Skeletal muscle training for spinal muscular atrophy type 3 (Protocol)

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Skeletal muscle training for spinal muscular atrophy type 3

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of skeletal muscle training on functional performance in people with spinal muscular atrophy (SMA) type 3 and to identify any adverse effects.

BACKGROUND

Description of the condition

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disease caused by a genetic mutation in the survival motor neuron 1 (SMN1) gene (5q11.2-q13.3) (Lefebvre 1995). With an incidence of one in 10,000 live births, it is the leading genetic cause of infant death (Lunn 2008; Mercuri 2012). SMA is characterized by degeneration of spinal cord α-motor neurons, which results in progressive proximal muscle weakness, fatigue, scoliosis, nutritional problems, respiratory complications, and severe functional limitations. SMA has a broad clinical spectrum but in general can be classified into four clinical types on the basis of age of onset and maximum motor function achieved (Mercuri 2012). SMA type 3 (Kugelberg-Welander disease) is the mildest subtype but shows large clinical heterogeneity, which can be further classified into type 3a (clinical symptoms before three years of age) and type 3b (clinical symptoms after three years of age) (Zerres 1997). Symptoms become evident after the age of 18 months. Children generally reach all major milestones, including independent walking, but their level of motor performance varies greatly. Some children are hardly able to stand up and take a few steps unaided, while others walk well, are able to climb stairs, and mainly experience problems in running and sports (Rudnik-Schöneborn 2001). Long-term follow-up studies (follow-up time of two to 20 years) in people with SMA type 2 and type 3 suggest a very slow deterioration of muscle strength and motor function that takes years to detect (Deymeer 2008; Kaufmann 2012; Werlauff 2012). Nevertheless, about 50% of people with SMA type 3 will lose independent ambulation during the second decade of life and only a small subgroup will remain ambulatory throughout life (Mercuri 2012; Russman 1996). In general people with SMA type 3b perform better on functional outcome measures, such as the six-minute walk test and the Hammersmith Functional Motor Scale Expanded, in comparison to people with SMA type 3a (Mazzone 2013; Montes
Description of the intervention

The intervention under consideration is skeletal muscle training for children and adults with SMA type 3. Training methods include strength and aerobic exercise training of skeletal muscles, but not respiratory muscle training. Types of exercise could be, for example, cycling on an ergometer, running on a treadmill, and lifting weights. The skeletal muscle training should aim to increase a person’s functional performance, muscle strength, cardiopulmonary exercise capacity, and quality of life, and reduce their levels of fatigue. This should be achieved without serious adverse events such as fatigue, pain, or significant increases in levels of biological markers for muscle damage. Among possible comparison interventions are placebo, and standard or usual care. The training can be given as monotherapy or in addition to usual practice and be executed in any setting or location, either individually or within a group.

How the intervention might work

The loss of α-motor neurons in the spinal cord leads to denervation of skeletal muscles, atrophy, and muscle weakness. Functional performance, especially level of ambulation, deteriorates in most people with SMA type 3, which may lead to inactivity and deconditioning. The slow progression of the disease, the relatively preserved residual strength, and a sedentary lifestyle make people with SMA type 3 a promising target population for physical training programs. Training may improve functional performance, muscle strength, and exercise capacity by optimizing resources in available muscle tissue or remaining metabolic function and counteracting further muscle deterioration that occurs secondary to inactivity. The effect will be likely to be dependent on the type of training. Strengthening training may increase muscle strength and, as a secondary effect, also improve functional performance of anti-gravity activities such as standing up, jumping, and stair climbing. Aerobic exercise training will enhance exercise capacity and also improve walking distance and endurance. Exercise might also have a neuroprotective effect, which could be explained by a relationship between the maturation state of the motor unit and resistance to neuronal cell death. Preclinical studies in SMA mouse models report positive effects of exercise on postnatal maturation of motor units, delayed motor neuron death, improved motor function, and survival (Biondi 2008; Grondard 2005). Biondi 2008 performed a progressive running wheel training program in SMA type 2 like mice and showed an exercise-induced acceleration of the motor-unit maturation on the level of the motor neuron, neuromuscular junction, and muscle fiber, and a delay in motor neuron death. In addition, Grondard 2005 reported a positive effect of exercise on muscle performance and physical activity measured respectively with a forelimb grip strength-/endurance test and an open-field ambulatory behavior test.

Why it is important to do this review

Skeletal muscle training has emerged as a potential intervention for people with inherited neuromuscular disorders for which no treatment is as yet available, including people with SMA. Skeletal muscle training may partly counteract disease progression and secondary deconditioning by improvement of a person’s functional performance (Voet 2013). For physically stronger people with SMA type 3b, physical training is a potentially easily accessible and affordable intervention, which could be provided through exercise groups or personal trainers working together with health practitioners. Other patients are more vulnerable to injury, have significant difficulty with transfers, uneven surfaces, and stairs, and therefore require specialized supervision. At a time when proposals exist for potential disease-modifying compounds aimed at splicing of the SMN2 gene and other compounds that directly target skeletal muscle, understanding the effects of conservative treatments is essential. There is currently no evidence available on skeletal muscle training in people with SMA type 3. The potential for combination therapies will be best exploited if we first understand the role of exercise therapy alone.

OBJECTIVES

To assess the effects of skeletal muscle training on functional performance in people with spinal muscular atrophy (SMA) type 3 and to identify any adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) and quasi-RCTs. Quasi-RCTs are studies that use a quasi-random method to allocate participants to groups, such as by alternation, date of birth, or case record number (Higgins 2011). In the ‘Discussion’ section of the Cochrane review we will describe any relevant cross-over studies, case control studies, multi- and single-case reports that fulfill the same standards regarding diagnostic criteria, description of intervention, and outcome measures.
as any RCTs that meet the inclusion criteria, but we will exclude them from the ‘Results’ section.
We will include trials that are reported as full-text articles, those published as abstracts only, and unpublished data. There will be no restrictions regarding language of publication.

**Types of participants**
People, from the age of five years old with a diagnosis of spinal muscular atrophy (SMA) type 3 (Kugelberg-Welander) who fulfill the clinical criteria and have a deletion or mutation of the survival motor neuron 1 (SMN1) gene (5q11.2-13.2) that is confirmed by genetic analysis (Wadman 2012). We will include studies of mixed populations e.g. studies that include mixed neuromuscular diseases or mixed SMA types and present data for people with SMA 3 separately).

**Types of interventions**
We will include trials that use any form of physical exercise training of skeletal muscles, including aerobic exercise and strength training, carried out for a training period of at least 12 weeks, compared with placebo, standard or usual care, or another type of non-physical intervention. Regarding co-interventions, we will only include trials that provide co-interventions to each group equally. We will exclude studies of respiratory muscle training or a non-exercised limb as a control. We will include trials that use training programs that are standardized on frequency, intensity, time, and type and use an incremental exercise protocol.

**Definitions**
- Physical exercise training or physical fitness training: “a planned, structured regimen of regular physical exercise deliberately performed to improve physical fitness. The ability to carry out daily tasks with vigor and alertness, without undue fatigue and with ample energy to enjoy [leisure] pursuits and to meet unforeseen emergencies”. Physical fitness is operationalized as “a set of measurable health and skill-related attributes” that include cardiorespiratory fitness, muscular strength and endurance, body composition and flexibility, balance, agility, reaction time, and power (Caspersen 1985; Garber 2011).
- Strength training: training performed primarily to improve muscle strength and endurance. It is typically performed by making repeated muscle contractions against resistance (Saunders 2004).
- Aerobic exercise training, or cardiorespiratory fitness training: training that consists of an activity or combination of activities that uses large muscle groups, that can be maintained continuously, for example walking-hiking, running-jogging, cycling-bicycling, or swimming (Pollock 1998).

**Types of outcome measures**
People with SMA type 3 demonstrate a reduced level of motor function, which slowly declines over time and may lead to the loss of ambulatory function. Functional performance scores, related to ambulatory function, seem therefore to be important primary outcomes measures. Muscle strength and aerobic capacity are possible determinants of motor function and functional capacity and can be influenced by skeletal exercise training. Improvement in physical fitness may secondarily result in less fatigue, higher levels of physical activity, and a better quality of life. The outcomes listed here are not eligibility criteria for this Cochrane review, but are outcomes of interest within the included trials.

Included trials must report outcomes and adverse effects at baseline and at training termination. When available, we will report additional measurements taken during the training program and after training termination.

**Primary outcomes**
When available, we will also report data on longer term outcomes.

**Aerobic exercise training**
- Change (standardized mean difference (SMD) 0.40 to 0.70) in walking distance on the validated six minute walk test from baseline to 12 weeks (Montes 2010). The six minute walk test remains stable over a one year period Mazzone 2013. Over a time period of 12 weeks, a positive effect of training should therefore be reflected by an increase in six minute walking distance. When available, we will also report data on longer term outcome.

**Strength training**
- Change (SMD 0.40 to 0.70) on validated functional performance scores, including the Hammersmith Functional Motor Scale Expanded (HFMSE) (Kauffmann 2012), Motor Function Measure (MFM) (Vuillerot 2013), and timed tests (10 meter walk/run test, Gowers time, Timed Up and Go Test (TUG)) (Dunaway 2014), from baseline to 12 weeks. Functional performance scores are lower in patients with SMA type 3 but decline only slowly over time (Kauffmann 2012; Mazzone 2013). Over a time period of 12 weeks, a positive effect of training should therefore be reflected by an increase in functional performance scores. We will convert scores on the HMFSE and MFM tests to percentage score or Z-scores and pool them.

**Secondary outcomes**
When available, we will also report data on longer term outcomes.
Aerobic exercise training
- Change (SMD 0.40 to 0.70) in cardiopulmonary exercise capacity measured with validated cycle ergometry (watts, mL/min) or treadmill testing (mL/min, time to limitation) from baseline to at least 12 weeks. We will convert scores on cycle ergometry and treadmill testing to percentage scores or Z-scores and pool them. Change in cardiopulmonary exercise capacity (secondary outcome 3) is specific to studies on aerobic and anaerobic exercise.

Strength training
- Change (SMD 0.40 to 0.70) in muscle strength, including maximal isometric and isokinetic voluntary contraction measured with validated dynamometry (Newton/N*m) and validated Manual Muscle Testing (MMT; ordinal scale) from baseline to at least 12 weeks. We will report scores on dynamometry and MMT separately. Change in muscle strength is specific to studies on strengthening training.

Aerobic exercise and strength training
- Change in scores (SMD of less than 0.40) on fatigue questionnaires such as the Fatigue Severity Scale and the Pediatric Quality of Life Inventory Multi Dimensional Fatigue Score (PedsQLMFS) from baseline to at least 12 weeks. We will convert scores on the different questionnaires to percentage scores or Z-scores and pool them.
- Change in level of physical activities on questionnaires (ordinal scale) or accelerometry (counts) from baseline to at least 12 weeks. We will report the total scores on questionnaires and accelerometry separately.
- Change in quality of life-questionnaires such as the Short Form 36 Health Survey (SF-36) and PedsQL Neuromuscular Module from baseline to at least 12 weeks. We will convert scores on the different questionnaires to percentages or Z-scores and pool them.
- Serious adverse events that lead to a cessation of the trial, such as debilitating fatigue, medical treatment, and hospitalization.

Search methods for identification of studies

Electronic searches
We will search for trials in the Cochrane Neuromuscular Specialized Register, which is maintained by the Trials Search Co-ordinator for Cochrane Neuromuscular. The Trials Search Co-ordinator will also check the Cochrane Central Register of Controlled Trials (CENTRAL) (current issue in the Cochrane Library), MEDLINE (January 1966 to current), EMBASE (January 1980 to current), CINAHL Plus (January 1937 to current), AMED (January 1985 to current), and LILACS (January 1982 to current). We will adapt the draft MEDLINE strategy in Appendix 1 to search the other databases.

We will also search the US National Institutes for Health Clinical Trials Registry (www.ClinicalTrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Portal (ICTRP) (apps.who.int/trialsearch). We will check the NHS Economic Evaluation Database (NHSEED) for economic evaluations. We will search the Database of Abstracts of Reviews of Effects (DARE) to provide information of relevance to the ‘Discussion’ section of the review. We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources
We will search reference lists of all included trials and review articles for additional references. We will search for errata or retraction of included trials.

Data collection and analysis

Selection of studies
Two review authors (BB and JM) will independently screen titles and abstracts of all potential studies we identify as a result of the literature searches and code them as either ‘retrieve’ (eligible or potentially eligible/unclear) or ‘do not retrieve’. We will retrieve the full-text study reports and publications of articles coded as ‘retrieve’. Two review authors (BB and JM) will independently screen the full-text articles and identify trials for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreements through discussion or, if required, we will consult a third review author (JdG). We will identify and exclude duplicates, and collate multiple reports of the same trial so that each trial rather than each report is the unit of interest in the Cochrane review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and a ‘Characteristics of excluded studies’ table.

Data extraction and management
We will use a data extraction form that we will initially pilot on at least one trial included in the review to collect study characteristics and outcome data. One review author (BB) will extract study characteristics from included trials. We will extract the following study characteristics.

1. Methods: study design, total duration of study, details of any ‘run in’ period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline characteristics, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (BB and JM) will independently extract outcome data from included trials. We will note in the 'Characteristics of included studies' table if the trials did not report outcome data in a usable way. We will resolve any disagreements by consensus or consult a third review author (JdG). One review author (BB) will transfer data into Review Manager (RevMan) (RevMan 2014). A second review author (JM) will check the outcome data entries. The same review author (JM) will spot-check study characteristics for accuracy against the trial report. When reports require translation, the translator will extract data directly using a data extraction form, or we will extract data from the translation provided. Where possible, a review author will check numerical data in the translation against the study report. To minimize bias in the review process, the review authors will not screen studies for inclusion, extract data, or assess the risk of bias in trials they are authors of. In such circumstances, we will involve a third review author (JdG).

**Assessment of risk of bias in included studies**

Two review authors (BB and JM) will independently perform 'Risk of bias' assessments for each included trial using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will resolve any disagreements by discussion or will involve a third review author (JdG). We will divide the 'Risk of bias' assessment for blinding into bias for subjective outcomes (questionnaires, visual analogue scales) and objective outcomes (physiological outcomes). We will assess the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We will grade each potential source of bias as either high, low, or unclear and provide a quote from the study report together with a justification for our judgment in the 'Risk of bias' table. We will summarize the 'Risk of bias' judgements across included trials for each of the listed domains. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trial author, we will note this in the 'Risk of bias' table. When considering treatment effects, we will take into account the risk of bias in the trials that contribute to that outcome.

**Assessment of bias in conducting the systematic review**

We will conduct the Cochrane review according to this published protocol. We will report any deviations from it in the 'Differences between protocol and review' section of the Cochrane review.

**Measures of treatment effect**

We will analyze dichotomous data as risk ratios and continuous data as mean difference, or as standardised mean difference for results across studies with outcomes that are conceptually the same but measured in different ways. We will enter data presented as a scale with a consistent direction of effect. We will undertake meta-analyses only where this is meaningful, that is if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense. We will narratively describe skewed data reported as medians and interquartile ranges.

**Unit of analysis issues**

Where multiple trial arms are reported in a single trial, we will include only the eligible arms. If two eligible comparisons (e.g. drug A versus placebo and drug B versus the same placebo group) are combined in the same meta-analysis, we will avoid double-counting by creating a single pair-wise comparison as recommended in the Cochrane Handbook for Systematic Reviews of Interventions, or alternatively, halve the control group (Higgins 2011).

**Dealing with missing data**

We will contact trial authors or trial sponsors to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a trial is available as an abstract only or when SMA subgroup data are not reported separately). Where this is not possible, and we consider the missing data to have introduced serious bias, we will explore the impact of inclusion of such trials in the overall assessment of results by a sensitivity analysis.

**Assessment of heterogeneity**

We will consider the clinical heterogeneity of trials when we decide whether to pool data or not. We will use the I² statistic to measure heterogeneity among the trials in each analysis (Higgins 2003).
If we identify substantial unexplained heterogeneity (e.g. over 50%), we will report it and explore possible causes by prespecified subgroup analysis.

**Assessment of reporting biases**

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study biases.

**Data synthesis**

We expect heterogeneity among trials and we will use a random-effects model. We will perform a sensitivity analysis with a fixed-effect model.

If the review includes more than one comparison that cannot be included in the same analysis, we will report the results for each comparison separately.

**'Summary of findings' tables**

We will create separate 'Summary of findings' tables for aerobic exercise training and strength training using the following outcomes.

**Aerobic exercise training**

**Primary outcome**

1. Six minute walk test; SMD six minute walking distance.

**Secondary outcomes**

1. Cardiopulmonary exercise capacity: SMD peak oxygen uptake, SMD peak work load.
2. Fatigue: SMD sum score fatigue questionnaire.
3. Physical activity: SMD sum score Physical Activity (PA) questionnaire or SMD sum score counts accelerometry.
4. Quality of life: SMD sum score Quality of Life (QoL) questionnaire.
5. Number of serious adverse events: SMD sum score number events.

**Strength training**

**Primary outcome**

1. Functional performance scores: SMD pooled data for HFMSE, MFM, and timed tests.

**Secondary outcomes**

1. Muscle strength: SMD Newton, SDM MRC sum score.
2. Fatigue: SMD sum score fatigue questionnaire.
3. Physical activity: SMD sum score PA questionnaire or SMD sum score counts accelerometry.
4. Quality of life: SMD sum score QoL questionnaire.
5. Number of serious adverse events: SMD sum score number events.

We will use the five Grading of Recommendations Assessment, Development and Evaluation (GRADE) considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence (studies that contribute data for the prespecified outcomes). We will use methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and construct 'Summary of findings' tables with GRADEpro Guideline Development Tool (GDT) software ([http://gradepro.org/](http://gradepro.org/)). We will use footnotes to justify our decisions to downgrade or upgrade the quality of the evidence, and we will comment where necessary to aid reader’s understanding of the Cochrane review.

**Subgroup analysis and investigation of heterogeneity**

We plan to perform the following subgroup analyses.

1. SMA type 3a.
2. SMA type 3b.
3. Children.
4. Adults.

We will use both primary and secondary outcome measures in all subgroup analyses.

We will use the formal test for subgroup interactions in RevMan (RevMan 2014).

**Sensitivity analysis**

We plan to undertake the following sensitivity analyses.

1. Repeat the analysis by excluding unpublished studies (if there are any).
2. Repeat the analysis by excluding studies at high risk of bias (sequence generation, allocation concealment, blinding of personnel, and outcome assessment).
3. If there are one or more very large trials, we will repeat the analysis by excluding these large trials to examine how much they dominate the results.

**Reaching conclusions**

We will base our review conclusions only on findings from the quantitative or narrative synthesis of included trials. We will avoid making recommendations for practice. Our implications for research will suggest priorities for future research and outline the remaining uncertainties in the area.
ACKNOWLEDGEMENTS

The National Institute for Health Research via Cochrane Infrastructure funding to Cochrane Neuromuscular supported this Cochrane review. The views and opinions expressed therein are those of the protocol authors and do not necessarily reflect those of the Systematic Reviews Programme, the NIHR, the NHS or the UK Department of Health. Cochrane Neuromuscular is also supported by the MRC Centre for Neuromuscular Disease.

We based the Methods section of this Cochrane protocol on a template developed by Cochrane Neuromuscular from an original created by the Cochrane Airways Group.

The Trials Search Co-ordinator of Cochrane Neuromuscular, Angela Gunn, developed the search strategy in consultation with the protocol authors.

REFERENCES

Additional references

Biondi 2008

Caspersen 1985

Deymeer 2008

Dunaway 2014

Garber 2011

Grondard 2005

Higgins 2003

Higgins 2011

Kaufmann 2012

Lefebvre 1995

Lunn 2008

Mazzone 2013

Mercuri 2012

Montes 2010
Montes J, McDermott MP, Martens WB, Dunaway S, Glanzman AM, Riley S, et al. Six-Minute Walk Test

NCT01166022

Pollock 1998

RevMan 2014 [Computer program]

Rudnik-Schöneborn 2001

Russman 1996

Saunders 2004
Saunders PU, Pyne DB, Telford RD, Hawley JA. Factors affecting running economy in trained distance runners.


Voet 2013

Vuillerot 2013

Wadman 2012

Werlauff 2012

Zerres 1997

* Indicates the major publication for the study

APPEndices

Appendix 1. MEDLINE (OvidSP) draft search strategy

Database: Ovid MEDLINE(R) <1946 to January Week 3 2016>

Search Strategy:
--------------------------------------------------------------------------------
1 randomized controlled trial.pt. (403784)
2 controlled clinical trial.pt. (89947)
3 randomized.ab. (301115)
4 placebo.ab. (154240)
5 drug therapy.fs. (1811440)
6 randomly.ab. (213411)
7 trial.ab. (310057)
8 groups.ab. (1352939)
9 or/1-8 (343203)

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10 exp animals/ not humans.sh. (4175116)
11 9 not 10 (2922350)
12 exp Muscular Atrophy, Spinal/ (3786)
13 muscular disorders, atrophic/ (325)
14 spinal muscular atrophy$.mp. (3676)
15 (Kugelberg adj Welander).mp. (184)
16 or/12-15 (5266)
17 ((aerobic or endurance or physical or strength or strengthening) adj5 (exercise or program or programme or training)).mp. (50247)
18 ((aerobic or anaerobic) adj5 conditioning).mp. (269)
19 ((aquatic or functional or kinesio*) adj5 therapy).mp. (5412)
20 ((cardio or excessive or exercise or muscle or power) adj5 training).mp. (18974)
21 (exercise adj5 (program or programme or therap*)).mp. (38405)
22 ((home or therapeutic) adj5 (exercise*1 or program or programme)).mp. (9011)
23 ((isokinetic or isometric or muscle or resistance) adj5 strength training).mp. (639)
24 ((muscle or resistance or resistive) adj5 exercise).mp. (13760)
25 (cycle ergometer or cycling or exercising or hydrotherapy or running or sports or swimming or treadmill).mp. (180859)
26 (weight adj5 (training or lifting)).mp. (6165)
27 whole body vibration.mp. (1140)
28 (strengthen*3 adj5 therap*).mp. (546)
29 resistance training.mp. (6363)
30 exp exercise/ (134044)
31 exp physical therapy modalities/ (119251)
32 or/17-31 (402461)
33 11 and 16 and 32 (23)

CONTRIBUTIONS OF AUTHORS

Each of the protocol authors contributed to the design and development of this Cochrane protocol. B Bartels (BB) will write the first draft and the other co-authors will contribute to subsequent revisions.

DECLARATIONS OF INTEREST

J Montes (JM) is an investigator in the recently completed trial on the effect of exercise training in ambulatory patients with SMA (NCT01166022). The United States Department of Defense funded the trial. However, since the completion of the trial, JM does not receive funding for this particular study (NCT01166022) and has no other conflicts of interest.

BB has no known conflicts of interest.

WL van der Pol has no known conflicts of interest. He has obtained research grants from Prinses Beatrix Spierfonds and Stichting Spieren voor Spieren, both non-profit foundations.

JF de Groot has no known conflicts of interest.
SOURCES OF SUPPORT

Internal sources

• University Medical Center Utrecht, Netherlands.

External sources

• None, Other.