relief: Continuous Passive Motion (CPM)

|   |                               | СРМ                 |                     | С            | ontrol  |                      |         | Mean Difference      | Mean Difference             |
|---|-------------------------------|---------------------|---------------------|--------------|---------|----------------------|---------|----------------------|-----------------------------|
| Study or Subgroup                       | Mean                          | SD                  | Total               | Mean         | SD      | Total                | Weight  | IV, Random, 95% CI   | IV, Random, 95% CI          |
| 14.1.1 WOMAC - 6 w                      | eeks                          |                     |                     |              |         |                      |         |                      |                             |
| Denis 2006                              | 7.36                          | 3.12                | 26                  | 7.96         | 4.96    | 27                   | 0.9%    | -0.60 [-2.82, 1.62]  |                             |
| Denis 2006                              | 5.54                          | 3.42                | 28                  | 7.96         | 4.96    | 27                   | 0.9%    | -2.42 [-4.68, -0.16] |                             |
| Lenssen 2008                            | 16.8                          | 0.74                | 30                  | 16.68        | 0.8     | 30                   | 29.8%   | 0.12 [-0.27, 0.51]   |                             |
| Subtotal (95% CI)                       |                               |                     | 84                  |              |         | 84                   | 31.6%   | -0.66 [-2.12, 0.81]  | •                           |
| Heterogeneity: Tau² =                   | = 1.03; C                     | hi² = 5.            | .03, df:            | = 2 (P =     | 0.08);  | I <sup>2</sup> = 60° | %       |                      |                             |
| Test for overall effect:                | Z = 0.88                      | ) (P = 0            | ).38)               |              |         |                      |         |                      |                             |
|   |                               |                     |                     |              |         |                      |         |                      |                             |
| 14.1.2 WOMAC - 3 m                      | onths                         |                     |                     |              |         |                      |         |                      |                             |
| Beaupre 2001                            | 14.6                          | 3.4                 | 34                  | 14.6         | 3.6     | 34                   | 1.6%    | 0.00 [-1.66, 1.66]   | _ <u>_</u>                  |
| Lenssen 2008                            | 16.54                         | 0.76                | 30                  | 16.5         | 0.18    | 30                   | 58.1%   | 0.04 [-0.24, 0.32]   | <b>–</b>                    |
| Maniar 2012                             | 3                             | 2.11                | 28                  | 3.2          | 2.98    | 28                   | 2.5%    | -0.20 [-1.55, 1.15]  |                             |
| Maniar 2012                             | 4                             | 3.34                | 30                  | 3.2          | 2.98    | 28                   | 1.7%    | 0.80 [-0.83, 2.43]   | <u>+</u>                    |
| Subtotal (95% CI)                       |                               |                     | 122                 |              |         | 120                  | 63.9%   | 0.05 [-0.22, 0.32]   | •                           |
| Heterogeneity: Tau² =                   | = 0.00; C                     | hi <b>=</b> 0.      | .96, df=            | = 3 (P =     | 0.81);  | I <sup>2</sup> = 0%  |         |                      |                             |
| Test for overall effect:                | Z = 0.37                      | ' (P = 0            | 0.71)               |              |         |                      |         |                      |                             |
| 444200000000000000000000000000000000000 |                               |                     |                     |              |         |                      |         |                      |                             |
| 14.1.3 WOWAC - 0 M                      | ontris                        |                     |                     |              |         |                      |         |                      |                             |
| Beaupre 2001                            | 15.2                          | 3                   | 34                  | 15.8         | 3.2     | 34                   | 2.1%    | -0.60 [-2.07, 0.87]  |                             |
| Kim 2009<br>Subtotal (05% CI)           | 3.5                           | 3.6                 | 50                  | 3.6          | 3.5     | 50                   | 2.3%    | -0.10 [-1.49, 1.29]  |                             |
| Subtotal (95% CI)                       |                               |                     | 84                  | =            |         | 84                   | 4.4%    | -0.34 [-1.33, 0.08]  | <b>T</b>                    |
| Heterogeneity: Tau*=                    | = U.UU; C                     | hif = U.            | .23, dt:            | = 1 (P =     | 0.63);  | 1*= 0%               |         |                      |                             |
| l est for overall effect                | Z = 0.65                      | ) (P = t            | J.5Z)               |              |         |                      |         |                      |                             |
| Total (95% CI)                          |                               |                     | 200                 |              |         | 289                  | 100.0%  | 0.03[.0.10.0.24]     |                             |
| Hotorogonoity Touž-                     |                               | hiz – C             | 74 df.              | - 0 /0 -     | 0.663   | 12 - 004             | 100.070 | 0.05 [-0.15, 0.24]   |                             |
| Telefoyeneity. Tau                      | - 0.00, C                     | n== 0.<br>L/D = 0   | .74, ui -<br>1.04 \ | - o (r –     | 0.56),  | - 0 %                |         |                      | -10 -5 Ó Ś 10               |
| Test for cubarous dif                   | . <u>2</u> = 0.24<br>foroneco | r (n = t<br>∘ Chi≇- | .01)<br>- 1 22      | df = 2/2     | 0 - 0 4 | 2) 12 -              | 0%      |                      | Favours CPM Favours control |
| rest for subgroup dif                   | ierences                      | . One:              | - 1.32,             | $u_1 = Z(1)$ | = 0.5   | 2), [*=              | 0.70    |                      |                             |

### eFigure 5. Pain relief: Preoperative Exercise

| Preopera                 | itive exer  | cise  | C   | ontrol  |   |   | Mean Difference   | Mean Difference   |  |  |
|--------------------------|---|---|---|---|---|---|---|---|--|--|
| Mean                     | SD  | Total   | Mean  | SD  | Total   | Weight  | IV, Random, 95% CI  | IV, Random, 95% Cl  |  |  |
| e - 6 weeks              | 5   |   |   |   |   |   |   |   |  |  |
| 1.3                      | 1.1   | 18  | 0.98  | 0.99  | 20  | 40.7%   | 0.32 [-0.35, 0.99]  |   |  |  |
| 5.6                      | 2.72  | 10  | 4.92  | 4.5   | 12  | 8.4%  | 0.68 [-2.37, 3.73]  |   |  |  |
|                          |   | 28  |   |   | 32  | 49.1%   | 0.34 [-0.32, 0.99]  | ◆   |  |  |
| 0.00; Chi <sup>2</sup> = | : 0.05, df:   | = 1 (P = I  | 0.82); I <sup>z</sup>   | = 0%  |   |   |   |   |  |  |
| Z = 1.01 (P :            | = 0.31)   |   |   |   |   |   |   |   |  |  |
| e - 12 week              | (S  |   |   |   |   |   |   |   |  |  |
| 2.9                      | 1.02  | 25  | 3.8   | 1.02  | 25  | 43.0%   | -0.90 [-1.47, -0.33]  | -   |  |  |
| 4.4                      | 3.2   | 10  | 3.58  | 4.4   | 12  | 7.9%  | 0.82 [-2.36, 4.00]  |   |  |  |
|                          |   | 35  |   |   | 37  | 50.9%   | -0.78 [-1.63, 0.07]   | $\bullet$   |  |  |
| 0.12; Chi <sup>2</sup> = | : 1.09, df:   | = 1 (P = I  | 0.30); l <sup>a</sup>   | = 8%  |   |   |   |   |  |  |
| Z = 1.80 (P =            | = 0.07)   |   |   |   |   |   |   |   |  |  |
|                          |   | 63  |   |   | 69  | 100.0%  | -0.14 [-1.11, 0.84]   | +   |  |  |
| 0.49; Chi <sup>2</sup> = | 8.45, df  | = 3 (P = I  | 0.04); I <sup>z</sup>   | = 65%   | )   |   |   |   |  |  |
| Z = 0.27 (P :            | = 0.78)   |   |   |   |   |   |   | -4 -2 U Z 4<br>Eavours Preop exercise Eavours control   |  |  |
| erences: Ch              | i <sup>z</sup> = 4.18,  | df = 1 (F   | 9 = 0.04  | ), l <sup>2</sup> = 7   | 6.1%  |   |   | ravours rreop, exercise rravours control  |  |  |
|                          | Preopera<br><u>Mean</u><br>e - 6 week<br>1.3<br>5.6<br>0.00; Chi <sup>#</sup> =<br>Z = 1.01 (P:<br>e - 12 week<br>2.9<br>4.4<br>0.12; Chi <sup>#</sup> =<br>Z = 1.80 (P:<br>0.49; Chi <sup>#</sup> =<br>Z = 0.27 (P:<br>erences: Ch | Preoperative exer   Mean SD   e - 6 weeks 1.3 1.1   5.6 2.72   0.00; Chi² = 0.05, df: Z   Z = 1.01 (P = 0.31) e   e - 12 weeks 2.9 1.02   4.4 3.2 0.12; Chi² = 1.09, df:   Z = 1.80 (P = 0.07) 0.49; Chi² = 8.45, df: Z = 0.27 (P = 0.78)   erences: Chi² = 4.18, dr: Z = 0.27 (P = 0.78) Z = 0.27 (P = 0.78) | Preoperative exercise   Mean SD Total   e - 6 weeks 1.3 1.1 18   5.6 2.72 10 28   0.00; Chi <sup>2</sup> = 0.05, df = 1 (P = 1 28 10 28   0.00; Chi <sup>2</sup> = 0.05, df = 1 (P = 1 29 1.02 25 4.4 3.2 10   e - 12 weeks 2.9 1.02 25 4.4 3.2 10   0.12; Chi <sup>2</sup> = 1.09, df = 1 (P = 1 25 3.6 3.5 3.12; Chi <sup>2</sup> = 1.09, df = 1 (P = 1 35   0.49; Chi <sup>2</sup> = 8.45, df = 3 (P = 1 63 0.49; Chi <sup>2</sup> = 8.45, df = 3 (P = 1 2 2.9 1.02   z = 0.27 (P = 0.78) 9 9 9 9 10 | Preoperative exercise C   Mean SD Total Mean   e - 6 weeks 1.3 1.1 18 0.98   5.6 2.72 10 4.92 28   0.00; Chi <sup>2</sup> = 0.05; df = 1 (P = 0.82); l <sup>2</sup> 2 10 4.92   2.00; Chi <sup>2</sup> = 0.05; df = 1 (P = 0.82); l <sup>2</sup> 2 3.8 4.4 3.2 10 3.58   0.12; Chi <sup>2</sup> = 1.09; df = 1 (P = 0.30); l <sup>2</sup> 3.5 3.5 3.5 3.5 3.5   0.12; Chi <sup>2</sup> = 1.09; df = 1 (P = 0.30); l <sup>2</sup> 63 0.49; Chi <sup>2</sup> = 8.45; df = 3 (P = 0.04); l <sup>2</sup> 5   2.9 2.7 (P = 0.78) 3 3.5 3.5 | Preoperative exercise Control   Mean SD Total Mean SD   e - 6 weeks 1.3 1.1 18 0.98 0.99   5.6 2.72 10 4.92 4.5   0.00; Chi² = 0.05, df = 1 (P = 0.82); l² = 0% 28 0.00; Chi² = 0.05, df = 1 (P = 0.82); l² = 0%   2 = 1.01 (P = 0.31) e - 12 weeks 2.9 1.02 25 3.8 1.02   4.4 3.2 10 3.58 4.4 35 0.12; Chi² = 1.09, df = 1 (P = 0.30); l² = 8% Z = 1.80 (P = 0.07) 63 0.49; Chi² = 8.45, df = 3 (P = 0.04); l² = 65% Z = 0.27 (P = 0.78) erences: Chi² = 4.18, df = 1 (P = 0.04), l² = 7 | Preoperative exercise Control   Mean SD Total Mean SD Total   e - 6 weeks 1.3 1.1 18 0.98 0.99 20   5.6 2.72 10 4.92 4.5 12   28 32 32   0.00; Chi² = 0.05, df = 1 (P = 0.82); i² = 0% Z = 1.01 (P = 0.31)   e - 12 weeks 2.9 1.02 25 3.8 1.02 25   4.4 3.2 10 3.58 4.4 12 35 37   0.12; Chi² = 1.09, df = 1 (P = 0.30); i² = 8% Z = 1.80 (P = 0.07) 63 69 0.49; Chi² = 8.45, df = 3 (P = 0.04); i² = 65% Z = 0.27 (P = 0.78) erences; Chi² = 4.18, df = 1 (P = 0.04), i² = 76.1% | Preoperative exercise Control   Mean SD Total Mean SD Total Weight   e 6 weeks 1.3 1.1 18 0.98 0.99 20 40.7%   5.6 2.72 10 4.92 4.5 12 8.4%   0.00; Chi <sup>2</sup> = 0.05, df = 1 (P = 0.82); l <sup>2</sup> = 0% 22 49.1%   c = 12 weeks 2.9 1.02 25 3.8 1.02 25 43.0%   4.4 3.2 10 3.58 4.4 12 7.9%   0.12; Chi <sup>2</sup> = 1.09, df = 1 (P = 0.30); l <sup>2</sup> = 8% 37 50.9% 37 50.9%   2.13: 0 (P = 0.07) 63 69 100.0% 0.49; Chi <sup>2</sup> = 8.45, df = 3 (P = 0.04); l <sup>2</sup> = 85% 2 2.0.27 (P = 0.78) 9 9 100.0% 0.49; Chi <sup>2</sup> = 4.18, df = 1 (P = 0.04); l <sup>2</sup> = 76.1% 65% 7 7 7 5 7 7 10 10 10 10 10 10 10 10 10 10 10 10 10 | Preoperative exercise Control Mean Difference   Mean SD Total Mean SD Total Weight IV, Random, 95% CI   e 6 weeks 1.3 1.1 18 0.98 0.99 20 40.7% 0.32 [-0.35, 0.99]   5.6 2.72 10 4.92 4.5 12 8.4% 0.68 [-2.37, 3.73]   28 32 49.1% 0.34 [-0.32, 0.99] 0.04 [-0.32, 0.99] 0.034 [-0.32, 0.99]   0.00; Chi <sup>#</sup> = 0.05, df = 1 (P = 0.82); I <sup>#</sup> = 0% 2 49.1% 0.34 [-0.32, 0.99]   2.9 1.02 25 3.8 1.02 25 43.0% -0.90 [-1.47, -0.33]   4.4 3.2 10 3.58 4.4 12 7.9% 0.82 [-2.36, 4.00]   35 37 50.9% -0.78 [-1.63, 0.07] 0.12; Chi <sup>#</sup> = 1.09, df = 1 (P = 0.30); I <sup>#</sup> = 8% 2 1.80 (P = 0.07)   63 69 100.0% -0.14 [-1.11, 0.84] 0.49; Chi <sup>#</sup> = 8.45, df = 3 (P = 0.04); I <sup>#</sup> = 86% 2 2.0.27 (P = 0.78) 2 2 2 |  |  |

#### eFigure 6. NSAID Consumption: Cryotherapy

|                                   | Cryotherapy Control<br>Mean SD Total Mean SD Total<br>y vs. nothing<br>1.9 0.73 30 3.8 0.63 30<br>30 30<br>applicable |                      |                   |           |         |                  |                       | Mean Difference                                      | Mean Difference                                    |
|-----------------------------------|---|----------------------|-------------------|-----------|---------|------------------|-----------------------|--|--|
| Study or Subgroup                 | Mean  | SD                   | Total             | Mean      | SD      | Total            | Weight                | IV, Random, 95% CI                                   | IV, Random, 95% CI                                 |
| 13.3.1 Cryotherapy v              | s. nothin   | g                    |                   |           |         |                  |                       |  |  |
| Morsi 2002<br>Subtotal (95% CI)   | 1.9   | 0.73                 | 30<br><b>30</b>   | 3.8       | 0.63    | 30<br><b>30</b>  | 25.6%<br><b>25.6%</b> | -1.90 [-2.25, -1.55]<br>- <b>1.90 [-2.25, -1.55]</b> | <b>→</b>   |
| Heterogeneity: Not ar             | oplicable   |                      |                   |           |         |                  |                       |  | •  |
| Test for overall effect:          | Z=10.7  | 9 (P <               | 0.0000            | 1)        |         |                  |                       |  |  |
| 13.3.2 Cryotherapy v              | s. comp   | ressio               | n                 |           |         |                  |                       |  |  |
| lvey 1994                         | 1.3   | 0.6                  | 30                | 1.6       | 0.8     | 28               | 25.4%                 | -0.30 [-0.67, 0.07]                                  |  |
| lvey 1994                         | 1.4   | 0.7                  | 30                | 1.6       | 0.8     | 28               | 25.3%                 | -0.20 [-0.59, 0.19]                                  |  |
| Su 2012<br>Subtotal (95% CI)      | 1.76  | 1.71                 | 103<br><b>163</b> | 2.36      | 2.29    | 84<br><b>140</b> | 23.7%<br><b>74.4%</b> | -0.60 [-1.19, -0.01]<br>- <b>0.31 [-0.55, -0.07]</b> | •  |
| Heterogeneity: Tau <sup>2</sup> = | : 0.00; CI  | hi² = 1.             | 24, df=           | = 2 (P =  | 0.54);  | l² = 0%          |                       |  | -  |
| Test for overall effect:          | Z = 2.52  | (P = 0               | .01)              |           |         |                  |                       |  |  |
| Total (95% CI)                    |   |                      | 193               |           |         | 170              | 100.0%                | -0.75 [-1.63, 0.12]                                  | •  |
| Heterogeneity: Tau <sup>2</sup> = | : 0.75; CI  | hi <sup>z</sup> = 5: | 5.70, df          | '= 3 (P · | < 0.00  | 001); P          | = 95%                 | -  |  |
| Test for overall effect:          | Z = 1.69  | (P = 0               | .09)              |           |         |                  |                       |  | -4 -2 U 2 4<br>Eavours Cryotherany Eavours control |
| Test for subgroup diff            | ferences  | : Chi²:              | = 54.47           | . df = 1  | (P < 0. | 00001)           | ), l² = 98.2          | ?%   |  |

### eFigure 7. Opioid consumption: Acupuncture

|                                   | Acup     | ounctu          | ге              | C         | ontrol  |                      |                       | Mean Difference  | Mean Difference                      |
|-----------------------------------|----------|-----------------|-----------------|-----------|---------|----------------------|-----------------------|--|--------------------------------------|
| Study or Subgroup                 | Mean     | SD              | Total           | Mean      | SD      | Total                | Weight                | IV, Random, 95% CI   | IV, Random, 95% CI                   |
| 13.5.1 Acupuncture v              | s. sharr | n acup          | ounctur         | е         |         |                      |                       |  |                                      |
| Chen 2015                         | 0.37     | 0.16            | 30              | 0.53      | 0.2     | 30                   | 29.3%                 | -0.16 [-0.25, -0.07]   |                                      |
| Tzeng 2015<br>Subtotal (95% CI)   | 0.42     | 0.11            | 16<br><b>46</b> | 0.45      | 0.11    | 14<br><b>44</b>      | 33.1%<br><b>62.4%</b> | -0.03 [-0.11, 0.05]<br>- <b>0.09 [-0.22, 0.03]</b>           | •                                    |
| Heterogeneity: Tau <sup>2</sup> = | 0.01; CI | hi² = 4         | .44, df=        | = 1 (P =  | 0.04);  | $ ^2 = 779$          | %                     |  |                                      |
| Test for overall effect:          | Z=1.43   | (P = 0          | 0.15)           |           |         |                      |                       |  |                                      |
| 13.5.2 Acupuncture v              | s. nothi | ng              |                 |           |         |                      |                       |  |                                      |
| Tzeng 2015<br>Subtotal (95% CI)   | 0.42     | 0.1             | 16<br><b>16</b> | 0.46      | 0.09    | 17<br><b>17</b>      | 37.6%<br><b>37.6%</b> | -0.04 [-0.11, 0.03]<br>- <b>0.04 [-0.11, 0.03]</b>           |                                      |
| Heterogeneity: Not ap             | plicable |                 |                 |           |         |                      |                       |  |                                      |
| Test for overall effect:          | Z = 1.21 | (P = 0          | 0.23)           |           |         |                      |                       |  |                                      |
| Total (95% CI)                    |          |                 | 62              |           |         | 61                   | 100.0%                | -0.07 [-0.15, 0.00]  | •                                    |
| Heterogeneity: Tau <sup>2</sup> = | 0.00; CI | hi <b>²</b> = 5 | .45, df=        | = 2 (P =  | 0.07);  | I <sup>2</sup> = 639 | %                     | -  |                                      |
| Test for overall effect: .        | Z = 1.90 | ) (P = 0        | D.06)           | -         |         |                      |                       | -0.5 -0.25 0 0.25 0.5<br>Eavours Acupuncture Eavours control |                                      |
| Test for subgroup diffe           | erences  | : Chi²:         | = 0.52,         | df = 1 (F | P = 0.4 | 7), l² =             | 0%                    |  | Favours Acupuncture Fravours control |

#### eFigure 8. Opioid consumption: Continuous Passive Motion (CPM)

|                                   |          | СРМ                |         | 0         | Control                     |                    |        | Mean Difference        | Mean Difference |                    |     |
|-----------------------------------|----------|--------------------|---------|-----------|-----------------------------|--------------------|--------|------------------------|-----------------|--------------------|-----|
| Study or Subgroup                 | Mean     | SD                 | Total   | Mean      | SD                          | Total              | Weight | IV, Random, 95% CI     |                 | IV, Random, 95% CI |     |
| 13.1.1 Opioids - 1 we             | ek       |                    |         |           |                             |                    |        |                        |                 |                    |     |
| MacDonald 2000                    | 88       | 51                 | 40      | 80        | 51                          | 40                 | 13.8%  | 8.00 [-14.35, 30.35]   |                 |                    |     |
| Pope 1997                         | 72.6     | 25.4               | 18      | 48.1      | 23.91                       | 19                 | 17.3%  | 24.50 [8.59, 40.41]    |                 | — <b>-</b>         |     |
| Pope 1997                         | 81.5     | 24.08              | 20      | 48.1      | 23.91                       | 19                 | 17.8%  | 33.40 [18.33, 48.47]   |                 | _ <b>_</b>         |     |
| Walker 1991                       | 96       | 32.75              | 12      | 148       | 64.25                       | 10                 | 6.3%   | -52.00 [-95.92, -8.08] |                 |                    |     |
| Subtotal (95% CI)                 |          |                    | 90      |           |                             | 88                 | 55.1%  | 11.12 [-12.21, 34.44]  |                 |                    |     |
| Heterogeneity: Tau <sup>2</sup> = | 419.09   | Chi <sup>2</sup> = | 14.69,  | df = 3 (F | = 0.003                     | 2); I <b>²</b> = 8 | 80%    |                        |                 |                    |     |
| Test for overall effect:          | Z = 0.93 | P = 0.1            | 35)     |           |                             |                    |        |                        |                 |                    |     |
|                                   |          |                    |         |           |                             |                    |        |                        |                 |                    |     |
| 13.1.2 Opioids - 2 we             | eks      |                    |         |           |                             |                    |        |                        |                 |                    |     |
| Colwell 1992                      | 9.6      | 3.75               | 12      | 14.8      | 6.4                         | 10                 | 22.8%  | -5.20 [-9.70, -0.70]   |                 | -                  |     |
| Harms 1991                        | 28       | 19                 | 55      | 29        | 16                          | 58                 | 22.1%  | -1.00 [-7.49, 5.49]    |                 |                    |     |
| Subtotal (95% CI)                 |          |                    | 67      |           |                             | 68                 | 44.9%  | -3.78 [-7.67, 0.11]    |                 | •                  |     |
| Heterogeneity: Tau <sup>2</sup> = | 0.70; C  | hi <b>²</b> = 1.0  | )9, df= | 1 (P = 0) | .30); I <b>²</b> :          | = 8%               |        |                        |                 |                    |     |
| Test for overall effect:          | Z = 1.90 | ) (P = 0.          | 06)     |           |                             |                    |        |                        |                 |                    |     |
|                                   |          |                    |         |           |                             |                    |        |                        |                 | -                  |     |
| Total (95% CI)                    |          |                    | 157     |           |                             | 156                | 100.0% | 6.58 [-6.33, 19.49]    |                 | -                  |     |
| Heterogeneity: Tau <sup>2</sup> = | 185.17   | Chi²=              | 38.98,  | df = 5 (F | < 0.00                      | 001); P            | = 87%  |                        | -100            | -50 0 50           | 100 |
| Test for overall effect:          | Z = 1.00 | ) (P = 0.)         |         | -100      | Favours CPM Favours control | 100                |        |                        |                 |                    |     |
| Test for subgroup diff            | erences  | : Chi² =           |         |           |                             |                    |        |                        |                 |                    |     |

#### eFigure 9. Acupuncture

|                                   | Acu                    | punctu           | ire       | C         | ontrol              |                             |        | Mean Difference       |          | Mean Difference       |            |
|-----------------------------------|------------------------|------------------|-----------|-----------|---------------------|-----------------------------|--------|-----------------------|----------|-----------------------|------------|
| Study or Subgroup                 | Mean                   | SD               | Total     | Mean      | SD                  | Total                       | Weight | IV, Random, 95% CI    |          | IV, Random, 95% CI    |            |
| 11.1.1 Acupuncture                | vs. shan               | n acup           | unctur    | е         |                     |                             |        |                       |          |                       |            |
| Chen 2015                         | 89                     | 75               | 30        | 37        | 21                  | 30                          | 54.6%  | 52.00 [24.13, 79.87]  |          | -                     |            |
| Tzeng 2015                        | 92                     | 81.7             | 14        | 90.7      | 94.9                | 17                          | 15.0%  | 1.30 [-60.88, 63.48]  |          |                       |            |
| Subtotal (95% CI)                 |                        |                  | 44        |           |                     | 47                          | 69.6%  | 34.58 [-12.61, 81.77] |          | •                     |            |
| Heterogeneity: Tau <sup>2</sup> : | = 680.87;              | ; Chi <b>≃</b> = | : 2.13, 1 | df = 1 (F | <sup>2</sup> = 0.14 | 4); I² = ∮                  | 53%    |                       |          |                       |            |
| Test for overall effect           | t: Z = 1.44            | 4 (P = 0         | ).15)     |           |                     |                             |        |                       |          |                       |            |
| 11.1.2 Acupuncture                | vs. nothi              | ing              |           |           |                     |                             |        |                       |          |                       |            |
| Tzeng 2015                        | 92                     | 81.7             | 16        | 34.1      | 22                  | 17                          | 30.4%  | 57.90 [16.52, 99.28]  |          |                       |            |
| Subtotal (95% CI)                 |                        |                  | 16        |           |                     | 17                          | 30.4%  | 57.90 [16.52, 99.28]  |          | •                     |            |
| Heterogeneity: Not a              | pplicable              |                  |           |           |                     |                             |        |                       |          |                       |            |
| Test for overall effect           | t: Z = 2.74            | 4 (P = 0         | ).006)    |           |                     |                             |        |                       |          |                       |            |
| Total (05% CI)                    |                        |                  | 60        |           |                     | 64                          | 100.0% | 46 17 [20 84 71 50]   |          |                       |            |
| Listeregeneitr Teu?               | - 402.05               | ONR-             | - 2 A C   | 46 – D.7E | - 0 - 1             | •••0<br>• = <b>z</b> i - 20 | 100.0% | 40.17 [20.04, 71.50]  |          | •                     |            |
| Heterogeneity: Tau-               | = 103.95)<br>NZ - 0.55 | Chine e          | 2.46,1    | ar = 2 (F | r = 0.2;            | 9); I= = -                  | 19%    |                       | -500 -25 | o ó 2                 | 250 500    |
| Test for overall effect           | l.∠=3.5/<br>#          | (r=t<br>         | .0004)    | 16-10     |                     | 7) 17 -                     | 004    |                       | Favou    | irs control Favours a | cupuncture |
| lest for subgroup di              | πerences               | : Unite          | = 0.53,   | at = 1 () | - = 0.4             | ∩, i*=                      | 0%     |                       |          |                       |            |

# **eFigure 10**: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation

|                                   | Intervention Control |                  |          |           |         |                      |        | Mean Difference      | Mean Difference             |
|-----------------------------------|----------------------|------------------|----------|-----------|---------|----------------------|--------|----------------------|-----------------------------|
| Study or Subgroup                 | Mean                 | SD               | Total    | Mean      | SD      | Total                | Weight | IV, Random, 95% CI   | IV, Random, 95% CI          |
| 16.1.1 LOW_LOW                    |                      |                  |          |           |         |                      |        |                      |                             |
| Bennet 2005                       | 3.6                  | 3                | 47       | 3.1       | 2.9     | 52                   | 9.6%   | 0.50 [-0.66, 1.66]   | - <b>+</b>                  |
| Bennet 2005                       | 2.6                  | 2.9              | 48       | 3.1       | 2.9     | 52                   | 9.9%   | -0.50 [-1.64, 0.64]  |                             |
| Lenssen 2003                      | 2.6                  | 1.8              | 20       | 4.7       | 2.6     | 19                   | 7.2%   | -2.10 [-3.51, -0.69] | <b>_</b>                    |
| MacDonald 2000                    | 5.1                  | 1.3              | 40       | 5.2       | 1.2     | 40                   | 21.6%  | -0.10 [-0.65, 0.45]  | -                           |
| Subtotal (95% CI)                 |                      |                  | 155      |           |         | 163                  | 48.3%  | -0.44 [-1.31, 0.42]  | ◆                           |
| Heterogeneity: Tau² =             | 0.49; C              | hi <b>=</b> 8.   | .67, df= | = 3 (P =  | 0.03);  | I <sup>z</sup> = 65° | %      |                      |                             |
| Test for overall effect:          | Z = 1.00             | ) (P = 0         | ).32)    |           |         |                      |        |                      |                             |
| 16.1.2 OTHER                      |                      |                  |          |           |         |                      |        |                      |                             |
| Bruun-Olsen 2009                  | 4                    | 23               | 30       | 4         | 21      | 33                   | 10.5%  | 0.001-1.09.1.091     |                             |
| May 1999                          | 15                   | 1.6              | 7        | 21        | 2.4     | 7                    | 3.6%   | -0.60[-2.74, 1.54]   |                             |
| McInnes 1992                      | 2.8                  | 2.05             | 47       | 3.6       | 2.05    | 45                   | 14.6%  | -0.80[-1.64_0.04]    |                             |
| Montgomery 1996                   | 5                    | 2.5              | 28       | 5         | 1.5     | 32                   | 10.9%  | 0.00 [-1.06, 1.06]   | _ <b>_</b>                  |
| Sahin 2006                        | 3.85                 | 1.29             | 14       | 3.5       | 1.34    | 14                   | 12.2%  | 0.35 [-0.62, 1.32]   | <u>_</u>                    |
| Subtotal (95% CI)                 |                      |                  | 126      |           |         | 131                  | 51.7%  | -0.20 [-0.68, 0.27]  | •                           |
| Heterogeneity: Tau <sup>2</sup> = | 0.00; C              | hi <b>²</b> = 3. | .59, df= | = 4 (P =  | 0.46);  | $ ^{2} = 0\%$        |        |                      |                             |
| Test for overall effect:          | Z = 0.84             | (P = 0           | ).40)    | ,         |         |                      |        |                      |                             |
|                                   |                      |                  |          |           |         |                      |        |                      |                             |
| Total (95% CI)                    |                      |                  | 281      |           |         | 294                  | 100.0% | -0.27 [-0.70, 0.16]  | • • •                       |
| Heterogeneity: Tau² =             | 0.14; C              | hi² = 1:         | 2.30, di | f= 8 (P = | = 0.14) | ); I <b>ž</b> = 39   | 5%     |                      | -4 -2 0 2 4                 |
| Test for overall effect:          | Z=1.24               | (P = 0           | 0.21)    |           |         |                      |        |                      | Favours CPM Favours control |
| Test for subgroup diff            | erences              | ∶Chi <b>²</b> ∶  | = 0.22.  | df = 1 (F | P = 0.6 | 64), I²=             | 0%     |                      |                             |

# **eFigure 11**: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation

|                                   | Inte       | rventio          | on       | С         | ontrol  |                      |        | Mean Difference      | Mean Difference                                    |
|-----------------------------------|------------|------------------|----------|-----------|---------|----------------------|--------|----------------------|--|
| Study or Subgroup                 | Mean       | SD               | Total    | Mean      | SD      | Total                | Weight | IV, Random, 95% CI   | IV, Random, 95% CI                                 |
| 16.2.1 LOW_LOW                    |            |                  |          |           |         |                      |        |                      |  |
| Radkowski 2007                    | 6          | 2.72             | 28       | 5.5       | 2.72    | 36                   | 18.6%  | 0.50 [-0.84, 1.84]   | _ <b></b>  |
| Thienpont 2014                    | 4          | 3                | 50       | 3.5       | 5       | 50                   | 15.2%  | 0.50 [-1.12, 2.12]   |  |
| Subtotal (95% CI)                 |            |                  | 78       |           |         | 86                   | 33.8%  | 0.50 [-0.53, 1.53]   | ◆  |
| Heterogeneity: Tau <sup>2</sup> = | = 0.00; Cl | hi <b>²</b> = 0  | .00, df: | = 1 (P =  | 1.00);  | l <sup>≈</sup> = 0%  |        |                      |  |
| Test for overall effect           | : Z = 0.95 | i (P = 0         | 0.34)    |           |         |                      |        |                      |  |
| 16.2.2 OTHER                      |            |                  |          |           |         |                      |        |                      |  |
| Albrecht 1997                     | 2.65       | 5.11             | 35       | 7         | 5.11    | 15                   | 6.0%   | -4.35 [-7.44, -1.26] |  |
| Albrecht 1997                     | 6          | 3.16             | 32       | 7         | 3.16    | 16                   | 12.5%  | -1.00 [-2.90, 0.90]  |  |
| Levy 1993                         | 7.4        | 2.7              | 40       | 7.8       | 2.7     | 40                   | 20.9%  | -0.40 [-1.58, 0.78]  |  |
| Morsi 2002                        | 4          | 0                | 30       | 6.9       | 0       | 30                   |        | Not estimable        |  |
| Smith 2002                        | 4.3        | 1.8              | 44       | 4.2       | 2       | 40                   | 26.8%  | 0.10 [-0.72, 0.92]   | _ <b>+</b> _                                       |
| Subtotal (95% CI)                 |            |                  | 181      |           |         | 141                  | 66.2%  | -0.80 [-2.01, 0.42]  | ◆  |
| Heterogeneity: Tau <sup>2</sup> = | = 0.88; Cl | hi² = 8          | .06, df: | = 3 (P =  | 0.04);  | l <sup>2</sup> = 63' | %      |                      |  |
| Test for overall effect           | : Z = 1.28 | ) (P = (         | 0.20)    |           |         |                      |        |                      |  |
| Total (95% CI)                    |            |                  | 259      |           |         | 227                  | 100.0% | -0.27 [-1.10, 0.55]  | •  |
| Heterogeneity: Tau <sup>2</sup> = | = 0.49; Cl | hi <b>=</b> 9    | .90, df: | = 5 (P =  | 0.08);  | l <sup>z</sup> = 49' | %      | -                    |  |
| Test for overall effect           | : Z = 0.65 | i (P = 0         | ).52)    |           |         |                      |        |                      | -4 -2 U Z 4<br>Eavours cryotherapy Eavours control |
| Test for subaroup dif             | ferences   | : Chi <b></b> ≇∘ | = 2.53.  | df = 1 (i | P = 0.1 | 1), I <sup>2</sup> = | 60.5%  |                      | ravours cryomerapy Favours control                 |

# **eFigure 12**: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation

|                                   | Inter   | venti   | on       | Co       | ontro | 1          |        | Mean Difference      | Mean Difference                               |
|-----------------------------------|---|---------|----------|----------|-------|------------|--------|----------------------|---|
| Study or Subgroup                 | Mean  | SD      | Total    | Mean     | SD    | Total      | Weight | IV, Random, 95% CI   | IV, Random, 95% CI                            |
| 16.3.1 LOW_LOW                    |   |         |          |          |       |            |        |                      |   |
| Moretti 2012                      | 2.4   | 1.6     | 15       | 4.9      | 1.8   | 15         | 31.2%  | -2.50 [-3.72, -1.28] | _ <b>_</b>                                    |
| Subtotal (95% CI)                 |   |         | 15       |          |       | 15         | 31.2%  | -2.50 [-3.72, -1.28] | ◆   |
| Heterogeneity: Not ap             | plicable  |         |          |          |       |            |        |                      |   |
| Test for overall effect:          | Z = 4.02  | (P < I  | 0.0001)  | )        |       |            |        |                      |   |
| 16.3.2 OTHER                      |   |         |          |          |       |            |        |                      |   |
| Adravanti 2014                    | 2.5   | 1.4     | 17       | 4.2      | 0.7   | 16         | 68.8%  | -1.70 [-2.45, -0.95] |   |
| Subtotal (95% CI)                 |   |         | 17       |          |       | 16         | 68.8%  | -1.70 [-2.45, -0.95] | ◆   |
| Heterogeneity: Not ap             | plicable  |         |          |          |       |            |        |                      |   |
| Test for overall effect:          | Z= 4.45   | (P < I  | 0.0000   | 1)       |       |            |        |                      |   |
| Total (95% CI)                    |   |         | 32       |          |       | 31         | 100.0% | -1.95 [-2.68, -1.22] | •   |
| Heterogeneity: Tau <sup>2</sup> = | 0.05; Cł  | ni² = 1 | .20, df: | = 1 (P = | 0.27  | ); l² = 1` | 7%     |                      |   |
| Test for overall effect:          | Z = 5.26  | (P < I  | 0.0000   | 1)       |       |            |        |                      | -4 -2 U 2 4<br>Equatra electrotherapy Equatra |
| Test for subgroup diff            | or subgroup differences: Chi <sup>2</sup> = 1.20, df = 1 (P = 0.27), l <sup>2</sup> = 16.8% |         |          |          |       |            |        |                      | Favours electronierapy Favours control        |

# **eFigure 13**: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation

|  | Inter     | ventio        | on              | Co       | ontro       | 1                      |                       | Mean Difference                                      | Mean Difference                     |
|--|-----------|---------------|-----------------|----------|-------------|------------------------|-----------------------|--|-------------------------------------|
| Study or Subgroup                      | Mean      | SD            | Total           | Mean     | SD          | Total                  | Weight                | IV, Random, 95% CI                                   | IV, Random, 95% CI                  |
| 16.4.1 LOW_LOW                         |           |               |                 |          |             |                        |                       |  |                                     |
| Tsang 2007<br><b>Subtotal (95% CI)</b> | 4.6       | 1.5           | 30<br><b>30</b> | 6        | 2.4         | 30<br><b>30</b>        | 19.4%<br><b>19.4%</b> | -1.40 [-2.41, -0.39]<br>- <b>1.40 [-2.41, -0.39]</b> | •                                   |
| Heterogeneity: Not ap                  | plicable  |               |                 |          |             |                        |                       |  |                                     |
| Test for overall effect:               | Z= 2.71   | (P = (        | 0.007)          |          |             |                        |                       |  |                                     |
| 16.4.2 OTHER                           |           |               |                 |          |             |                        |                       |  |                                     |
| Chen 2015                              | 5.7       | 1.7           | 15              | 6.5      | 1.5         | 15                     | 17.0%                 | -0.80 [-1.95, 0.35]                                  |                                     |
| Chen 2015                              | 4.5       | 1.3           | 30              | 5.3      | 1.4         | 30                     | 26.7%                 | -0.80 [-1.48, -0.12]                                 |                                     |
| Mikashima 2012<br>Subtotal (95% CI)    | 5.8       | 0.5           | 40<br>85        | 5.9      | 0.6         | 40<br>85               | 37.0%<br><b>80.6%</b> | -0.10 [-0.34, 0.14]<br>- <b>0.43 [-0.98, 0.12]</b>   | •                                   |
| Heterogeneity: Tau <sup>2</sup> =      | 0.14; Cł  | ni² = 4       | .67, df:        | = 2 (P = | 0.10        | ); I² = 5              | 7%                    |  | -                                   |
| Test for overall effect:               | Z=1.53    | (P = (        | 0.13)           |          |             |                        |                       |  |                                     |
| Total (95% CI)                         |           |               | 115             |          |             | 115                    | 100.0%                | -0.66 [-1.29, -0.03]                                 | •                                   |
| Heterogeneity: Tau <sup>2</sup> =      | 0.26; Cł  | ni <b>=</b> 9 | .79, df:        | = 3 (P = | 0.02        | ); l <sup>z</sup> = 6  | 9%                    | -  |                                     |
| Test for overall effect:               | Z= 2.05   | (P = 0)       | 0.04)           |          | -4 -2 U Z 4 |                        |                       |  |                                     |
| Test for subgroup diff                 | ferences: | Chi²          | = 2.71,         | df=1 (   | P = 0       | .10), I <sup>z</sup> a | = 63.1%               |  | Favours acupuncture Favours control |

**eFigure 14**: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation

|                                   | Inte      | erventio           | n        | C         | ontrol   |                        |        | Mean Difference        | Mean Difference     |
|-----------------------------------|-----------|--------------------|----------|-----------|----------|------------------------|--------|------------------------|---------------------|
| Study or Subgroup                 | Mean      | SD                 | Total    | Mean      | SD       | Total                  | Weight | IV, Random, 95% CI     | IV, Random, 95% CI  |
| 16.5.1 LOW_LOW                    |           |                    |          |           |          |                        |        |                        |                     |
| MacDonald 2000                    | 88        | 51                 | 40       | 80        | 51       | 40                     | 25.8%  | 8.00 [-14.35, 30.35]   |                     |
| Subtotal (95% CI)                 |           |                    | 40       |           |          | 40                     | 25.8%  | 8.00 [-14.35, 30.35]   | <b>+</b>            |
| Heterogeneity: Not a              | oplicable |                    |          |           |          |                        |        |                        |                     |
| Test for overall effect           | Z = 0.70  | ) (P = 0.          | 48)      |           |          |                        |        |                        |                     |
| 16.5.2 OTHER                      |           |                    |          |           |          |                        |        |                        |                     |
| Pope 1997                         | 81.5      | 24.08              | 20       | 48.1      | 23.91    | 19                     | 29.6%  | 33.40 [18.33, 48.47]   | -                   |
| Pope 1997                         | 72.6      | 25.4               | 18       | 48.1      | 23.91    | 19                     | 29.2%  | 24.50 [8.59, 40.41]    |                     |
| Walker 1991                       | 96        | 32.75              | 12       | 148       | 64.25    | 10                     | 15.4%  | -52.00 [-95.92, -8.08] | <b>_</b> _          |
| Subtotal (95% CI)                 |           |                    | 50       |           |          | 48                     | 74.2%  | 10.40 [-20.54, 41.34]  | <b>+</b>            |
| Heterogeneity: Tau <sup>2</sup> = | = 584.37; | Chi <b>≃</b> =     | 12.99, ( | df = 2 (P | = 0.00   | 2); I <b>2</b> = 8     | 85%    |                        |                     |
| Test for overall effect           | Z = 0.66  | 6 (P = 0.          | 51)      |           |          |                        |        |                        |                     |
| Total (95% CI)                    |           |                    | 90       |           |          | 88                     | 100.0% | 11.12 [-12.21, 34.44]  | •                   |
| Heterogeneity: Tau <sup>2</sup> = | = 419.09  | Chi <sup>2</sup> = | 14.69, ( | df = 3 (P | = 0.003  | 2); I <sup>2</sup> = 8 | B0%    |                        |                     |
| Test for overall effect           | Z = 0.93  | )<br>(P = 0.       | 35)      |           |          |                        |        |                        | -200 -100 0 100 200 |
| Test for subgroup dif             | ferences  | : Chi²=            | 0.02, d  | f=1 (P    | = 0.90), | l <sup>2</sup> = 09    | 6      |                        |                     |

## **eFigure 15**: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation

|   | Inte                 | rventio                           | n  | C        | ontrol              |                              |                       | Mean Difference                                    | Mean Difference  |
|---|----------------------|-----------------------------------|--|----------|---------------------|------------------------------|-----------------------|--|--|
| Study or Subgroup   | Mean                 | SD                                | Total                                    | Mean     | SD                  | Total                        | Weight                | IV, Random, 95% CI                                 | IV, Random, 95% CI                                     |
| 16.6.1 LOW_LOW  |                      |                                   |  |          |                     |                              |                       |  |  |
| Thienpont 2014<br>Subtotal (95% CI)   | 0.792                | 0.563                             | 50<br>50                                 | 0.802    | 0.542               | 50<br>50                     | 16.4%<br><b>16.4%</b> | -0.01 [-0.23, 0.21]<br>-0.01 [-0.23, 0.21]         | <b></b>  |
| Heterogeneity: Not ap   | plicable             |                                   |  |          |                     |                              |                       |  |  |
| Test for overall effect: 2  | Z = 0.09             | (P = 0.9                          | 93)                                      |          |                     |                              |                       |  |  |
| 16.6.2 OTHER  |                      |                                   |  |          |                     |                              |                       |  |  |
| Gibbons 2001  | 0.65                 | 0.31                              | 30                                       | 0.6      | 0.31                | 30                           | 19.1%                 | 0.05 [-0.11, 0.21]                                 | _ <b>_</b>   |
| Kullenberg 2006   | 0.37                 | 0.11                              | 43                                       | 0.43     | 0.05                | 40                           | 23.2%                 | -0.06 [-0.10, -0.02]                               | -  |
| Levy 1993   | 0.53                 | 0.2                               | 40                                       | 0.96     | 0.3                 | 40                           | 21.0%                 | -0.43 [-0.54, -0.32]                               |  |
| Smith 2002<br>Subtotal (95% CI)   | 0.32                 | 0.29                              | 44<br>157                                | 0.42     | 0.31                | 40<br><b>150</b>             | 20.3%<br>83.6%        | -0.10 [-0.23, 0.03]<br>- <b>0.14 [-0.32, 0.05]</b> | -  |
| Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect: 2                   | 0.03; Ch<br>Z = 1.47 | ni <sup>z</sup> = 41.<br>(P = 0.1 | .27,df=<br>14)                           | = 3 (P < | 0.0000′             | 1); I² = 9                   | 33%                   |  |  |
| Total (95% CI)<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect: 3 | 0.03; Cł<br>Z = 1.44 | $hi^2 = 41.$<br>(P = 0.1          | <b>207</b><br>.77, df=<br>15)<br>0.77, d | = 4 (P < | 0.0000 <sup>,</sup> | 200<br>1); I² = 9<br>IZ = 00 | <b>100.0%</b><br>90%  | -0.12 [-0.28, 0.04]                                | -1 -0.5 0 0.5 1<br>Favours cryotherapy Favours control |

# **eFigure 16**: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation

|   | Inter                  | ventio                        | on                | Co         | ontrol  |                      |        | Mean Difference      | Mean Difference                     |
|---|------------------------|-------------------------------|-------------------|------------|---------|----------------------|--------|----------------------|-------------------------------------|
| Study or Subgroup   | Mean                   | SD                            | Total             | Mean       | SD      | Total                | Weight | IV, Random, 95% CI   | IV, Random, 95% CI                  |
| 16.7.1 LOW_LOW  |                        |                               |                   |            |         |                      |        |                      |                                     |
| lvey 1994   | 1.3                    | 0.6                           | 30                | 1.6        | 0.8     | 28                   | 44.0%  | -0.30 [-0.67, 0.07]  | -=+                                 |
| lvey 1994   | 1.4                    | 0.7                           | 30                | 1.6        | 0.8     | 28                   | 39.1%  | -0.20 [-0.59, 0.19]  |                                     |
| Subtotal (95% CI)   |                        |                               | 60                |            |         | 56                   | 83.1%  | -0.25 [-0.52, 0.01]  | •                                   |
| Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect: | : 0.00; Cł<br>Z = 1.86 | ni <sup>z</sup> = 0<br>(P = 0 | .14, df:<br>).06) | = 1 (P = 1 | 0.71);  | I <sup>≠</sup> =0%   |        |                      |                                     |
| 16.7.2 OTHER  |                        |                               |                   |            |         |                      |        |                      |                                     |
| Su 2012   | 1.76                   | 1.71                          | 103               | 2.36       | 2.29    | 84                   | 16.9%  | -0.60 [-1.19, -0.01] |                                     |
| Subtotal (95% CI)   |                        |                               | 103               |            |         | 84                   | 16.9%  | -0.60 [-1.19, -0.01] | •                                   |
| Heterogeneity: Not ap   | plicable               |                               |                   |            |         |                      |        |                      |                                     |
| Test for overall effect:                                      | Z = 1.99               | (P = 0                        | 0.05)             |            |         |                      |        |                      |                                     |
| Total (95% CI)  |                        |                               | 163               |            |         | 140                  | 100.0% | -0.31 [-0.55, -0.07] | ◆                                   |
| Heterogeneity: Tau <sup>2</sup> =                             | 0.00; Cł               | ni² = 1                       | .24, df :         | = 2 (P = I | 0.54);  | I <sup>z</sup> = 0%  |        |                      |                                     |
| Test for overall effect:                                      | Z= 2.52                | (P = 0)                       | ).01)             |            |         |                      |        |                      | -4 -2 U 2 4                         |
| Test for subaroup diff  | erences                | Chi²∶                         | = 1.10,           | df = 1 (F  | e = 0.2 | 9), I <sup>2</sup> = | 9.3%   |                      | Favours cryotherapy Favours control |

## **eFigure 17**: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation

|                                     | Inter    | ventio  | on              | Co       | ontrol | I                     |                       | Mean Difference                                      | Mean Difference                        |
|-------------------------------------|----------|---------|-----------------|----------|--------|-----------------------|-----------------------|--|--|
| Study or Subgroup                   | Mean     | SD      | Total           | Mean     | SD     | Total                 | Weight                | IV, Random, 95% CI                                   | IV, Random, 95% CI                     |
| 16.8.1 LOW_LOW                      |          |         |                 |          |        |                       |                       |  |  |
| Borckardt 2013<br>Subtotal (95% CI) | 6.3      | 5.6     | 20<br><b>20</b> | 12.3     | 6.6    | 19<br><b>19</b>       | 32.3%<br><b>32.3%</b> | -6.00 [-9.85, -2.15]<br>- <b>6.00 [-9.85, -2.15]</b> |  |
| Heterogeneity: Not ap               | plicable |         |                 |          |        |                       |                       |  |  |
| Test for overall effect: .          | Z = 3.05 | (P = (  | 0.002)          |          |        |                       |                       |  |  |
| 16.8.2 OTHER                        |          |         |                 |          |        |                       |                       |  |  |
| Walker 1991                         | 6.6      | 5.7     | 18              | 8.7      | 5      | 12                    | 32.1%                 | -2.10 [-5.96, 1.76]                                  |  |
| Walker 1991<br>Subtotal (95% CI)    | 6.2      | 4.9     | 18<br><b>36</b> | 8.7      | 5      | 12<br><b>24</b>       | 35.7%<br><b>67.7%</b> | -2.50 [-6.12, 1.12]<br>- <b>2.31 [-4.96, 0.33]</b>   | •                                      |
| Heterogeneity: Tau <sup>2</sup> =   | 0.00; Cł | ni² = 0 | .02, df:        | = 1 (P = | 0.88   | ); I <sup>z</sup> = 0 | %                     |  |  |
| Test for overall effect:            | Z=1.72   | (P = (  | 0.09)           |          |        |                       |                       |  |  |
| Total (95% CI)                      |          |         | 56              |          |        | 43                    | 100.0%                | -3.50 [-5.90, -1.10]                                 | •                                      |
| Heterogeneity: Tau <sup>2</sup> =   | 0.77; Cł | ni² = 2 | .42, df         | = 2 (P = | 0.30   | ); l² = 1             | 7%                    |  | -20 -10 0 10 20                        |
| Test for overall effect: .          | Z = 2.86 | (P = (  | 0.004)          |          |        |                       |                       |  | Favours electrotherapy Favours control |
| Test for subgroup diffe             | erences  | Chi²    | = 2.39,         | df=1 (   | P = 0  | .12), I²÷             | = 58.2%               |  |  |

# **eFigure 18**: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation

|   | Inte                 | rventio                          | on                    | C         | ontrol  |                     |                           | Mean Difference                           | Mean Difference                            |
|---|----------------------|----------------------------------|-----------------------|-----------|---------|---------------------|---------------------------|---|--|
| Study or Subgroup   | Mean                 | SD                               | Total                 | Mean      | SD      | Total               | Weight                    | IV, Random, 95% CI                        | IV, Random, 95% CI                         |
| 16.9.1 LOW_LOW  |                      |                                  |                       |           |         |                     |                           |   |  |
| Lenssen 2008<br>Subtotal (95% CI)                               | 16.54                | 0.76                             | 30<br><b>30</b>       | 16.5      | 0.18    | 30<br><b>30</b>     | 90.9%<br><b>90.9%</b>     | 0.04 [-0.24, 0.32]<br>0.04 [-0.24, 0.32]  |  |
| Heterogeneity: Not ap   | plicable             |                                  |                       |           |         |                     |                           |   |  |
| Test for overall effect:  | Z = 0.28             | (P = 0                           | 1.78)                 |           |         |                     |                           |   |  |
| 16.9.2 OTHER  |                      |                                  |                       |           |         |                     |                           |   |  |
| Beaupre 2001  | 14.6                 | 3.4                              | 34                    | 14.6      | 3.6     | 34                  | 2.6%                      | 0.00 [-1.66, 1.66]                        |  |
| Maniar 2012   | 4                    | 3.34                             | 30                    | 3.2       | 2.98    | 28                  | 2.7%                      | 0.80 [-0.83, 2.43]                        |  |
| Maniar 2012<br>Subtotal (95% Cl)                                | 3                    | 2.11                             | 28<br><mark>92</mark> | 3.2       | 2.98    | 28<br>90            | 3.9%<br><mark>9.1%</mark> | -0.20 [-1.55, 1.15]<br>0.15 [-0.73, 1.03] | •  |
| Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect: . | 0.00; Cl<br>Z = 0.33 | hi² = 0.<br>: (P = 0             | 90, df=<br>1.74)      | = 2 (P =  | 0.64);  | I² = 0%             |                           |   |  |
| Total (95% CI)  |                      |                                  | 122                   |           |         | 120                 | 100.0%                    | 0.05 [-0.22, 0.32]                        | +  |
| Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:   | 0.00; Cl<br>Z = 0.37 | hi <sup>2</sup> = 0.<br>' (P = 0 | 96, df=<br>1.71)      | = 3 (P =  | 0.81);  | l <sup>2</sup> = 0% |                           |   | -4 -2 0 2 4<br>Favours CPM Favours control |
| Test for subgroup diffe   | erences              | : Chi <sup>z</sup> :             | = 0.05,               | df = 1 (F | P = 0.8 | 2), f² =            | 0%                        |   |  |

# **eFigure 19**: Subgroup Sensitivity Analysis Comparing Studies Based on Allocation Concealment and Random Sequence Generation

|                                   | Inter    | ventio         | n       | С         | ontrol             |                      |        | Mean Difference    | Mean Difference                           |
|-----------------------------------|----------|----------------|---------|-----------|--------------------|----------------------|--------|--------------------|---|
| Study or Subgroup                 | Mean     | SD             | Total   | Mean      | SD                 | Total                | Weight | IV, Random, 95% CI | IV, Random, 95% CI                        |
| 16.10.1 LOW_LOW                   |          |                |         |           |                    |                      |        |                    |   |
| Calatayud 2016                    | 1.3      | 1.1            | 18      | 0.98      | 0.99               | 20                   | 47.8%  | 0.32 [-0.35, 0.99] |   |
| Gstoettner 2011                   | 1.3      | 1.1            | 18      | 0.98      | 0.99               | 20                   | 47.8%  | 0.32 [-0.35, 0.99] |   |
| Subtotal (95% CI)                 |          |                | 36      |           |                    | 40                   | 95.6%  | 0.32 [-0.15, 0.79] | ◆   |
| Heterogeneity: Tau <sup>2</sup> = | 0.00; Cł | ni² = 0.       | 00, df= | = 1 (P =  | 1.00);             | $ ^{2} = 0\%$        |        |                    |   |
| Test for overall effect:          | Z = 1.33 | (P = 0         | .18)    |           |                    |                      |        |                    |   |
| 16.10.2 OTHER                     |          |                |         |           |                    |                      |        |                    |   |
| McKay 2012                        | 5.6      | 2.72           | 10      | 4.92      | 4.5                | 12                   | 2.3%   | 0.68 [-2.37, 3.73] |   |
| McKay 2012                        | 4.4      | 3.2            | 10      | 3.58      | 4.4                | 12                   | 2.1%   | 0.82 [-2.36, 4.00] |   |
| Subtotal (95% CI)                 |          |                | 20      |           |                    | 24                   | 4.4%   | 0.75 [-1.46, 2.95] |   |
| Heterogeneity: Tau <sup>2</sup> = | 0.00; Ch | ni² = 0.       | 00, df= | = 1 (P =  | 0.95);             | l² = 0%              |        |                    |   |
| Test for overall effect:          | Z = 0.66 | (P = 0         | .51)    |           |                    |                      |        |                    |   |
| Total (95% CI)                    |          |                | 56      |           |                    | 64                   | 100.0% | 0.34 [-0.12, 0.80] | ◆   |
| Heterogeneity: Tau <sup>2</sup> = | 0.00; Cł | ni² = 0.       | 14, df= | = 3 (P =  | 0.99);             | l <sup>2</sup> = 0%  |        |                    |   |
| Test for overall effect:          | Z=1.44   | (P = 0         | .15)    |           |                    |                      |        |                    | -4 -2 U Z 4                               |
| Test for subgroup diff            | erences: | Chi <b></b> ≇∍ | = 0.14, | df = 1 (i | <sup>o</sup> = 0.7 | 1), I <sup>2</sup> = | 0%     |                    | Favours preoperative exer Favours control |

# **eFigure 20**: Subgroup Sensitivity Analysis Comparing Studies Based on How Pain Outcome Was Considered (Either Primary or Secondary)

| 1                                      | Intervent              | on             | C          | ontrol  |                    |        | Mean Difference      | Mean Difference             |
|--|------------------------|----------------|------------|---------|--------------------|--------|----------------------|-----------------------------|
| Study or Subgroup Me                   | an SD                  | Total          | Mean       | SD      | Total              | Weight | IV, Random, 95% CI   | IV, Random, 95% CI          |
| 16.18.1 Primary                        |                        |                |            |         |                    |        |                      |                             |
| Bruun-Olsen 2009                       | 4 2.3                  | 30             | 4          | 2.1     | 33                 | 5.1%   | 0.00 [-1.09, 1.09]   |                             |
| Bruun-Olsen 2009                       | 2.9 2.2                | 30             | 1.9        | 1.5     | 33                 | 6.2%   | 1.00 [0.06, 1.94]    |                             |
| Lenssen 2003 🛛 🔅                       | 2.6 1.8                | 20             | 4.7        | 2.6     | 19                 | 3.5%   | -2.10 [-3.51, -0.69] |                             |
| Lenssen 2003 🛛 🔅                       | 2.3 2.6                | 20             | 4.5        | 2.4     | 18                 | 2.9%   | -2.20 [-3.79, -0.61] |                             |
| Montgomery 1996                        | 5 2.5                  | 28             | 5          | 1.5     | 32                 | 5.3%   | 0.00 [-1.06, 1.06]   |                             |
| Sahin 2006 3.                          | .85 1.29               | 14             | 3.5        | 1.34    | 14                 | 5.9%   | 0.35 [-0.62, 1.32]   |                             |
| Sahin 2006 1.                          | .21 1.12               | 14             | 1.14       | 1.16    | 14                 | 7.0%   | 0.07 [-0.77, 0.91]   |                             |
| Subtotal (95% CI)                      |                        | 156            |            |         | 163                | 35.9%  | -0.27 [-1.03, 0.49]  | -                           |
| Heterogeneity: Tau <sup>2</sup> = 0.73 | 3; Chi <b>ž</b> = 3    | 20.69, dt      | f=6(P=     | = 0.002 | 2); I <b>z</b> = 7 | 71%    |                      |                             |
| Test for overall effect: Z = 0         | 0.70 (P =              | 0.49)          |            |         |                    |        |                      |                             |
| 40.40.2.0                              |                        |                |            |         |                    |        |                      |                             |
| 16.18.2 Secondary                      |                        |                |            |         |                    |        |                      |                             |
| Bennet 2005                            | 3.6 3                  | 47             | 3.1        | 2.9     | 52                 | 4.6%   | 0.50 [-0.66, 1.66]   |                             |
| Bennet 2005                            | 2.6 2.9                | 48             | 3.1        | 2.9     | 52                 | 4.8%   | -0.50 [-1.64, 0.64]  |                             |
| Chen 2013 5.                           | .12 1.39               | 68             | 4.77       | 1.56    | 39                 | 9.9%   | 0.35 [-0.24, 0.94]   |                             |
| Chen 2013 3.                           | .22 1.28               | 68             | 3.05       | 1.54    | 39                 | 10.2%  | 0.17 [-0.40, 0.74]   |                             |
| Chen 2013 0.                           | .37 0.6                | 68             | 0.21       | 0.47    | 39                 | 15.2%  | 0.16 [-0.05, 0.37]   | <b>*</b>                    |
| MacDonald 2000                         | 5.1 1.3                | 40             | 5.2        | 1.2     | 40                 | 10.5%  | -0.10 [-0.65, 0.45]  |                             |
| May 1999 - 1                           | 1.5 1.6                | 7              | 2.1        | 2.4     | 7                  | 1.7%   | -0.60 [-2.74, 1.54]  |                             |
| McInnes 1992                           | 2.8 2.05               | 47             | 3.6        | 2.05    | 45                 | 7.1%   | -0.80 [-1.64, 0.04]  |                             |
| Subtotal (95% CI)                      |                        | 393            |            |         | 313                | 64.1%  | 0.07 [-0.14, 0.29]   | •                           |
| Heterogeneity: Tau <sup>2</sup> = 0.01 | l;Chi <sup>z</sup> = i | '.95, df=      | = 7 (P =   | 0.34);  | $ ^{2} = 129$      | %      |                      |                             |
| Test for overall effect: Z = 0         | 0.67 (P =              | 0.50)          |            |         |                    |        |                      |                             |
| Total (95% CI)                         |                        | 549            |            |         | 476                | 100.0% | -0.05 [-0.35, 0.25]  | •                           |
| Hotorogeneity: Tou <sup>2</sup> – 0.14 | t: ⊂hi≅ – 1            | 0 1 2 di       | f = 1,4 /P | - n n-  | 1): IZ = 4         | 57%    | 0.00 [ 0.00, 0.20]   |                             |
| Tect for overall effect: 7 – 0         | +, OUL - 7             | 0.74)<br>0.74) | - 14 (F    | - 0.0   | ·//                | 12.70  |                      | -4 -2 0 2 4                 |
| Test for subgroup differen             | 0.00 (r. –             | 0.(4)          | A6 A (1    |         | 0) 17              | ~~     |                      | Favours CPM Favours control |

# **eFigure 21**: Subgroup Sensitivity Analysis Comparing Studies Based on How Pain Outcome Was Considered (Either Primary or Secondary)

|                                     | Inte      | erventio             | n                | C         | ontrol                |                    |               | Mean Difference                                   | Mean Difference                     |
|-------------------------------------|-----------|----------------------|------------------|-----------|-----------------------|--------------------|---------------|---|-------------------------------------|
| Study or Subgroup                   | Mean      | SD                   | Total            | Mean      | SD                    | Total              | Weight        | IV, Random, 95% CI                                | IV, Random, 95% Cl                  |
| 16.19.1 Primary                     |           |                      |                  |           |                       |                    |               |   |                                     |
| Albrecht 1997                       | 2.65      | 5.11                 | 35               | 7         | 5.11                  | 15                 | 2.0%          | -4.35 [-7.44, -1.26]                              |                                     |
| Albrecht 1997                       | 6         | 3.16                 | 32               | 7         | 3.16                  | 16                 | 4.0%          | -1.00 [-2.90, 0.90]                               |                                     |
| Albrecht 1997                       | 5.12      | 4.54                 | 32               | 6.5       | 4.54                  | 16                 | 2.5%          | -1.38 [-4.10, 1.34]                               |                                     |
| Albrecht 1997                       | 2.34      | 4.89                 | 35               | 6.5       | 4.89                  | 15                 | 2.2%          | -4.16 [-7.12, -1.20]                              |                                     |
| Thienpont 2014<br>Subtotal (95% CI) | 4         | 3                    | 50<br><b>184</b> | 3.5       | 5                     | 50<br>112          | 4.8%<br>15.5% | 0.50 [-1.12, 2.12]<br>- <b>1.79 [-3.62, 0.04]</b> |                                     |
| Heterogeneity: Tau <sup>2</sup> =   | = 2.82; C | hi <b></b> ² = 12    | .15, df:         | = 4 (P =  | 0.02); l <sup>a</sup> | = 67%              |               |   |                                     |
| Test for overall effect:            | Z = 1.91  | (P = 0.              | 06)              |           |                       |                    |               |   |                                     |
|                                     |           |                      |                  |           |                       |                    |               |   |                                     |
| 16.19.2 Secondary                   |           |                      |                  |           |                       |                    |               |   |                                     |
| Gibbons 2001                        | 6.7       | 3.101                | 30               | 6.2       | 3.101                 | 30                 | 5.0%          | 0.50 [-1.07, 2.07]                                | _ <del></del>                       |
| Gibbons 2001                        | 3.8       | 2.41                 | 30               | 4.2       | 2.41                  | 30                 | 6.3%          | -0.40 [-1.62, 0.82]                               |                                     |
| Kullenberg 2006                     | 2.1       | 4.55                 | 43               | 2.2       | 1                     | 40                 | 5.6%          | -0.10 [-1.49, 1.29]                               | <del></del>                         |
| Kullenberg 2006                     | 0.8       | 4.09                 | 43               | 1.2       | 3.19                  | 40                 | 5.0%          | -0.40 [-1.97, 1.17]                               |                                     |
| Levy 1993                           | 7.4       | 2.7                  | 40               | 7.8       | 2.7                   | 40                 | 6.4%          | -0.40 [-1.58, 0.78]                               | —                                   |
| Levy 1993                           | 5.9       | 2.4                  | 40               | 7.3       | 1.5                   | 40                 | 7.7%          | -1.40 [-2.28, -0.52]                              |                                     |
| Levy 1993                           | 5.6       | 1.6                  | 40               | 6.9       | 1.9                   | 40                 | 8.2%          | -1.30 [-2.07, -0.53]                              |                                     |
| Morsi 2002                          | 4         | 0                    | 30               | 6.9       | 0                     | 30                 |               | Not estimable                                     |                                     |
| Morsi 2002                          | 5.5       | 0                    | 30               | 9         | 0                     | 30                 |               | Not estimable                                     |                                     |
| Morsi 2002                          | 5         | 2.73                 | 30               | 7         | 2.63                  | 30                 | 5.7%          | -2.00 [-3.36, -0.64]                              | _ <b>—</b>                          |
| Radkowski 2007                      | 6         | 2.72                 | 28               | 5.5       | 2.72                  | 36                 | 5.8%          | 0.50 [-0.84, 1.84]                                | - <del></del>                       |
| Radkowski 2007                      | 7.1       | 2.75                 | 28               | 6.3       | 3.75                  | 36                 | 4.9%          | 0.80 [-0.79, 2.39]                                |                                     |
| Smith 2002                          | 4.3       | 1.8                  | 44               | 4.2       | 2                     | 40                 | 8.0%          | 0.10 [-0.72, 0.92]                                | +                                   |
| Smith 2002                          | 4.3       | 2                    | 44               | 4.8       | 1.9                   | 40                 | 7.9%          | -0.50 [-1.33, 0.33]                               |                                     |
| Smith 2002                          | 4.2       | 1.8                  | 44               | 3.5       | 1.9                   | 40                 | 8.1%          | 0.70 [-0.09, 1.49]                                |                                     |
| Subtotal (95% CI)                   |           |                      | 544              |           |                       | 542                | 84.5%         | -0.35 [-0.83, 0.13]                               | •                                   |
| Heterogeneity: Tau <sup>2</sup> =   | = 0.44; C | hi <b>²</b> = 29     | .80, df:         | = 12 (P = | = 0.003)              | ); I² = 6I         | D%            |   |                                     |
| Test for overall effect:            | Z=1.41    | (P = 0.              | 16)              |           |                       |                    |               |   |                                     |
| Total (95% CI)                      |           |                      | 728              |           |                       | 654                | 100.0%        | -0.51 [-1.00, -0.02]                              | ◆                                   |
| Heterogeneity: Tau <sup>2</sup> =   | = 0.61; C | hi² = 44             | .24, df:         | = 17 (P = | = 0.000               | 3); I <b>2</b> = I | 62%           |   |                                     |
| Test for overall effect:            | Z = 2.08  | 6 (P = 0.            | 04)              |           |                       |                    |               |   | Favours cryotherapy Eavours control |
| Test for subgroup diff              | ferences  | : Chi <sup>z</sup> = | 2.23, c          | lf = 1 (P | = 0.14),              | l² = 55            | .1%           |   |                                     |

# **eFigure 22**: Subgroup Sensitivity Analysis Comparing Studies Based on How Pain Outcome Was Considered (Either Primary or Secondary)

|                                   | Inte      | erventio               | n                | 0         | Control   |                      |                       | Mean Difference                                    | Mean Difference             |
|-----------------------------------|-----------|------------------------|------------------|-----------|-----------|----------------------|-----------------------|--|-----------------------------|
| Study or Subgroup                 | Mean      | SD                     | Total            | Mean      | SD        | Total                | Weight                | IV, Random, 95% Cl                                 | IV, Random, 95% Cl          |
| 16.20.1 Primary                   |           |                        |                  |           |           |                      |                       |  |                             |
| Harms 1991<br>Subtotal (95% CI)   | 28        | 19                     | 55<br><b>55</b>  | 29        | 16        | 58<br>58             | 25.1%<br><b>25.1%</b> | -1.00 [-7.49, 5.49]<br>- <b>1.00 [-7.49, 5.49]</b> | <b>*</b>                    |
| Heterogeneity: Not ap             | oplicable | ,                      |                  |           |           |                      |                       |  |                             |
| Test for overall effect           | Z = 0.30  | ) (P = 0.1             | 76)              |           |           |                      |                       |  |                             |
| 16.20.2 Secondary                 |           |                        |                  |           |           |                      |                       |  |                             |
| Colwell 1992                      | 9.6       | 3.75                   | 12               | 14.8      | 6.4       | 0                    |                       | Not estimable                                      |                             |
| MacDonald 2000                    | 88        | 51                     | 40               | 80        | 51        | 40                   | 19.3%                 | 8.00 [-14.35, 30.35]                               | _ <b>_</b>                  |
| Pope 1997                         | 81.5      | 24.08                  | 20               | 48.1      | 23.91     | 19                   | 22.4%                 | 33.40 [18.33, 48.47]                               |                             |
| Pope 1997                         | 72.6      | 25.4                   | 18               | 48.1      | 23.91     | 19                   | 22.0%                 | 24.50 [8.59, 40.41]                                |                             |
| Walker 1991<br>Subtotal (95% CI)  | 96        | 32.75                  | 12<br><b>102</b> | 148       | 64.25     | 10<br>88             | 11.1%<br><b>74.9%</b> | -52.00 [-95.92, -8.08]<br>11.12 [-12.21, 34.44]    |                             |
| Heterogeneity: Tau <sup>2</sup> = | 419.09    | ; Chi <sup>z</sup> = 1 | 14.69,           | df = 3 (F | e = 0.002 | 2); I <b>z</b> = 8   | 30%                   |  |                             |
| Test for overall effect           | Z = 0.93  | 8 (P = 0.3             | 35)              |           |           |                      |                       |  |                             |
| Total (95% CI)                    |           |                        | 157              |           |           | 146                  | 100.0%                | 8.38 [-11.05, 27.81]                               | •                           |
| Heterogeneity: Tau <sup>2</sup> = | 379.87    | ; Chi² = :             | 29.09,           | df = 4 (F | ° < 0.000 | 001); I <sup>z</sup> | = 86%                 | -  |                             |
| Test for overall effect           | Z = 0.84  | 4 (P = 0               | 40)              |           |           |                      |                       |  | Favours CPM Favours control |
| Test for subgroup dif             | ferences  | : Chi <sup>2</sup> =   | 0.96, d          | f=1 (P    | = 0.33),  | $ ^{2} = 0\%$        | 6                     |  |                             |

# **eFigure 23**: Subgroup Sensitivity Analysis Comparing Studies Based on How Pain Outcome Was Considered (Either Primary or Secondary)

|                                     | Inte                   | erventio  | n        | C        | Control  |                       |                       | Mean Difference                                    | Mean Difference                     |
|-------------------------------------|------------------------|-----------|----------|----------|----------|-----------------------|-----------------------|--|-------------------------------------|
| Study or Subgroup                   | Mean                   | SD        | Total    | Mean     | SD       | Total                 | Weight                | IV, Random, 95% CI                                 | IV, Random, 95% CI                  |
| 16.21.1 Primary                     |                        |           |          |          |          |                       |                       |  |                                     |
| Thienpont 2014<br>Subtotal (95% CI) | 0.792                  | 0.563     | 50<br>50 | 0.802    | 0.542    | 50<br><mark>50</mark> | 11.4%<br><b>11.4%</b> | -0.01 [-0.23, 0.21]<br>- <b>0.01 [-0.23, 0.21]</b> | <b>↓</b>                            |
| Heterogeneity: Not ap               | oplicable              |           |          |          |          |                       |                       |  |                                     |
| Test for overall effect:            | Z = 0.09               | (P = 0.9) | 93)      |          |          |                       |                       |  |                                     |
| 16 01 0 Cocondony                   |                        |           |          |          |          |                       |                       |  |                                     |
| TO.21.2 Secondary                   |                        |           |          |          |          |                       |                       |  |                                     |
| Gibbons 2001                        | 0.65                   | 0.31      | 30       | 0.6      | 0.31     | 30                    | 13.8%                 | 0.05 [-0.11, 0.21]                                 |                                     |
| Kullenberg 2006                     | 0.37                   | 0.11      | 43       | 0.43     | 0.05     | 40                    | 17.6%                 | -0.06 [-0.10, -0.02]                               | •                                   |
| Levy 1993                           | 0.53                   | 0.2       | 40       | 0.96     | 0.3      | 40                    | 15.5%                 | -0.43 [-0.54, -0.32]                               | +                                   |
| Smith 2002                          | 0.32                   | 0.29      | 44       | 0.42     | 0.31     | 40                    | 14.9%                 | -0.10 [-0.23, 0.03]                                |                                     |
| Walker 1991                         | 0.622                  | 0.169     | 15       | 0.844    | 0.293    | 15                    | 13.2%                 | -0.22 [-0.39, -0.05]                               |                                     |
| Webb 1998                           | 0.57                   | 0.23      | 15       | 0.71     | 0.23     | 16                    | 13.6%                 | -0.14 F-0.30, 0.021                                |                                     |
| Subtotal (95% CI)                   |                        |           | 187      |          |          | 181                   | 88.6%                 | -0.15 [-0.29, -0.02]                               | •                                   |
| Heterogeneity: Tau <sup>2</sup> =   | : 0.02 <sup>,</sup> CI | hi² = 43  | 79 df:   | = 5 (P < | 0 0000   | 1): IP = 1            | 89%                   |  | -                                   |
| Test for overall effect:            | 7 = 2.20               | (P = 0.0  | 13)      | • •      |          | .,,                   |                       |  |                                     |
|                                     | 2-2.20                 | , (i = 0  | ,        |          |          |                       |                       |  |                                     |
| Total (95% CI)                      |                        |           | 237      |          |          | 231                   | 100.0%                | -0.13 [-0.26, -0.01]                               | •                                   |
| Heterogeneity: Tau <sup>2</sup> =   | = 0.02: CI             | hi² = 44. | 38. df=  | = 6 (P < | 0.0000   | 1);                   | 86%                   |  |                                     |
| Test for overall effect:            | 7=217                  | P = 0.0   | 13)      |          |          |                       |                       |  | -2 -1 0 1 2                         |
| Test for subaroun diff              | ferences               | ∵Chi²=    | 117 d    | f= 1 (P  | = 0.28)  | $l^2 = 1.4$           | 9%                    |  | Favours cryotherapy Favours control |
| reactor adoptioup uni               | erences                |           | 1.17.0   | -100     | - 0.20), | 1 - 14                | .5.0                  |  |                                     |



**eFigure 24:** Funnel Plot of Comparison for CPM Trials Measured in Terms of Reported Points in the VAS Scale at 1 Week



**eFigure 25:** Funnel Plot of Comparison for CPM Trials Measured in Terms of Opioid Consumption (mg/kg/48 Hours of Morphine Equivalent)

**eFigure 26:** Funnel Plot of Comparison for Cryotherapy Trials Measured in Terms of Reported Points in the VAS Scale



**eFigure 27:** Funnel Plot of Comparison for Cryotherapy Trials Measured in Terms of Opioid Consumption (mg/kg/48 Hours of Morphine Equivalent)



**eFigure 28:** Funnel Plot of Comparison for Electrotherapy Trials Measured in Terms of Reported Points in the VAS Scale at 1 Week







### eFigure 30: Subgroup Sensitivity Analysis Comparing Studies by Type of Control.

|                                   | Сгус       | yotherapy Control  |         |          |                    |         |        | Mean Difference      | Mean Difference                     |
|-----------------------------------|------------|--------------------|---------|----------|--------------------|---------|--------|----------------------|-------------------------------------|
| Study or Subgroup                 | Mean       | SD                 | Total   | Mean     | SD                 | Total   | Weight | IV, Random, 95% CI   | IV, Random, 95% CI                  |
| 4.1.1 Cryotherapy vs              | s. nothing |                    |         |          |                    |         |        |                      |                                     |
| Albrecht 1997                     | 2.65       | 5.11               | 35      | 7        | 5.11               | 15      | 4.4%   | -4.35 [-7.44, -1.26] | <b>-</b>                            |
| Albrecht 1997                     | 6          | 3.16               | 32      | 7        | 3.16               | 16      | 9.8%   | -1.00 [-2.90, 0.90]  |                                     |
| Kullenberg 2006                   | 2.1        | 4.55               | 43      | 2.2      | 1                  | 40      | 14.8%  | -0.10 [-1.49, 1.29]  | -+-                                 |
| Morsi 2002                        | 4          | 0                  | 30      | 6.9      | 0                  | 30      |        | Not estimable        |                                     |
| Subtotal (95% CI)                 |            |                    | 140     |          |                    | 101     | 29.0%  | -1.41 [-3.44, 0.62]  | ◆                                   |
| Heterogeneity: Tau <sup>2</sup> = | = 2.10; Cł | ni² = 6.0          | 6, df=  | 2 (P = 0 | .05); l² =         | = 67%   |        |                      |                                     |
| Test for overall effect           | : Z = 1.36 | (P = 0.1           | 17)     |          |                    |         |        |                      |                                     |
| 1120                              |            |                    |         |          |                    |         |        |                      |                                     |
| 4.1.2 Cryotherapy vs              | s. compre  | ession             |         |          |                    |         |        |                      |                                     |
| Gibbons 2001                      | 6.7        | 3.101              | 30      | 6.2      | 3.101              | 30      | 12.8%  | 0.50 [-1.07, 2.07]   |                                     |
| Levy 1993                         | 7.4        | 2.7                | 40      | 7.8      | 2.7                | 40      | 17.9%  | -0.40 [-1.58, 0.78]  | -                                   |
| Radkowski 2007                    | 6          | 2.72               | 28      | 5.5      | 2.72               | 36      | 15.5%  | 0.50 [-0.84, 1.84]   |                                     |
| Smith 2002                        | 4.3        | 1.8                | 44      | 4.2      | 2                  | 40      | 24.8%  | 0.10 [-0.72, 0.92]   | +                                   |
| Subtotal (95% CI)                 |            |                    | 142     |          |                    | 146     | 71.0%  | 0.11 [-0.45, 0.67]   | <b>♦</b>                            |
| Heterogeneity: Tau <sup>2</sup> = | = 0.00; Cł | ni <b>=</b> 1.2    | 8, df = | 3 (P = 0 | .74); l² =         | = 0%    |        |                      |                                     |
| Test for overall effect           | : Z = 0.38 | (P = 0.7)          | 70)     |          |                    |         |        |                      |                                     |
|                                   |            |                    | 202     |          |                    | 247     | 400.0% | 0.24 [ 0.00 0.40]    |                                     |
| Total (95% CI)                    |            |                    | 282     |          |                    | 247     | 100.0% | -0.21 [-0.89, 0.48]  | · · · · · ·                         |
| Heterogeneity: Tau <sup>2</sup> = | = 0.32; Cł | ni² = 9.9          | 3, df = | 6 (P = 0 | .13); I <b>≥</b> = | = 40%   |        |                      | -10 -5 0 5 10                       |
| Test for overall effect           | : Z = 0.59 | (P = 0.5           | 55)     |          |                    |         |        |                      | Favours cryotherapy Favours control |
| Test for subgroup dif             | ferences   | Chi <sup>2</sup> = | 2.00, d | f=1 (P   | = 0.16),           | l² = 50 | .1%    |                      |                                     |

### eFigure 31: Subgroup Sensitivity Analysis Comparing Studies by Type of Control

|                                   | Сгус     | thera                | erapy Control |           |         |                      |        | Mean Difference      | Mean Difference                             |
|-----------------------------------|----------|----------------------|---------------|-----------|---------|----------------------|--------|----------------------|---|
| Study or Subgroup                 | Mean     | SD                   | Total         | Mean      | SD      | Total                | Weight | IV, Random, 95% CI   | IV, Random, 95% CI                          |
| 5.1.1 Cryotherapy vs.             | nothing  |                      |               |           |         |                      |        |                      |   |
| Albrecht 1997                     | 5.12     | 4.54                 | 32            | 6.5       | 4.54    | 16                   | 10.2%  | -1.38 [-4.10, 1.34]  |   |
| Albrecht 1997                     | 2.34     | 4.89                 | 35            | 6.5       | 4.89    | 15                   | 9.0%   | -4.16 [-7.12, -1.20] |   |
| Subtotal (95% CI)                 |          |                      | 67            |           |         | 31                   | 19.3%  | -2.71 [-5.43, 0.01]  |   |
| Heterogeneity: Tau <sup>2</sup> = | 1.76; Cl | ni² = 1.             | 84, df :      | = 1 (P =  | 0.18);  | $l^{2} = 46^{\circ}$ | %      |                      |   |
| Test for overall effect:          | Z = 1.95 | (P = 0               | 1.05)         |           |         |                      |        |                      |   |
| 5.1.2 Cryotherapy vs.             | compre   | ession               |               |           |         |                      |        |                      |   |
| Levy 1993                         | 5.9      | 2.4                  | 40            | 7.3       | 1.5     | 40                   | 30.2%  | -1.40 [-2.28, -0.52] |   |
| Morsi 2002                        | 5.5      | 0                    | 30            | 9         | 0       | 30                   |        | Not estimable        |   |
| Smith 2002                        | 4.3      | 2                    | 44            | 4.8       | 1.9     | 40                   | 30.9%  | -0.50 [-1.33, 0.33]  |   |
| Thienpont 2014                    | 4        | 3                    | 50            | 3.5       | 5       | 50                   | 19.6%  | 0.50 [-1.12, 2.12]   |   |
| Subtotal (95% CI)                 |          |                      | 164           |           |         | 160                  | 80.7%  | -0.64 [-1.57, 0.30]  | ◆   |
| Heterogeneity: Tau² =             | 0.38; CI | ni² = 4.             | 75, df :      | = 2 (P =  | 0.09);  | I <sup>2</sup> = 58° | %      |                      |   |
| Test for overall effect:          | Z=1.34   | (P = 0               | 1.18)         |           |         |                      |        |                      |   |
| Total (95% CI)                    |          |                      | 231           |           |         | 191                  | 100.0% | -1.00 [-2.01, 0.02]  | •   |
| Heterogeneity: Tau <sup>z</sup> = | 0.69; Cl | ni² = 9.             | 80, df :      | = 4 (P =  | 0.04);  | I <sup>z</sup> = 599 | %      | -                    |   |
| Test for overall effect:          | Z=1.93   | (P = 0               | .05)          |           |         |                      |        |                      | -4 -2 U Z 4<br>Equates existences - Equates |
| Test for subgroup diff            | erences  | : Chi <del>"</del> ⊧ | = 1.99,       | df = 1 (F | P = 0.1 | 6), I <sup>z</sup> = | 49.8%  |                      | Favours cryourerapy Favours control         |

### eFigure 32: Subgroup Sensitivity Analysis Comparing Studies by Type of Control

|                                      | Сгус      | othera           | ру              | C          | ontrol  |                        |                       | Mean Difference                                    | Mean Difference                     |
|--------------------------------------|-----------|------------------|-----------------|------------|---------|------------------------|-----------------------|--|-------------------------------------|
| Study or Subgroup                    | Mean      | SD               | Total           | Mean       | SD      | Total                  | Weight                | IV, Random, 95% CI                                 | IV, Random, 95% CI                  |
| 6.1.1 Cryotherapy vs                 | . nothing | )                |                 |            |         |                        |                       |  |                                     |
| Kullenberg 2006<br>Subtotal (95% Cl) | 0.8       | 4.09             | 43<br><b>43</b> | 1.2        | 3.19    | 40<br><b>40</b>        | 14.0%<br><b>14.0%</b> | -0.40 [-1.97, 1.17]<br>- <b>0.40 [-1.97, 1.17]</b> | •                                   |
| Heterogeneity: Not ap                | oplicable | !                |                 |            |         |                        |                       |  |                                     |
| Test for overall effect:             | Z = 0.50  | ) (P = 0         | ).62)           |            |         |                        |                       |  |                                     |
| 6.1.2 Cryotherapy vs                 | . compr   | ession           | I               |            |         |                        |                       |  |                                     |
| Gibbons 2001                         | 3.8       | 2.41             | 30              | 4.2        | 2.41    | 30                     | 16.6%                 | -0.40 [-1.62, 0.82]                                |                                     |
| Levy 1993                            | 5.6       | 1.6              | 40              | 6.9        | 1.9     | 40                     | 20.1%                 | -1.30 [-2.07, -0.53]                               | -                                   |
| Morsi 2002                           | 5         | 2.73             | 30              | 7          | 2.63    | 30                     | 15.6%                 | -2.00 [-3.36, -0.64]                               |                                     |
| Radkowski 2007                       | 7.1       | 2.75             | 28              | 6.3        | 3.75    | 36                     | 13.8%                 | 0.80 [-0.79, 2.39]                                 | +                                   |
| Smith 2002                           | 4.2       | 1.8              | 44              | 3.5        | 1.9     | 40                     | 19.9%                 | 0.70 [-0.09, 1.49]                                 | -                                   |
| Subtotal (95% CI)                    |           |                  | 172             |            |         | 176                    | 86.0%                 | -0.45 [-1.53, 0.63]                                | ♠                                   |
| Heterogeneity: Tau² =                | = 1.17; C | hi <b>²</b> = 21 | 0.14, di        | f= 4 (P :  | = 0.00  | 05); I <sup>2</sup> =  | 80%                   |  |                                     |
| Test for overall effect:             | Z = 0.82  | ? (P = 0         | ).41)           |            |         |                        |                       |  |                                     |
| Total (95% CI)                       |           |                  | 215             |            |         | 216                    | 100.0%                | -0.44 [-1.37, 0.49]                                | •                                   |
| Heterogeneity: Tau <sup>2</sup> =    | = 0.97; C | hi <b>²</b> = 21 | 0.14, di        | f = 5 (P = | = 0.00  | 1); I <sup>2</sup> = 3 | 75%                   | -  |                                     |
| Test for overall effect:             | Z = 0.94  | l (P = 0         | ).35)           |            |         |                        |                       |  | Eavours cryotherapy Eavours control |
| Test for subgroup dif                | ferences  | : Chi <b></b> ⁼⊧ | = 0.00.         | df = 1 (F  | P = 0.9 | 6), I <sup>2</sup> =   | 0%                    |  | ravous orjourcrapy ravous control   |

### eFigure 33: Subgroup Sensitivity Analysis Comparing Studies by Type of Control

|                                   | Сгу       | otherap                | y               | 0         | Control    |                        |        | Mean Difference      | Mean Difference   |
|-----------------------------------|-----------|------------------------|-----------------|-----------|------------|------------------------|--------|----------------------|---|
| Study or Subgroup                 | Mean      | SD                     | Total           | Mean      | SD         | Total                  | Weight | IV, Random, 95% CI   | IV, Random, 95% CI  |
| 7.1.1 Cryotherapy vs.             | . nothing | ]                      |                 |           |            |                        |        |                      |   |
| Walker 1991                       | 0.622     | 0.169                  | 15              | 0.844     | 0.293      | 15                     | 13.2%  | -0.22 [-0.39, -0.05] |   |
| Webb 1998                         | 0.57      | 0.23                   | 15              | 0.71      | 0.23       | 16                     | 13.6%  | -0.14 [-0.30, 0.02]  |   |
| Subtotal (95% CI)                 |           |                        | 30              |           |            | 31                     | 26.8%  | -0.18 [-0.30, -0.06] | •   |
| Heterogeneity: Tau <sup>2</sup> = | 0.00; C   | hi² = 0.4              | 6, df =         | 1 (P = 0  | .50); I² = | = 0%                   |        |                      |   |
| Test for overall effect:          | Z = 2.98  | 8 (P = 0.)             | 003)            |           |            |                        |        |                      |   |
| 712 Cryotherapy vs                | compre    | noiese                 |                 |           |            |                        |        |                      |   |
| Cibbono 2004                      | 0.05      | 0.04                   | 20              | 0.0       | 0.24       | 20                     | 42.00  | 0.051044.0041        |   |
| Kullophorg 2001                   | 0.00      | 0.31                   | 30              | 0.0       | 0.31       | 30                     | 13.8%  | 0.05[0.11,0.21]      | _ <sup>_</sup>  |
| Kullenberg 2006                   | 0.37      | 0.11                   | 43              | 0.43      | 0.05       | 40                     | 17.0%  | -0.06 [-0.10, -0.02] |   |
| Levy 1993<br>Cmith 2002           | 0.00      | 0.2                    | 40              | 0.90      | 0.3        | 40                     | 10.0%  | -0.43 [-0.34, -0.32] |   |
| Smiri 2002                        | 0.32      | 0.29                   | 44              | 0.42      | 0.31       | 40                     | 14.970 | -0.10[-0.23, 0.03]   |   |
| Subtotal (95% CI)                 | 0.792     | 0.005                  | 207             | 0.002     | 0.042      | 200                    | 73.2%  | -0.01[-0.23, 0.21]   |   |
| Hotorogeneity: Tou <sup>2</sup> – | 0.02.0    | bi <b>Z</b> – ∦1       | 77 df-          | - 1 /0 -  | 0 0000     | 1\· IZ = (             | 20%    | -0.12 [-0.20, 0.04]  | $\overline{}$   |
| Telefogeneily, rau –              | 7 - 1 44  | 111 — 41.<br>170 — 0 · | 77, ui -<br>16) | - 4 (1- 5 | 0.0000     | 1), 1 = 3              | 50 70  |                      |   |
| restion overall ellect.           | 2 - 1.44  | (F = 0.                | 10)             |           |            |                        |        |                      |   |
| Total (95% CI)                    |           |                        | 237             |           |            | 231                    | 100.0% | -0.13 [-0.26, -0.01] | ◆   |
| Heterogeneity: Tau <sup>2</sup> = | 0.02; C   | hi <sup>z</sup> = 44.  | 38, df=         | = 6 (P <  | 0.0000     | 1); I <sup>z</sup> = 8 | 86%    |                      |   |
| Test for overall effect:          | Z= 2.17   | ' (P = 0.)             | 03)             |           |            |                        |        |                      | - I - U.S U U.S I<br>Eavours cryothorapy, Eavours control |
| Test for subgroup diff            | erences   | : Chi² =               | 0.38, d         | f=1 (P    | = 0.54),   | l² = 0%                | 6      |                      | Tavours cryourerapy Pavours control                       |

### eFigure 34: Subgroup Sensitivity Analysis Comparing Studies by Type of Control

|   | Acu                   | ounctu                       | ire                   | С         | ontrol             |                              |                             | Mean Difference                               | Mean Difference                     |
|---|-----------------------|------------------------------|-----------------------|-----------|--------------------|------------------------------|-----------------------------|---|-------------------------------------|
| Study or Subgroup   | Mean                  | SD                           | Total                 | Mean      | SD                 | Total                        | Weight                      | IV, Random, 95% CI                            | CI IV, Random, 95% CI               |
| 11.1.1 Acupuncture  | vs. sharr             | 1 acup                       | unctur                | е         |                    |                              |                             |   |                                     |
| Chen 2015   | 89                    | 75                           | 30                    | 37        | 21                 | 30                           | 54.6%                       | 52.00 [24.13, 79.87]                          | 7] 🚽                                |
| Tzeng 2015<br>Subtotal (95% CI)                               | 92                    | 81.7                         | 14<br><mark>44</mark> | 90.7      | 94.9               | 17<br><b>47</b>              | 15.0%<br><mark>69.6%</mark> | 1.30 [-60.88, 63.48]<br>34.58 [-12.61, 81.77] |                                     |
| Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect: | = 680.87;<br>Z = 1.44 | Chi <sup>2</sup> =<br>(P = 0 | : 2.13, i<br>).15)    | df=1 (F   | ? = 0.1            | 4); I² = (                   | 53%                         |   |                                     |
| 11.1.2 Acupuncture  | vs. nothi             | ng                           |                       |           |                    |                              |                             |   |                                     |
| Tzeng 2015<br>Subtotal (95% CI)                               | 92                    | 81.7                         | 16<br><b>16</b>       | 34.1      | 22                 | 17<br><b>17</b>              | 30.4%<br><b>30.4%</b>       | 57.90 [16.52, 99.28]<br>57.90 [16.52, 99.28]  |                                     |
| Heterogeneity: Not ap<br>Test for overall effect:             | plicable<br>Z = 2.74  | (P = 0                       | ).006)                |           |                    |                              |                             |   |                                     |
| Total (95% CI)  |                       |                              | 60                    |           |                    | 64                           | 100.0%                      | 46.17 [20.84, 71.50]                          | •                                   |
| Heterogeneity: Tau <sup>2</sup> =                             | 103.95;               | Chi <b>²</b> =               | 2.46, 1               | df = 2 (F | e = 0.2            | 9); <b>i<sup>2</sup> =</b> 1 | 19%                         |   |                                     |
| Test for overall effect:                                      | Z= 3.57               | (P = 0                       | ).0004)               |           |                    |                              |                             |   | -500 -250 0 250 500                 |
| Test for subgroup dif   | ferences              | ∶Chi <b></b> ⁼∶              | = 0.53,               | df = 1 (i | <sup>o</sup> = 0.4 | 7), l² =                     | 0%                          |   | Favours control Favours acupuncture |

### eFigure 35: Subgroup Sensitivity Analysis Comparing Studies by Type of Control

|   | Acup                                | unctu  | re                           | Co                    | ontro           | I                       |                             | Mean Difference                            | Mean Difference                                      |
|---|-------------------------------------|--|------------------------------|-----------------------|-----------------|-------------------------|-----------------------------|--|--|
| Study or Subgroup   | Mean                                | SD   | Total                        | Mean                  | SD              | Total                   | Weight                      | IV, Random, 95% CI                         | IV, Random, 95% CI                                   |
| 11.2.1 Acupuncture  | /s. sham                            | acup   | unctur                       | e                     |                 |                         |                             |  |  |
| Chen 2015   | 3.7                                 | 1.6  | 30                           | 5.3                   | 2               | 30                      | 28.6%                       | -1.60 [-2.52, -0.68]                       |  |
| Tzeng 2015<br>Subtotal (95% CI)   | 4.2                                 | 1  | 16<br><b>46</b>              | 4.5                   | 1               | 14<br><b>44</b>         | 34.6%<br><mark>63.2%</mark> | -0.30 [-1.02, 0.42]<br>-0.92 [-2.19, 0.35] |  |
| Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:               | 0.67; Ch<br>Z = 1.41                | ni <sup>2</sup> = 4.<br>(P = 0                       | .79, df=<br>1.16)            | = 1 (P =              | 0.03)           | i; <b> ²</b> = 79       | 3%                          |  |  |
| 11.2.2 Acupuncture  | vs. nothir                          | Ig   |                              |                       |                 |                         |                             |  |  |
| Tzeng 2015<br>Subtotal (95% CI)   | 4.2                                 | 1  | 16<br><b>16</b>              | 4.6                   | 0.9             | 17<br><b>17</b>         | 36.8%<br><b>36.8%</b>       | -0.40 [-1.05, 0.25]<br>-0.40 [-1.05, 0.25] | <b>↓</b>   |
| Heterogeneity: Not ap<br>Test for overall effect:                           | plicable<br>Z = 1.21                | (P = 0   | 1.23)                        |                       |                 |                         |                             |  |  |
| Total (95% CI)  |                                     |  | 62                           |                       |                 | 61                      | 100.0%                      | -0.71 [-1.44, 0.02]                        | ▲  |
| Heterogeneity: Tau² =<br>Test for overall effect:<br>Test for subgroup difl | : 0.26; Ch<br>Z = 1.91<br>ferences: | ii <sup>2</sup> = 5.<br>(P = 0<br>Chi <sup>2</sup> : | .60, df=<br>1.06)<br>= 0.50, | = 2 (P =<br>df = 1 (F | 0.06)<br>P = 0. | (; l² = 64<br>48), l² = | 4%<br>= 0%                  |  | -10 -5 0 5 10<br>Favours acupuncture Favours control |

### eFigure 36: Subgroup Sensitivity Analysis Comparing Studies by Type of Control

|                                   | Inte                | Intervention        |                  |            | ontrol  |                        |        | Mean Difference            |                             |
|-----------------------------------|---------------------|---------------------|------------------|------------|---------|------------------------|--------|----------------------------|-----------------------------|
| Study or Subgroup                 | Mean                | SD                  | Total            | Mean       | SD      | Total                  | Weight | IV, Random, 95% CI         | IV, Random, 95% CI          |
| 16.23.1 CPM vs Std o              | are                 |                     |                  |            |         |                        |        |                            |                             |
| Bennet 2005                       | 3.6                 | 3                   | 47               | 3.1        | 2.9     | 52                     | 9.6%   | 0.50 [-0.66, 1.66]         | - <b>+</b> •                |
| Bennet 2005                       | 2.6                 | 2.9                 | 48               | 3.1        | 2.9     | 52                     | 9.9%   | -0.50 [-1.64, 0.64]        |                             |
| Lenssen 2008                      | 2.6                 | 1.8                 | 20               | 4.7        | 2.6     | 19                     | 7.2%   | -2.10 [-3.51, -0.69]       |                             |
| MacDonald 2000                    | 5.1                 | 1.3                 | 40               | 5.2        | 1.2     | 40                     | 21.6%  | -0.10 [-0.65, 0.45]        |                             |
| McInnes 1992                      | 2.8                 | 2.05                | 47               | 3.6        | 2.05    | 45                     | 14.6%  | -0.80 [-1.64, 0.04]        |                             |
| Sahin 2006                        | 3.85                | 1.29                | 14               | 3.5        | 1.34    | 14                     | 12.2%  | 0.35 [-0.62, 1.32]         |                             |
| Subtotal (95% CI)                 |                     |                     | 216              |            |         | 222                    | 75.1%  | -0.36 [-0.95, 0.24]        | ◆                           |
| Heterogeneity: Tau² =             | 0.30; C             | hi <sup>z</sup> = 1 | 1.76, d          | f = 5 (P : | = 0.04) | ); I <sup>z</sup> = 53 | 7%     |                            |                             |
| Test for overall effect:          | Z = 1.17            | ' (P = 0            | 0.24)            |            |         |                        |        |                            |                             |
| 16.23.2 CPM vs Exer               | cise                |                     |                  |            |         |                        |        |                            |                             |
| Bruun-Olsen 2009                  | 4                   | 2.3                 | 30               | 4          | 2.1     | 33                     | 10.5%  | 0.00 <b>[</b> -1.09, 1.09] | _ <b>_</b>                  |
| Montgomery 1996                   | 5                   | 2.5                 | 28               | 5          | 1.5     | 32                     | 10.9%  | 0.00 [-1.06, 1.06]         | <b>_</b>                    |
| Subtotal (95% CI)                 | -                   |                     | 58               | -          |         | 65                     | 21.4%  | 0.00 [-0.76, 0.76]         | ◆                           |
| Heterogeneity: Tau <sup>2</sup> = | 0.00; C             | hi² = 0             | .00. df=         | = 1 (P =   | 1.00);  | $ ^{2} = 0\%$          |        |                            |                             |
| Test for overall effect:          | Z = 0.00            | ) (P = 1            | 1.00)            |            |         |                        |        |                            |                             |
| 16.23.3 CPM vs LLM                | B AND S             | td car              | e                |            |         |                        |        |                            |                             |
| May 1999                          | 15                  | 1.6                 | - 7              | 21         | 24      | 7                      | 3.6%   | -0.60[-2.74, 1.54]         |                             |
| Subtotal (95% CI)                 | 1.0                 | 1.0                 | 7                | 2.1        | 2.1     | 7                      | 3.6%   | -0.60 [-2.74, 1.54]        |                             |
| Heterogeneity: Not ar             | nlicable            |                     |                  |            |         |                        |        |                            |                             |
| Test for overall effect:          | Z = 0.55            | 5 (P = 0            | 0.58)            |            |         |                        |        |                            |                             |
| Total (95% CI)                    |                     |                     | 281              |            |         | 294                    | 100.0% | -0.27 [-0.70, 0.16]        | •                           |
| Heterogeneity: Tau <sup>2</sup> = | 0.14:0              | hi <b></b> z = 1    | 2 30 d           | f = 8 (P : | = 0.14  | ): IZ = 3/             | 596    |                            |                             |
| Tect for overall effect:          | 7 = 1.24            | – 1<br>L (P = 0     | 2.00, u<br>1.21) |            | - 0.14  | /, i = 3.              | 5,0    |                            | -4 -2 0 2 4                 |
| Teet for eubaroun diff            | 2 - 1.29<br>oroncoc | r (i — U<br>⊴ Chi≩- | -064             | df = 2/0   | 9 – N 7 | 2) 12-                 | n%     |                            | Favours CPM Favours control |
| reactor aupproup un               | cicilles            |                     | - 0.04,          | ui – 2 (i  | - 0.7   | 57.1 -                 | 0.0    |                            |                             |

### eFigure 37: Subgroup Sensitivity Analysis Comparing Studies by Type of Control

|                                       | Inter     | venti           | on                    | С         | ontrol  |                      |                             | Mean Difference                                 | Mean Difference              |
|---------------------------------------|-----------|-----------------|-----------------------|-----------|---------|----------------------|-----------------------------|---|------------------------------|
| Study or Subgroup                     | Mean      | SD              | Total                 | Mean      | SD      | Total                | Weight                      | IV, Random, 95% CI                              | IV, Random, 95% CI           |
| 16.25.1 CPM+Act exe                   | ercise vs | s Stan          | dard T                | reat      |         |                      |                             |   |                              |
| Bruun-Olsen 2009<br>Subtotal (95% CI) | 2.9       | 2.2             | 30<br><mark>30</mark> | 1.9       | 1.5     | 33<br><b>33</b>      | 39.5%<br><b>39.5%</b>       | 1.00 [0.06, 1.94]<br><b>1.00 [0.06, 1.94]</b>   | •                            |
| Heterogeneity: Not ap                 | plicable  |                 |                       |           |         |                      |                             |   |                              |
| Test for overall effect:              | Z = 2.09  | (P = (          | 0.04)                 |           |         |                      |                             |   |                              |
| 16.25.2 Aggressive (                  | CPM vs S  | td tre          | at                    |           |         |                      |                             |   |                              |
| Chen 2013<br>Subtotal (95% CI)        | 3.22      | 1.28            | 68<br><mark>68</mark> | 3.05      | 1.54    | 39<br><b>39</b>      | 60.5%<br><mark>60.5%</mark> | 0.17 [-0.40, 0.74]<br><b>0.17 [-0.40, 0.74]</b> | <b>‡</b>                     |
| Heterogeneity: Not ap                 | plicable  |                 |                       |           |         |                      |                             |   |                              |
| Test for overall effect:              | Z = 0.58  | (P = (          | ).56)                 |           |         |                      |                             |   |                              |
| Total (95% CI)                        |           |                 | 98                    |           |         | 72                   | 100.0%                      | 0.50 [-0.30, 1.29]                              | •                            |
| Heterogeneity: Tau <sup>2</sup> =     | 0.19; Cł  | ni <b>≈</b> = 2 | .19, df :             | = 1 (P =  | 0.14);  | l <sup>2</sup> = 54  | %                           | _   |                              |
| Test for overall effect:              | Z = 1.23  | (P = (          | ).22)                 | •         |         |                      |                             |   | -4 -2 U 2 4                  |
| Test for subgroup diff                | erences:  | Chi²            | = 2.19,               | df = 1 (i | P = 0.1 | 4), l <sup>2</sup> = | 54.4%                       |   | Favours CFIM Favours control |

### eFigure 38: Subgroup Sensitivity Analysis Comparing Studies by Type of Control

|                                   | Inter     | venti         | on                    | Co   | ontro | 1                     |                             | Mean Difference                                    | Mean Difference    |
|-----------------------------------|-----------|---------------|-----------------------|--|-------|-----------------------|-----------------------------|--|--------------------|
| Study or Subgroup                 | Mean      | SD            | Total                 | Mean                                       | SD    | Total                 | Weight                      | IV, Random, 95% CI                                 | IV, Random, 95% CI |
| 16.22.1 CPM-new vs                | CPM-sta   | indar         | d                     |  |       |                       |                             |  |                    |
| Kim 2009<br>Subtotal (95% CI)     | 3.5       | 3.6           | 50<br><mark>50</mark> | 3.6  | 3.5   | 50<br><mark>50</mark> | 52.9%<br><mark>52.9%</mark> | -0.10 [-1.49, 1.29]<br>- <b>0.10 [-1.49, 1.29]</b> |                    |
| Heterogeneity: Not ap             | plicable  |               |                       |  |       |                       |                             |  |                    |
| Test for overall effect:          | Z = 0.14  | (P = 1        | 0.89)                 |  |       |                       |                             |  |                    |
| 16.22.2 CPM vs Std r              | ehabilata | ation         | progra                | mme  |       |                       |                             |  |                    |
| Beaupre 2001<br>Subtotal (95% CI) | 15.2      | 3             | 34<br><b>34</b>       | 15.8                                       | 3.2   | 34<br><b>34</b>       | 47.1%<br><b>47.1%</b>       | -0.60 [-2.07, 0.87]<br>- <b>0.60 [-2.07, 0.87]</b> | -                  |
| Heterogeneity: Not ap             | plicable  |               |                       |  |       |                       |                             |  |                    |
| Test for overall effect:          | Z = 0.80  | (P = 1        | 0.43)                 |  |       |                       |                             |  |                    |
| Total (95% CI)                    |           |               | 84                    |  |       | 84                    | 100.0%                      | -0.34 [-1.35, 0.68]                                | •                  |
| Heterogeneity: Tau <sup>2</sup> = | 0.00; Ch  | ni² = 0       | .23, df:              | = 1 (P =                                   | 0.63  | ); I <sup>2</sup> = 0 | %                           |  |                    |
| Test for overall effect:          | Z= 0.65   | (P = 1        |                       | -4 -2 U 2 4<br>Equatra CPM Equatra control |       |                       |                             |  |                    |
| Test for subgroup diff            | erences:  | Chi <b></b> ≇ |                       | Favours CFIM Favours control               |       |                       |                             |  |                    |

**eFigure 39**: Subgroup Sensitivity Analysis Comparing Studies by Time (Studies Divided If Published Prior or Comprising Year 2000 or From 2001 Onwards)

|  | Intervention   |            |         | Control   |          |                   |        | Mean Difference      | Mean Difference                      |  |  |  |
|--|--|------------|---------|-----------|----------|-------------------|--------|----------------------|--------------------------------------|--|--|--|
| Study or Subgroup  | Mean   | SD         | Total   | Mean      | SD       | Total             | Weight | IV, Random, 95% CI   | IV, Random, 95% Cl                   |  |  |  |
| 16.15.1 >2000  |  |            |         |           |          |                   |        |                      |                                      |  |  |  |
| Gibbons 2001   | 0.65   | 0.31       | 30      | 0.6       | 0.31     | 30                | 14.1%  | 0.05 [-0.11, 0.21]   |                                      |  |  |  |
| Kullenberg 2006  | 0.37   | 0.11       | 43      | 0.43      | 0.05     | 40                | 17.9%  | -0.06 [-0.10, -0.02] | •                                    |  |  |  |
| Smith 2002   | 0.35   | 0.29       | 44      | 0.47      | 0.31     | 40                | 15.2%  | -0.12 [-0.25, 0.01]  |                                      |  |  |  |
| Thienpont 2014   | 0.792  | 0.563      | 50      | 0.802     | 0.542    | 50                | 11.7%  | -0.01 [-0.23, 0.21]  |                                      |  |  |  |
| Subtotal (95% CI)  |  |            | 167     |           |          | 160               | 58.8%  | -0.06 [-0.09, -0.02] | •                                    |  |  |  |
| Heterogeneity: Tau² =  | Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.91, df = 3 (P = 0.41); i <sup>2</sup> = 0%    |            |         |           |          |                   |        |                      |                                      |  |  |  |
| Test for overall effect:   | Z = 3.36   | i (P = 0.1 | 0008)   |           |          |                   |        |                      |                                      |  |  |  |
|  |  |            |         |           |          |                   |        |                      |                                      |  |  |  |
| 16.15.2 <=2000   |  |            |         |           |          |                   |        |                      |                                      |  |  |  |
| Levy 1993  | 0.53   | 0.2        | 40      | 0.96      | 0.3      | 40                | 15.8%  | -0.43 [-0.54, -0.32] |                                      |  |  |  |
| Walker 1991  | 0.65   | 0.17       | 15      | 0.83      | 0.4      | 15                | 11.5%  | -0.18 [-0.40, 0.04]  |                                      |  |  |  |
| Webb 1998  | 0.57   | 0.23       | 15      | 0.71      | 0.23     | 16                | 13.8%  | -0.14 [-0.30, 0.02]  |                                      |  |  |  |
| Subtotal (95% CI)  |  |            | 70      |           |          | 71                | 41.2%  | -0.26 [-0.47, -0.05] | •                                    |  |  |  |
| Heterogeneity: Tau² =  | Heterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup> = 10.00, df = 2 (P = 0.007); i <sup>2</sup> = 80% |            |         |           |          |                   |        |                      |                                      |  |  |  |
| Test for overall effect:   | Z= 2.47  | ' (P = 0.) | 01)     |           |          |                   |        |                      |                                      |  |  |  |
|  |  |            |         |           |          |                   |        |                      |                                      |  |  |  |
| Total (95% CI) 237 231 10  |  |            |         |           |          |                   | 100.0% | -0.13 [-0.25, -0.01] | $\bullet$                            |  |  |  |
| Heterogeneity: Tau <sup>z</sup> = 0.02; Chi <sup>z</sup> = 42.96, df = 6 (P < 0.00001); I <sup>z</sup> = 86% |  |            |         |           |          |                   |        |                      |                                      |  |  |  |
| Test for overall effect: Z = 2.09 (P = 0.04)   |  |            |         |           |          |                   |        |                      |                                      |  |  |  |
| Test for subgroup diff   | erences  | : Chi² =   | 3.60, d | lf = 1 (P | = 0.06), | . <b>I</b> ² = 72 | .2%    |                      | , areas algenterapy i arouro control |  |  |  |

**eFigure 40**: Subgroup Sensitivity Analysis Comparing Studies by Time (Studies Divided If Published Prior or Comprising Year 2000 or From 2001 Onwards)

|   | Intervention |                    |                 | Control  |        |                 |                       | Mean Difference                                      | Mean Difference                        |
|---|--------------|--------------------|-----------------|----------|--------|-----------------|-----------------------|--|--|
| Study or Subgroup                             | Mean         | SD                 | Total           | Mean     | SD     | Total           | Weight                | IV, Random, 95% CI                                   | IV, Random, 95% CI                     |
| 16.16.1 >2000                                 |              |                    |                 |          |        |                 |                       |  |  |
| Borckardt 2013<br>Subtotal (95% CI)           | 6.3          | 5.6                | 20<br><b>20</b> | 12.3     | 6.6    | 19<br><b>19</b> | 32.3%<br><b>32.3%</b> | -6.00 [-9.85, -2.15]<br>- <b>6.00 [-9.85, -2.15]</b> | <b></b>                                |
| Heterogeneity: Not ap                         | plicable     |                    |                 |          |        |                 |                       |  |  |
| Test for overall effect:                      | Z = 3.05     | (P = 0             | .002)           |          |        |                 |                       |  |  |
| 16.16.2 <=2000                                |              |                    |                 |          |        |                 |                       |  |  |
| Walker 1991                                   | 6.6          | 5.7                | 18              | 8.7      | 5      | 12              | 32.1%                 | -2.10 [-5.96, 1.76]                                  |  |
| Walker 1991                                   | 6.2          | 4.9                | 18              | 8.7      | 5      | 12              | 35.7%                 | -2.50 [-6.12, 1.12]                                  |  |
| Subtotal (95% CI)                             |              |                    | 36              |          |        | 24              | 67.7%                 | -2.31 [-4.96, 0.33]                                  | ◆                                      |
| Heterogeneity: Tau <sup>2</sup> =             | 0.00; Cł     | ni <b>=</b> 0.     | 02, df:         | = 1 (P = | 0.88)  | ; I² = 0        | %                     |  |  |
| Test for overall effect:                      | Z=1.72       | (P = 0             | 1.09)           |          |        |                 |                       |  |  |
| Total (95% CI)                                |              |                    | 56              |          |        | 43              | 100.0%                | -3.50 [-5.90, -1.10]                                 | •                                      |
| Heterogeneity: Tau <sup>2</sup> =             | 0.77; Cł     | ni² = 2.           | 42, df:         | = 2 (P = | 0.30)  | ; l² = 1        | 7%                    |  |  |
| Test for overall effect: Z = 2.86 (P = 0.004) |              |                    |                 |          |        |                 |                       |  | -20 -10 0 10 20                        |
| Test for subgroup diff                        | erences:     | Chi <sup>2</sup> : | = 2.39,         | df = 1 ( | P = 0. | 12), P          | = 58.2%               |  | Tavours electronierapy Tavours control |

**eFigure 41**: Results of the Meta-regression for the Distribution of Age in the Groups (Treatment vs Control)

. metareg AGE Group, wsse ( SD) Meta-regression Number of obs = 28 tau2 = .6622 REML estimate of between-study variance % residual variation due to heterogeneity I-squared\_res = 0.00% Proportion of between-study variance explained Adj R-squared = 53.35% With Knapp-Hartung modification AGE Coef. Std. Err. t P>|t| [95% Conf. Interval] -4.86628 -1.365645 1.703033 -0.80 0.430 2.134991 Group

57.70

0.000

66.28128

71.17813

**eFigure 42**: Results of the Meta-regression for the Distribution of Sex in the Groups (Treatment vs Control)

68.7297 1.19114

. metareg SEX Group1, wsse ( SD1)

\_cons

| Meta-regressio | on            | Number of obs | =        | 57     |               |    |         |
|----------------|---------------|---------------|----------|--------|---------------|----|---------|
| REML estimate  | of between-s  | tau2          | =        | 213.6  |               |    |         |
| % residual var | riation due t | I-squared_res | =        | 95.96% |               |    |         |
| Proportion of  | between-stud  | y variance e  | xplained |        | Adj R-squared | =  | -1.26%  |
| With Knapp-Har | tung modific  | ation         |          |        |               |    |         |
| SEX            | Coef.         | Std. Err.     | t        | P> t   | [95% Conf.    | In | terval] |
| Group1<br>cons | 2.310076      | 4.002792      | 0.58     | 0.566  | -5.711698     | 1  | 0.33185 |