

GRONINGEN MANIPULATION STUDY. THE EFFECT OF MANIPULATION OF THE STRUCTURES OF THE SHOULDER GIRDLE AS ADDITIONAL TREATMENT FOR SYMPTOM RELIEF AND FOR PREVENTION OF CHRONICITY OR RECURRENCE OF SHOULDER SYMPTOMS. DESIGN OF A RANDOMIZED CONTROLLED TRIAL WITHIN A COMPREHENSIVE PROGNOSTIC COHORT STUDY

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ABSTRACT

Background: We present the design of the Groningen Manipulation Study. This randomized controlled trial is part of the Dutch Shoulder Disability Study, a comprehensive prognostic cohort study on shoulder disorders, with randomized controlled interventions in subcohorts.

Objective: To evaluate the effectiveness of manipulative treatment of the structures of the shoulder girdle, in addition to standard treatment by the general practitioner for relief of shoulder symptoms and prevention of persistent or recurrent shoulder symptoms.

Methods: A total of 250 patients with shoulder symptoms and a functional limitation of the shoulder girdle will be included from 30 general practices in Groningen, The Netherlands. All participating patients receive standard treatment by the general practitioner and will be randomly allocated to additional manipulative treatment. Evaluation measurements take place 6, 12, 26, and 52 weeks after randomization.

Conclusion: The short-term primary outcome measure is the proportion of patients with relief of shoulder complaints and the long-term primary outcome is the proportion of patients without persistent or recurrent shoulder symptoms. Dependent and independent variables include a structured medical history, a physical examination of the shoulder and shoulder girdle, and a measure of the mobility of the cervico-thoracic spine with a 6-degree-of-freedom electromagnetic tracking device. (J Manipulative Physiol Ther 2002;25:543-9)

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INTRODUCTION

Shoulder complaints are common. The annual incidence of shoulder complaints in Dutch General Practices is estimated at 10 to 25 per 1000 each year.^{1,2} Shoulder complaints are characterized by functional disability, which are caused mostly by pain in the deltoid region at rest and are aggravated by movement. In The Netherlands, shoulder complaints are usually treated in general practice according to the Guidelines for Shoulder Complaints of the Dutch College of General Practitioners (version 1999), which will be referred to as standard treatment in this paper.³ The standard treatment includes information, advice, and non-medication therapy; during the first 2 weeks, a wait-and-see-policy with information and advice about shoulder complaints, possibly supplemented with analgesics or nonsteroidal anti-inflammatory drugs, is followed. If the shoulder complaints decrease, this treatment can be continued for 1 to 2 weeks. If minor or no results are shown with this approach, up to 3 corticosteroid injections (in the subacromial space or glenohumeral joint) can be given. Physiotherapy is considered in persistent complaints after 6 weeks or more. There is convincing evidence of short-term beneficial effects of NSAIDs⁴ and injections with steroids.⁵ There is some evidence for active physical exercises.⁶ However, conclusive evidence is lacking because of unsatisfactory methodology.

In primary care, shoulder complaints have an unfavorable outcome. Only about 50% of all new episodes of shoulder complaints resolve within 6 months,^{7,8} and 40% of all patients still have disability in activities of daily living after 1 year.¹

Although promising results have been reported from a limited number of clinical studies,^{9,10} to date, the effect of manipulative treatment of the structures of the shoulder girdle in the treatment of shoulder complaints remains unresolved. This randomized clinical trial is designed to study the clinical effectiveness and cost-effectiveness of manipulative treatment of the structures of the shoulder girdle in addition to standard treatment. This study is funded by The Netherlands Scientific Organization (NWO grant number 904-65-901) and approved by the Medical Ethics Committee of the University Hospital of Groningen, The Netherlands, and the Committee for Scientific Research in General Practice, Department of General Practitioners, Groningen, The Netherlands.

Role of the Shoulder Girdle in Shoulder Complaints

Shoulder complaints are often concurrent with neck pain.¹¹ In clinical practice, the mobility of the shoulder girdle (cervical and upper thoracic spine and the adjacent ribs) is found to have a considerable influence on the mobility of the scapulo-humeral joint. Sobel et al² reported that in some (22 of 101) patients with shoulder complaints, no disorders could be detected in the anatomic region of the

shoulder. Reduced mobility of the shoulder girdle might therefore be an important factor in the development and persistence of shoulder complaints.

Thus far, there is only limited evidence from the available literature to support this suggestion. Norlander et al¹² showed that the cervico-thoracic mobility is related to the development of shoulder pain. Patients with reduced mobility of the cervico-thoracic spine have a 3-fold risk for development of shoulder disorders.¹³ In addition, Winters et al,⁷ showed that in many patients with persistent shoulder complaints, the only disorder that could be detected was a reduced mobility of the shoulder girdle. On reexamination of all the patients with shoulder complaints who were seen 6 months earlier, Winters et al¹⁴ found that 80% of the patients had a reduced mobility of the shoulder girdle, although no shoulder complaints were reported. This could suggest that such reduction of shoulder girdle and/or cervical mobility might be an explanation for the high recurrence rate of shoulder complaints.

Available Literature

There are many clinical studies on shoulder complaints but scientific evidence for the efficacy of manipulative treatment of shoulder complaints is lacking.¹⁵ We performed a literature search in Medline (1966-2000), Embase (1974-2000), and the Cochrane Library with the subject headings "manipulation," "orthopedic," and "clinical trials" in combination with the word "shoulder." These are broad terms but the search did find 2 articles of the clinical trial of Winters et al.¹⁴ In this trial, physiotherapy, manipulation, and injections with corticosteroids for treatment of shoulder complaints were compared. The authors concluded that for treating shoulder complaints based on reduced mobility of the shoulder girdle, manipulation is more effective in the short-term than the other interventions studied.⁹ However after a 2-year follow-up period, there were no significant differences between treatments.¹⁰ Most research on the efficacy of manipulative treatment has been focused on the treatment of low back and neck pain.^{16,17} The reported effects of manipulation for low back and neck pain tend to be favorable. However, a critical appraisal of review articles on neck pain demonstrated that there is not enough evidence among the reviews to draw a strong conclusion.¹⁸

Possible Workings Mechanisms of Manipulative Therapy

Spinal manipulative techniques aim to restore mobility between adjacent vertebrae. The normal motion of adjacent vertebrae can be blocked by an entrapment of a meniscoid.¹⁹ Reflexogenic mechanisms can most likely explain the relation between a reduced mobility of the cervico-thoracic spine and shoulder complaints. A deviant biomechanic relation between adjacent vertebrae can compress nerve roots,²⁰ which stimulates paraspinal receptors and

activates segmental-related muscle function,^{21,22} for example resulting in hypertension or muscle spasm. This can cause a deviant movement pattern and posture of the scapulo-humeral joint,²³ which in turn can provoke pain and restricted mobility.

Spinal manipulative techniques applied on the segmental level may restore the mobility of adjacent vertebrae and alleviate compression on nerve roots, which leads to a decrease in muscle tension and restoration of mobility of structures in the shoulder girdle. This could result in symptom relief of shoulder complaints and could prevent recurrent or chronic shoulder problems. Although clinical findings seem to support this mechanism, there is limited scientific evidence to consider this mechanism as a valid explanation for the effect of manipulation.

Reasons for Publishing a Protocol

There are several reasons for publishing a study protocol before obtaining research data. The main reason is to reflect on the study design independently of the results. To interpret the results of a study, reporting a detailed description of the protocol is necessary. Another reason is to prevent publication bias. Unfavorable results appear to be difficult to publish, whereas favorable findings have minor problems getting published. By publishing the protocol, we intend to publish favorable and unfavorable results. The third reason arises from experience that randomized controlled studies tend to deviate from its original protocol, mainly because of practical problems. A deviation of the study protocol may have an effect on the study results. By publishing, we also test our implementation of the protocol, and we have to describe and motivate protocol deviations.

DISCUSSION

Study Design

Context. The Groningen Manipulation Study is part of the Dutch Shoulder Disability Study (DSDS). This is a comprehensive, prognostic cohort study on shoulder disorders, with randomized controlled intervention studies in subcohorts. In this cohort study, approximately 2000 patients with shoulder complaints will be included and observed for 6 months. The major outcome of this cohort study is to establish which putative prognostic factors and indicators for treatment susceptibility predict the outcome of shoulder complaints after 6 months. The outlined Groningen Manipulation Study is 1 of 3 nested randomized controlled trials. In this relatively new design, patients in the cohort study are asked to participate in the randomized controlled trial if they meet specific selection criteria. Two other randomized clinical trials will evaluate the cost-effectiveness and effectiveness of a cognitive behavioral therapy on the prevention of chronicity of shoulder complaints and a graded activity program on treatment of chronic shoulder complaints compared with standard treatment.

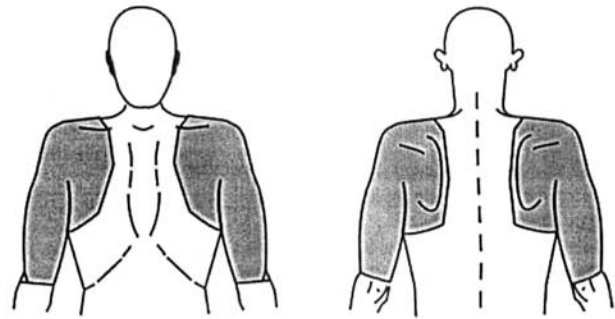


Fig 1. Localization of shoulder pain.

Research question. The Groningen Manipulation Study has 2 major objectives. The short-term objective is to evaluate the effect of additional manipulation of the structures of the shoulder girdle for relief of symptoms of shoulder complaints, and the long-term objective is to evaluate the effect on the prevention of persistence and recurrence of shoulder complaints. The main research question for the Groningen Manipulation Study asks, “Is manipulative treatment of the structures of the shoulder girdle, in addition to the standard treatment, effective and cost-effective in treating shoulder complaints and preventing persistent or recurrent shoulder complaints after 6 and 12 months in patients with shoulder complaints and reduced mobility of the shoulder girdle?”

Patient selection. Patients with shoulder complaints are recruited in general practices in Groningen, The Netherlands. Shoulder complaints are defined as pain in the shoulder and upper arm (the shaded area in Fig 1) at rest or provoked or aggravated by movement. Extension of the pain from the shaded area to the region between the scapulae to the cervical spine or to the lower part of the arm does not lead to the exclusion of the patient. Physical examination must indicate the shoulder complaints are concurrent, with a functional limitation of the structures of shoulder girdle. Only new episodes of shoulder complaints are included but there is no limitation on the duration of complaints before the first consultation. Additional criteria for exclusion are given in Table 1.

Method. Participating patients are randomly allocated either to manipulative therapy in addition to standard treatment or to standard treatment alone. All patients will receive standard treatment by their general practitioner. Allocation to manipulative therapy will be based on the severity of complaints at baseline (stepped-care provision). We believe that glenohumeral shoulder pain needs to be reduced before treatment by a manipulative therapist. Therefore, patients with moderate to severe glenohumeral complaints will receive additional manipulative treatment after 2 to 3 weeks; patients with mild inflammatory complaints will receive immediately. Based on the assessment at 6 weeks, patients without shoulder complaints and without functional limitation of the shoulder girdle will not receive further treatment but will attend follow-up assessments. Patients with shoul-

Table 1. *Exclusion criteria*

Consultation or treatment in the past 3 months for shoulder complaints
Clear treatment preference
Contraindications for manipulative treatment
Presence of specific rheumatic disorders
Shoulder complaints caused by acute severe trauma or previous (orthopedic) surgery
Signs of cervical nerve root compression
Presence of dementia or other psychiatric, emotional, or behavioral disorders
Extrinsic shoulder disorders, i.e. complaints caused by general internal pathologic conditions (of thoracic and abdominal organs)
Not being able to fill in questionnaires in Dutch

der complaints and/or a functional limitation of the shoulder girdle are allowed to receive treatment again. Evaluation assessments are scheduled at 12, 26, and 52 weeks after inclusion (Fig 2).

Informed consent procedure. Patients are initially recruited by the general practitioner, who informs the patient about the study and provides an informational brochure. The general practitioner reports the patient to the executing researcher, who continues the recruitment and provides further information. In the research center, selection criteria are verified by the conducting researcher. Next, demographic and prognostic information, including baseline values of outcome variables are documented.

Randomization. Patients will be randomly assigned either to manipulative therapy and standard treatment or to standard treatment alone. An independent coworker will generate a random list that, by permutation of randomized blocks with a block size of $n = 6$, will be stratified for the general practitioner. For the concealed treatment allocation previously prepared numbered, opaque sealed envelopes containing the treatment allocation will be used. The conducting researcher, who conducts this procedure, is unaware of the contents of the envelope.

Interventions. All patients will receive standard treatment by their general practitioner. All participating general practitioners will be educated and trained to apply the treatment according to the guidelines. Manipulative treatment will be applied up to 3 times in a 6-week period, according to the principles of the School for Manipulative Therapy in Eindhoven or Amersfoort, The Netherlands. Manipulative treatment consists of mobilization and manipulation (high-velocity thrust) techniques of the cervical spine, the upper thoracic spine, and the upper ribs (on the segmental level). Experienced physical therapists, who are postgraduates at the School for Manipulative Therapy, a member of the International Federation of Orthopedic and Manipulative Therapists (IFOMT), will provide the manipulative treatment. Variations in manipulative treatment among the executing therapists will be minimized by a special training session in which a protocol for the applied treatment was

drawn up. Other interventions (exercises, advice about posture, treatment of the shoulder joint) will be discouraged and considered deviations from the treatment protocol.

Blinding. This study is a single-blind trial because the patients are aware of the applied treatment. The research-assistant, who is responsible for the follow-up measurements, will be unaware of the allocated treatment. The conducting researcher is still blinded during data analysis.

Measurements. The primary outcome variables are the proportion of patients without shoulder complaints (no pain and full range of motion) and the proportion of patients without persistent or recurrent shoulder complaints. A complete overview of clinical outcome measures, prognostic variables, process variables, and possible confounders is given in Table 2.

Flock of Birds. The Flock of Birds (Ascension Technology Corporation, Burlington, Vt) is a 6-degree-of-freedom electromagnetic measuring device, which is used to measure the mobility of the cervical spine and upper thoracic spine. The Flock of Birds system consists of a standard range electromagnetic transmitter and 3 receivers. The patient sits in a comfortable position in a chair, with 1 receiver taped on the sternum and 1 receiver taped on the forehead. The third receiver is mounted on a stylus to palpate 7 standardized bony landmarks (bridge of the nose, chin, processus xiphoideus, incisura jugularis, base of skull, and processus spinosus of C7 and T8). Two local coordinate systems fixed to the forehead and the thorax were defined based on these bony landmarks. Five movements will be conducted actively and passively (axial rotation in neutral, flexion and extension position, flexion extension and lateral bending). The relative motion of the head is measured with respect to the thorax by the 2 Flock of Birds receivers. The measurements from the 2 receivers are then recalculated to position and orientation of the head coordinate system with respect to thorax coordinate system. This will be recorded and translated into a degree of freedom. The Flock of Birds system is a valid and reproducible system for measuring the mobility of the cervical spine.²⁴

Data analysis. The study groups will be compared at baseline for their prognostic status (ie, distribution of all independent variables and the baseline values of the outcome variables). According to the intention-to-treat principle, differences between groups will be calculated for each outcome measure with a 95% confidence interval (Table 2). The study groups will be compared for their mean changes by an independent sample Student *t* test (for continuous outcome variables) and the chi-square test (for categorical outcome variables). The influence of group differences for putative prognostic indicators on treatment outcome, such as presence of glenohumeral shoulder pain, age, sex, disease characteristics, treatment preference and credibility, coping and depression, will be assessed in a multivariable linear regression analysis.

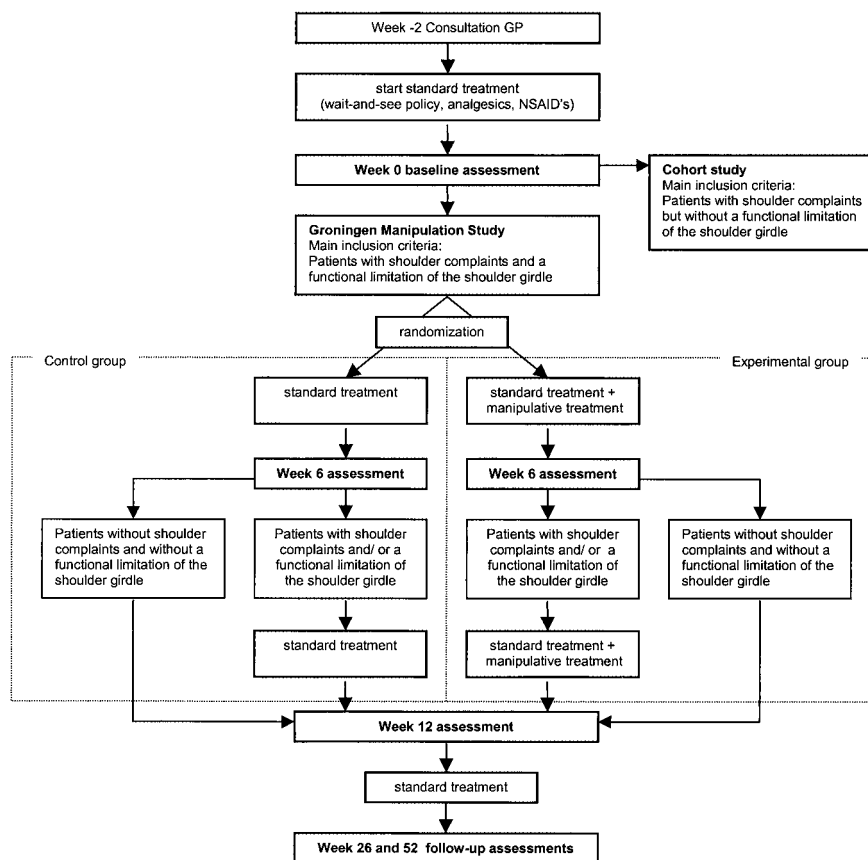


Fig 2. Scheme of study design.

Sample size. Sample size calculations are based on the proportion of 50% of patients without shoulder complaints in the control group after 6 months, a 2-sided α of 0.05, a statistical power ($1-\beta$) of 0.80, and an attrition rate of 10%. We need 250 patients (125 in each treatment group) to detect a difference of 20% between the experimental and the control groups after 6 months.

CONCLUSION

This study is designed to evaluate the effectiveness of additional manipulative treatment for short-term relief of shoulder complaints and long-term prevention of chronicity and recurrences of shoulder complaints. This design provides the opportunity to evaluate the (additional) value of manipulative therapy, without depriving the participating patients of the usual standard treatment. In addition, the effect of the standard treatment and additional manipulative treatment will be evaluated as they are applied in everyday practice. It is unfeasible to blind patients to the applied treatment, which increases the risk of information bias. We try to minimize these types of bias by assessing patient preferences before randomization and excluding patients with a clear preference for a specific treatment. Another way

is to make the research assistant for the treatment allocation unaware. We explicitly ask patients not to tell the research assistant which treatment they have received.

The standard treatment is given according to the Guidelines of the Dutch College of General Practitioners. Each general practitioner could interpret these guidelines differently. By a stratified randomization procedure, we balance the standard treatment between experimental and control groups and thus minimize possible bias. General practitioners might adjust their treatment if they know the patient is already receiving manipulative therapy. Therefore, the general practitioners will be kept unaware of the allocated treatment for 12 weeks. Again, patients are asked not to inform the general practitioner.

Patient recruitment is an uncontrollable factor in conducting pragmatic randomized trials. For the patient recruitment, we depend on the cooperation of the participating general practitioners. It is necessary to interest general practitioners in the trial for a sufficient patient recruitment, which can be achieved by a relevant research question and in practice applicable results.²⁵ To gain and maintain their interest, we discuss the implementation of the trial with the general practitioners in special information sessions. Monthly news-

Table 2. Overview of variables

Variable	Measure	Range or unit	Mode
Demographic variables			
Age, sex, employment status	T ₀		Structured medical history
Baseline status	T ₀		
Specific disease characteristics:			
Affected side		dominant/nondominant	1 item
Possible cause of complaints			1 item
Duration of complaints		months	1 item
History of shoulder complaints			3 items
History of neck complaints			3 items
Co-morbidity			inventory
Physical activity		inactive-very active	5 item questionnaire
Workload			1 item
Treatment credibility and preference			4 items
Prognostic variables			
Mobility glenohumeral joint (HIB, HIN, active and passive abduction, passive exorotation)	T ₀ , T ₆ , T ₁₂ , T ₂₆ , T ₅₂	pain/mobility	physical examination
Mobility cervicothoracic spine	T ₀ , T ₆ , T ₁₂ , T ₂₆ , T ₅₂	pain/mobility	physical examination
Psychosocial variables			
Kinesiophobia	T ₀	0-15 (low-high kinesiophobia)	3 item questionnaire
Fear avoidance and beliefs	T ₀	0-25 (low-high fear avoidance and beliefs)	5 item questionnaire
Coping with pain (26)	T ₀	0-158 (low-high coping)	43 item questionnaire
Anxiety (27)	T ₀	0-12 (low-high anxiety)	12 item questionnaire
Depression (27)	T ₀	0-6 ((low-high depression)	6 item questionnaire
Somatization (27)	T ₀	0-32 (low-high somatization)	16 item questionnaire
Distress (27)	T ₀	0-32 (low-high distress)	16 item questionnaire
Job content (28)	T ₀	0-108 (low-high job content)	27 item questionnaire
Primary outcome variables			
Perceived recovery of complaints	T ₆ , T ₁₂ , T ₂₆ , T ₅₂	1-8 (complete recovery-severe deterioration)	1 item
Severity of main complaint (29)	T ₀ , T ₆ , T ₁₂ , T ₂₆ , T ₅₂	0-10 (no-high complaint)	8-dimension inventory + 11-point Likert scale
Functional limitation in daily activities (30)	T ₀ , T ₆ , T ₁₂ , T ₂₆ , T ₅₂	0-16 (no-severe limitation)	16-item questionnaire
Shoulder pain (31)	T ₀ , T ₆ , T ₁₂ , T ₂₆ , T ₅₂	7-28 (no-severe pain)	6-item questionnaire + 11-point Likert scale
General health (32)	T ₀ , T ₆ , T ₁₂ , T ₂₆ , T ₅₂	0-100 (worst-best imaginable health)	6-item questionnaire + visual analogue scale
Costs (33)	T ₀ -T ₂₆ (continuous)	Dutch guilders/Euro's	cost-diary
Process variable			
Mobility of cervicothoracic spine (24)	T ₀ , T ₆ , T ₁₂ , T ₂₆ , T ₅₂	no-normal mobility (degrees)	6-degrees-of-freedom electromagnetic measuring device

T₀, baseline measurement; T₆, T₁₂, T₂₆, T₅₂ are follow-up assessments at 6, 12, 26, and 52 weeks after inclusion. The principal researcher conducts the baseline measure (T₀); the research-assistant conducts the follow-up assessments (T₆, T₁₂, T₂₆, T₅₂).
HIB, Hand-in-back mobility test; HIN, hand-in-neck mobility test.

letters are sent to inform the general practitioners about the progress of the study. We measure the mobility of the cervical and upper thoracic spine by the Flock of Birds system, a relatively new but promising device. The Flock of Birds system is easy to use, and a measurement is completed within 15 minutes. By means of the Flock of Birds system, we hope to gain more insight into the role of the shoulder girdle in shoulder complaints.

REFERENCES

- van der Windt DA, Koes BW, Boeke AJ, Deville W, De Jong BA, Bouter LM. Shoulder disorders in general practice: prognostic indicators of outcome. *Br J Gen Pract* 1996;46:519-23.
- Sobel JS, Winters JC, Groenier KH, Arendzen JH, Meyboom-de Jong B. Kenmerken van schouderklachten in de huisartspraktijk. *Huis Wet* 1996;39:169-73.
- Winters JC, de Jongh AC, van der Windt DAWM, Jonquière

- M, van der Heijden GJMG, Sobel JS, et al. NHG-Standaard Schouderklachten (versie 1999). Huisarts Wet 1999;42:222-31.
4. van der Windt DA, van der Heijden GJ, Scholten RJ, Koes BW, Bouter LM. The efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) for shoulder complaints. A systematic review. *J Clin Epidemiol* 1995;48:691-704.
 5. van der Heijden GJ, van der Windt DA, Kleijnen J, Koes BW, Bouter LM. Steroid injections for shoulder disorders: a systematic review of randomized clinical trials. *Br J Gen Pract* 1996;46:309-16.
 6. van der Heijden GJ, van der Windt DA, de Winter AF. Physiotherapy for patients with soft tissue shoulder disorders: a systematic review of randomised clinical trials. *BMJ* 1997; 315:25-30.
 7. Winters JC, Sobel JS, Groenier KH, Arendzen JH, Meyboom-de Jong B. The long-term course of shoulder complaints: a prospective study in general practice. *Rheumatology (Oxford)* 1999;38:160-3.
 8. Croft P, Pope D, Silman A. The clinical course of shoulder pain: prospective cohort study in primary care. Primary Care Rheumatology Society Shoulder Study Group. *BMJ* 1996; 313:601-2.
 9. Winters JC, Sobel JS, Groenier KH, Arendzen JH, Meyboom-de Jong B. Comparison of physiotherapy, manipulation, and corticosteroid injection for treating shoulder complaints in general practice: randomised, single blind study. *BMJ* 1997; 314:1320-5.
 10. Winters JC, Jorritsma W, Groenier KH, Sobel JS, Meyboom-de Jong B, Arendzen JH. Treatment of shoulder complaints in general practice: long term results of a randomized, single blind study comparing physiotherapy, manipulation, and corticosteroid injection. *BMJ* 1999;318:1395-6.
 11. Lamberts H, Wood M, Hofmans-Okkens IM. The international classification of primary care in the European community. Oxford: Oxford University Press, 1993.
 12. Norlander S, Astc-Norlander U, Nordgren B, Sahlstedt B. Mobility in the cervico-thoracic motion segment: an indicative factor of musculo-skeletal neck-shoulder pain. *Scand J Rehabil Med* 1996;28:183-92.
 13. Norlander S, Gustavsson BA, Lindell J, Nordgren B. Reduced mobility in the cervico-thoracic motion segment-a risk factor for musculoskeletal neck-shoulder pain: a two-year prospective follow-up study. *Scand J Rehabil Med* 1997;29:167-74.
 14. Winters JC, Sobel JS, Groenier KH, Arendzen JH, Meyboom-de Jong B. The course of pain and the restriction of mobility in patients with shoulder complaints in general practice. *Rheumatol Int* 1997;16:219-25.
 15. van der Heijden GJ. Shoulder disorders: a state-of-the-art review. *Baillieres Best Pract Res Clin Rheumatol* 1999;13: 287-309.
 16. Bronfort G. Spinal manipulation: current state of research and its indications. *Neurol Clin* 1999;17:91-111.
 17. Koes BW, Assendelft WJ, van der Heijden GJ, Bouter LM, Knipschild PG. Spinal manipulation and mobilization for back and neck pain: a blinded review. *BMJ* 1991;303:1298-1303.
 18. Hoving JL, Gross AR, Gasner D, Kay T, Kennedy C, Hondras MA, et al. A critical appraisal of review articles on the effectiveness of conservative treatment for neck pain. *Spine* 2001;26:196-205.
 19. Wolf J. The reversible deformation of the joint cartilage surface and its possible role in joint blockage. In: Lewit K, Gutmann G, editors. *Functional pathology of the motor system, Rehabilitica*. Bratislava: Ozbor, 1975. p. 30.
 20. Giles LG. Mechanisms of neurovascular compression within the spinal and intervertebral canals. *J Manipulative Physiol Ther* 2000;23:107-11.
 21. Herzog W, Scheele D, Conway PJ. Electromyographic responses of back and limb muscles associated with spinal manipulative therapy. *Spine* 1999;24:146-52.
 22. Symons BP, Herzog W, Leonard T, Nguyen H. Reflex responses associated with activator treatment. *J Manipulative Physiol Ther* 2000;23:155-9.
 23. Sobel JS, Kremer I, Winters JC, Arendzen JH, Meyboom-de Jong B. The influence of the mobility in the cervicothoracic spine and the upper ribs (shoulder girdle) on the mobility of the scapulohumeral joint. *J Manipulative Physiol Ther* 1996; 19:469-74.
 24. Koerhuis CL, Winters JC, van der Helm FCT, Hof AL. Assessment of neck mobility by means of the 'Flock of Birds' electromagnetic tracking system. In press. *Clin Biomech* 2002.
 25. van der Windt DA, Koes BW, van Aarst M, Heemskerk MA, Bouter LM. Practical aspects of conducting a pragmatic randomised trial in primary care: patient recruitment and outcome assessment. *Br J Gen Pract* 2000;50:371-4.
 26. Vlaeyen JW, Geurts SM, Kole-Snijders AM, Schuerman JA, Groenman NH, van Eek H. What do chronic pain patients think of their pain? Towards a pain cognition questionnaire. *Br J Clin Psychol* 1990;29:383-94.
 27. Terluin B. De Vierdimensionale Klachtenlijst (4DKL) in de huisartspraktijk. *De Psycholoog* 1998:18-24.
 28. Karasek R, Brisson C, Kawakami N, Houtman I, Bongers P, Amick B. The Job Content Questionnaire (JCQ): an instrument for internationally comparative assessments of psychosocial job characteristics. *J Occup Health Psychol* 1998;3:322-55.
 29. Beurskens AJ, de Vet HC, Koke AJ, Lindeman E, van der Heijden GJ, Regtop W, et al. A patient-specific approach for measuring functional status in low back pain. *J Manipulative Physiol Ther* 1999;22:144-8.
 30. van der Heijden GJ, Leffers P, Bouter LM. Shoulder disability questionnaire design and responsiveness of a functional status measure. *J Clin Epidemiol* 2000;53:29-38.
 31. Winters JC, Sobel JS, Groenier KH, Arendzen JH, Meyboom-de Jong B. A shoulder pain score: a comprehensive questionnaire for assessing pain in patients with shoulder complaints. *Scand J Rehabil Med* 1996;28:163-7.
 32. Brooks RG. EuroQol: the current state of play. *Health Policy* 1996;37:53-72.
 33. Goossens ME, Rutten-van Molken MP, Vlaeyen JW, van der Linden SM. The cost diary: a method to measure direct and indirect costs in cost-effectiveness research. *J Clin Epidemiol* 2000;53:688-95.