

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



Section 1.	Identifying Info	rmation	
1. Given Name (Fi Kenneth	irst Name)	2. Surname (Last Name) Svendsen	3. Effective Date (07-August-2008) 20-October-2011
4. Are you the corresponding author?		Yes 🖌 No	Corresponding Author's Name Gert Bronfort, DC, PhD
5. Manuscript Titl Spinal manipula trial	e tion, medication, or ł	nome exercise with advice	for acute and subacute neck pain:A randomized controlled
6. Manuscript Ide M11-0299	ntifying Number (if you	know it)	

Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

The Work Under Consideration f	or Pub	lication				
Туре	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	\checkmark					×
						ADD
2. Consulting fee or honorarium	\checkmark					×
						ADD
3. Support for travel to meetings for the study or other purposes	\checkmark					×
						ADD
 Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like 	\checkmark					×
						ADD
5. Payment for writing or reviewing the manuscript	\checkmark					×
						ADD
 Provision of writing assistance, medicines, equipment, or administrative support 	\checkmark					×



The Work Under Consideration for Publication							
	Туре	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
							ADD
7. Other		\checkmark					×
							ADD

* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities out	side the	submit	ted work			
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
1. Board membership	\checkmark					×
						ADD
2. Consultancy	\checkmark					×
						ADD
3. Employment	\checkmark					×
						ADD
4. Expert testimony	\checkmark					×
						ADD
5. Grants/grants pending	\checkmark					×
						ADD
Payment for lectures including service on speakers bureaus	\checkmark					×
						ADD
7. Payment for manuscript preparation	\checkmark					×



Relevant financial activities outs	ide the	submit	ted work			
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
						ADD
 Patents (planned, pending or issued) 	\checkmark					×
						ADD
9. Royalties	\checkmark					×
						ADD
10. Payment for development of educational presentations	\checkmark					×
						ADD
11. Stock/stock options	\checkmark					×
						ADD
 Travel/accommodations/ meeting expenses unrelated to activities listed** 	\checkmark					×
						ADD
13. Other (err on the side of full disclosure)	\checkmark					×
						ADD

* This means money that your institution received for your efforts.

** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section 4.

4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

✓ No other relationships/conditions/circumstances that present a potential conflict of interest

Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Hide All Table Rows Checked 'No'

SAVE



Evaluation and Feedback

Please visit <u>http://www.icmje.org/cgi-bin/feedback</u> to provide feedback on your experience with completing this form.



Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



Section 1.	Identifying Infor	mation	
1. Given Name (Fi Alfred	rst Name)	2. Surname (Last Name) Anderson	3. Effective Date (07-August-2008) 02-November-2011
4. Are you the corresponding author?		Yes 🖌 No	Corresponding Author's Name Gert Bronsfort
5. Manuscript Title spinal manipulat trial	e tion, medication, or h	ome exercise with advice	for acute and subacute neck pain: A randomized controlled
6. Manuscript Idei	ntifying Number (if you	know it)	

unknown

Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

The Work Under Consideration f	for Pub	lication				
Туре	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant	\checkmark					×
						ADD
2. Consulting fee or honorarium	\checkmark					×
						ADD
3. Support for travel to meetings for the study or other purposes	\checkmark					×
						ADD
 Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like 	\checkmark					×
						ADD
5. Payment for writing or reviewing the manuscript	\checkmark					×
						ADD
 Provision of writing assistance, medicines, equipment, or administrative support 	✓					×



The Work Under Consideration for Publication							
	Туре	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
							ADD
7. Other		\checkmark					×
							ADD

* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities out	Relevant financial activities outside the submitted work						
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments		
1. Board membership	\checkmark					×	
						ADD	
2. Consultancy	\checkmark					×	
						ADD	
3. Employment	\checkmark					×	
						ADD	
4. Expert testimony	\checkmark					×	
						ADD	
5. Grants/grants pending	\checkmark					×	
						ADD	
Payment for lectures including service on speakers bureaus	\checkmark					×	
						ADD	
7. Payment for manuscript preparation	\checkmark					×	



Relevant financial activities outs	ide the	submit	ted work			
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
						ADD
 Patents (planned, pending or issued) 	\checkmark					×
						ADD
9. Royalties	\checkmark					×
						ADD
10. Payment for development of educational presentations	\checkmark					×
						ADD
11. Stock/stock options	\checkmark					×
						ADD
 Travel/accommodations/ meeting expenses unrelated to activities listed** 	\checkmark					×
						ADD
13. Other (err on the side of full disclosure)	\checkmark					×
						ADD

* This means money that your institution received for your efforts.

** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

✓ No other relationships/conditions/circumstances that present a potential conflict of interest

Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Hide All Table Rows Checked 'No'

SAVE



Evaluation and Feedback

Please visit <u>http://www.icmje.org/cgi-bin/feedback</u> to provide feedback on your experience with completing this form.

- 1 Spinal manipulation, medication, or home exercise with advice for acute and subacute
- 2 neck pain: A randomized controlled trial
- 3 Gert Bronfort, DC, PhD*; Roni Evans, DC, MS; Alfred V. Anderson, DC, MD;
- 4 Kenneth H. Svendsen, MS; Yiscah Bracha, MS; Richard H. Grimm, MD, MPH, PhD

5 **Author Affiliations:**

- 6 From Northwestern Health Sciences University, Minneapolis, MN; Pain Management and
- 7 Rehabilitation Center, Minneapolis, MN; Berman Center for Outcomes and Clinical Research at
- 8 the Minneapolis Medical Research Foundation, Minneapolis, MN
- 9 *Corresponding author responsible for publication and reprints
- 10 Running Title: Conservative interventions for acute/subacute neck pain

11 Word count: 3505

1 Abstract

Background: Mechanical neck pain is a common condition, afflicting an estimated 70% of all
individuals at some time in their lives. Very little research exists to guide the choice of therapy
for acute and subacute neck pain.

5 Objective: To determine the relative efficacy of spinal manipulation therapy, medication, and
6 home exercise with advice for acute and subacute neck pain in both the short and long term.

7 **Design:** Randomized controlled trial

8 **Setting:** 1 university research center, 1 pain management clinic in Minnesota

9 Patients: 272 persons, 18-65 years of age with non-specific neck pain 2-12 weeks duration

10 Interventions: 12 weeks of spinal manipulation therapy (SMT), medication (MED), or home
11 exercise with advice (HEA)

Measurements: The primary outcome was patient-rated pain measured at 2, 4, 8, 12, 26, and 52 weeks post-randomization. Secondary measures were self-reported disability, global improvement, medication use, satisfaction, general health status (SF-36 physical and mental health scales), and adverse events. Blinded evaluation of neck motion was performed at 4 and 12 weeks.

17 **Results:** For pain, there was a statistically significant advantage of SMT over MED after 8, 12,
18 26, and 52 weeks (p<=0.01). HEA was superior to MED at 26 weeks (p=0.02). No important

- 1 differences in pain were found between SMT and HEA at any time point. Results for most of the
- 2 secondary outcomes were similar to the primary outcome.
- 3 **Limitations:** Inability to blind patients and providers. No specific criteria for defining clinically
- 4 important group differences were pre-specified or available from the literature.
- 5 **Conclusion:** For patients with acute and subacute neck pain, spinal manipulation was more
- 6 effective than medication management in both the short and long term. However, a few
- 7 instructional sessions of home exercises with advice resulted in outcomes similar to those of
- 8 spinal manipulation at most time points.
- 9 **Primary Funding Source**: National Institute of Health's National Center for Complementary
- 10 and Alternative Medicine (grant R01 AT000707).
- 11 ClinicalTrials.gov Identifier: NCT00029770

1 Introduction

Neck pain is a prevalent condition, with nearly three quarters of individuals experiencing it at
some time in their lives. (1,2) It is one of the most commonly reported symptoms in primary care
settings, (3,4) resulting in millions of ambulatory healthcare visits each year and rising
healthcare costs. (5-8) While not life threatening, neck pain can have a negative effect on
productivity and overall quality of life. (1,9-11)

Spinal manipulation is a manual therapy commonly applied by chiropractors, physical therapists,
osteopaths, and other healthcare providers for neck pain conditions. (12) Similarly, home
exercise programs and medications are widely used to manage neck pain. (13) Recent
Cochrane reviews report insufficient evidence to assess the effectiveness of commonly used
medications or home exercise programs for the treatment of acute neck pain. (13,14) Similarly,
the evidence for spinal manipulation is also limited, with only low quality evidence supporting its
use for neck pain of short duration. (15)

14 The purpose of this randomized trial was to test the hypothesis that spinal manipulation therapy

15 (SMT) is more effective than medical care (MED) and home exercise with advice (HEA) for

16 acute and subacute neck pain.

17 Methods

18 Setting

19 The trial was conducted from 2001 to 2007 in Minneapolis, Minnesota. All eligibility screening,

20 randomization, and short term data collection activities occurred at a university affiliated

research center; long term data collection took place by mail. Spinal manipulation and
instruction in home exercise were provided at a university affiliated outpatient clinic. Medical
treatment was provided at a pain management clinic. The study was approved by the
institutional review boards of Northwestern Health Sciences University and Hennepin County
Medical Center. Written informed consent was obtained from all participants.

6 Participants

7 Participants were recruited using targeted mailings to neck pain patients registered with Blue 8 Cross/Blue Shield Minnesota and through newspaper and radio advertisements. Interested 9 individuals were screened for eligibility at two baseline appointments by clinicians blinded to the 10 randomization schedule. Inclusion criteria were 18 to 65 years of age, primary complaint of 11 mechanical, non-specific neck pain (equivalent to grades I and II classification according to the 12 Neck Pain Task Force (16,17)), 2–12 weeks duration of current neck pain episode, and neck 13 pain score of 3 or greater on a 0–10 numerical rating scale. Participants were asked to refrain 14 from seeking additional treatment for neck pain by non-study healthcare providers during the 15 12-week intervention phase.

Exclusion criteria were cervical spine instability, fracture, neck pain referred from peripheral joints or viscera, progressive neurological deficits, existing cardiac disease requiring medical treatment, blood clotting disorders, diffuse idiopathic hyperostosis, inflammatory or destructive tissue changes of the cervical spine, infectious disease or other severe disabling health problems, substance abuse, pregnant or nursing women, previous cervical spine surgery, and pending or current litigation. In addition, participants were excluded if they had received any of the study treatments within the last three months.

1 Randomization and Interventions

Randomization using permutated blocks of different sizes (18) took place at the second baseline appointment. The randomization schedule was prepared off-site by the study statistician prior to participant enrollment and was concealed from the investigators, treatment providers, and research staff using consecutively numbered, sealed, opaque envelopes. As patients became eligible, envelopes were opened in consecutive order by a research staff member in the presence of the patient.

8 The intervention protocol was tested in a previous pilot study by our research team. (19) 9 Maximum treatment duration was 12 weeks. Treatment providers were trained in the study 10 intervention protocols and were required to document treatment activities in a standardized 11 clinical record. These records were routinely monitored by research staff to ensure protocol 12 adherence.

13 Spinal Manipulation Therapy (SMT) Group

14 Six chiropractors with a minimum of 5 years experience served as the primary providers of 15 treatment. Visits lasted 15-20 minutes and included a brief history and examination of the 16 cervical and thoracic spine. The primary focus of treatment was spinal manipulation of areas of 17 the spine with segmental hypomobility using diversified techniques including low amplitude 18 spinal adjustments (a high velocity type of joint thrust manipulation) and mobilization (a low 19 velocity type of joint oscillation). (20) The specific spinal level to be treated and the number of 20 treatment sessions over the 12 week period was left to the discretion of the provider based on 21 manual palpation of the spine and associated musculature, as well as the patient's response to 22 treatment. (21) Adjunct therapy common to clinical practice included limited light soft tissue

massage, assisted stretching, and hot and cold packs to facilitate the manipulation treatment.
 Advice to stay active or modify activity was recommended as needed.

3 Medication (MED) Group

4 A licensed medical physician provided care to participants in the MED group with the focus of 5 treatment on prescription medication. Visits lasted 15-20 minutes and included a brief history 6 and examination. The first line of therapy was nonsteroidal anti-inflammatory drugs (NSAIDs) 7 and/or acetaminophen. (22,23) Patients who did not respond to the first line of therapy, as well 8 as those intolerant to NSAIDs, were prescribed narcotic medications. Muscle relaxants were 9 also used. Advice to stay active or modify activity was issued as needed. The choice of 10 medications and number of visits was made by the physician based on the patient's history and 11 response to treatment.

12 Home Exercise with Advice (HEA) Group

13 Home exercise with advice was provided in two one-hour sessions, 1-2 weeks apart at the 14 university-affiliated outpatient clinic. Six therapists provided instruction to patients. The primary 15 focus was simple self-mobilization exercise (gentle controlled movement) of the neck and 16 shoulder joints, including neck retraction, extension, flexion, rotation and lateral bending 17 motions, as well as scapular retraction, with no resistance. The delivery method was one-on-18 one and the program was individualized in terms of the patient's abilities, tolerance, and 19 activities of daily living. Patients were instructed to do 5-10 repetitions of each exercise, up to 20 6-8 times per day. A booklet (24) and laminated cards of prescribed exercises were provided. 21 Sessions were supplemented with information regarding the basic anatomy of the cervical spine 22 and advice including postural instructions and practical demonstrations of lifting, pushing, 23 pulling, and other daily actions.

1 Outcomes and Measurements

2 We collected patient demographic and clinical characteristics at the initial baseline appointment 3 through self-report questionnaires, clinical history, and physical examination. Self-reported 4 outcomes (e.g., pain) were measured six times during the 12-week treatment period (at two 5 baseline appointments and 2, 4, 8, and 12 weeks post-randomization). In addition, self-report 6 outcomes were collected twice during the post-treatment period (at 26 and 52 weeks) via mailed 7 questionnaire. All self-report questionnaires were completed by patients independently free of 8 investigator, study staff, or treatment provider influence. Patients were asked in each 9 questionnaire if anyone attempted to influence their responses. Objective measures of cervical 10 spine motion were measured at 4 and 12 weeks by seven trained examiners masked to 11 treatment assignment. (25) Blinding was maintained by systematically instructing patients not to 12 reveal treatment information and by ensuring examiners had no exposure to activities in the 13 outpatient clinics.

We chose patient-rated pain, a priori, as the primary outcome measure, using the 11-box
numerical rating scale: 0 (no symptoms) to 10 (highest severity of pain). (26-29) Secondary
outcomes included the Neck Disability Index (NDI), (30) global improvement, (31-33) medication
use, (34) satisfaction with care, (25,34) the Medical Outcomes Study Short Form 36-item Health
Survey (SF-36 D), (35), and cervical spine motion (CA6000). (36,37)

Prior to randomization, patients were asked in the self-report questionnaire how they expected
their neck pain to change in response to treatment. Response choices were: much better,
better, no change, worse, and much worse. Patients were also asked to report additional
healthcare use by non-study providers in the self-report questionnaires at all time points.

Patients were posed standardized questions at each treatment visit to assess side effects since
 the last visit; responses were documented in the clinical record.

3 Statistical Analyses

4 The sample size calculation was based on an ability to detect a 0.8 point difference between the 5 highest and lowest of the group means in patient-rated neck pain (the primary outcome) at the 6 end of 12 weeks of treatment. This difference was informed by previous neck pain trials 7 conducted by our group (19,25) and the ability to detect a small-medium effect size. The 8 standard deviation (SD) used was 1.8 (pain scale: 0-10) based on our pilot study and estimates 9 from the literature. (25,38) With a power of 0.90 and a 3-group design tested at an alpha level of 10 0.05 (two-tailed test), 75 participants per group were required (SPSS SamplePower® 1.0, 11 International Business Machines Corp., Armonk, New York). We allowed for a loss to follow up 12 rate of up to 15%. Therefore, we aimed to recruit 90 patients per group for a total of 270 13 participants.

14 In primary analyses, we evaluated changes in neck pain between baseline and week 12 and 15 performed longitudinal analyses using week 2, 4, 8, and 12 data (short term outcome). In 16 secondary (exploratory) analyses of both primary and secondary outcomes, we evaluated 17 changes in patient-rated outcomes between baseline and weeks 2, 4, 8, 12, 26, and 52, and performed longitudinal analyses using weeks 2, 4, 8, 12, 26, and 52 (long term outcome). Both 18 19 types of analyses were conducted using linear mixed models analysis (MIXED procedure in 20 SAS 9.1®, SAS Institute Inc., Cary, NC) with baseline values as outcomes. (39-42) Clinical and 21 demographic variables showing group differences at baseline were used as covariates in the 22 analysis if they were at least moderately correlated with changes in outcomes. (43,44)

23 The study database was prepared by data managers blinded to study allocation.

The intention-to-treat principle was adhered to by including all participants with baseline data in
 the analyses regardless of loss to follow up.

To protect against increased risk of Type I errors, we used Fisher's (protected) least significant
difference test. (45,46)

5 The mixed model analysis included all patients that had at least baseline assessments. In the 6 event of missing data, the reasons were explored and the pattern of the missing data was 7 determined to select the best method of data imputation. The original analyses were then 8 repeated with data fully imputed (using the MI procedure SAS 9.1) as sensitivity analyses to 9 assess the impact of the missing data. (47-51)

No pre-specified thresholds for clinically important group differences were set since they have
not been established in the literature. To facilitate interpretation of the magnitude of group

12 differences, responder analyses were conducted for pain reduction by group (absolute risk

reduction) of 50%, 75%, and 100% (including 95% CIs) at the end of the treatment phase and at

14 week 26 and 52 follow-up. (52-55)

15 Role of Funding Sources

16 The trial was funded by the National Institute of Health's National Center for Complementary

17 and Alternative Medicine (grant R01 AT000707). The funding source had no role in the study

18 design, collection, analysis, data interpretation, or writing of this report.

1 **Results**

2 A total of 504 individuals were evaluated for eligibility, of whom 272 were randomized: 90 to the

3 MED group, 91 to SMT, and 91 to HEA. A summary of patient recruitment, participation, and

4 attrition across the length of the study is summarized in Figure 1.

- 5 Demographic and clinical characteristics of the randomized participants are summarized in
- 6 Table 1. Potentially important between-group differences were noted for sex, duration of neck
- 7 pain, pain during the night, and expectation of change in neck pain.
- 8 Table 2 provides details of the three different study interventions.

9 **Primary Outcomes**

10 There were statistically significant differences in patient-rated pain improvement with SMT 11 compared to medical therapy at 12 weeks (0.94 (0.37 to 1.51) greater reduction in pain from 12 baseline with SMT than with medical therapy on a 0-10 pain scale; p=.001) and in longitudinal 13 analyses incorporating pain ratings every two weeks from baseline to 12 weeks (0.55 (0.10- to 14 1.00) greater reduction in pain with SMT than with medical therapy; p=0.017); and at 12 weeks 15 a statistically significantly higher absolute proportion of patients in the SMT group experienced 16 reductions of pain of at least 50% (Table 3). Differences between patient-rated pain 17 improvement with SMT and with home exercise were smaller and not statistically significant; 18 differences with home exercise and medical therapy were also not statistically significant, 19 although a higher absolute proportion of patients performing home exercise experienced 20 reductions of pain at 12 weeks of at least 75% compared to those receiving medical therapy.

Findings from longer term analyses were comparable: patient-rated pain improvement favored SMT over medical therapy, but not SMT over home exercise or home exercise over medical therapy at 26 and 52 weeks compared to baseline. A higher absolute proportion of SMT compared to medical therapy patients experienced reductions of pain of at least 50% at 26 but not 52 weeks; there were no differences in those proportions at any time in comparisons of SMT and home exercise, and a higher absolute proportion of home exercise compared to medical therapy patients experienced reductions of pain of at least 75% at 26 but not 52 weeks.

Adjustment for baseline imbalances in sex, cause of pain, and depression did not change thegroup differences in pain outcomes.

10 Secondary Outcomes

11 Most of the secondary outcomes showed a similar pattern of group difference to the primary

12 outcomes. (For all secondary outcomes results, see Appendix Tables 1-4.) SMT was superior to

13 medical therapy at the end of treatment and during follow-up in terms of global improvement,

14 patient satisfaction, and SF-36-assessed physical but not mental function; SMT was also

15 superior to medical therapy in measures of long-term medication use (1.26 (0.53 to 1.99) fewer

16 days per week of medication use at 1 year; p<0.001).

17 The SMT and HEA groups performed similarly to one another on most of the secondary

18 outcomes. An advantage of SMT over HEA was observed for satisfaction with care in both the

19 short and long term.

20 Home exercise with advice was superior to medical therapy in both the short and long term for

21 satisfaction with care, and in long-term medication use (1.00 (0.27 to 1.73) fewer days per week

22 use at 1 year; p=0.008).

Changes in cervical spine motion after 4 and 12 weeks are shown in Appendix Table 4. Overall,
 the greatest changes in cervical spine motion were observed in the HEA group. Results of the
 group differences in 3-dimensional cervical spine motion patterns will be reported elsewhere.

Of all participants, one indicated that someone tried to influence his responses; as this was a
week 52 questionnaire collected by mail independent of study staff; this is unlikely to be of
consequence.

7 Missing Data Analysis

8 Among the 272 participants randomized, 219 (80.5%) provided data on neck pain at every visit. 9 We considered loss to follow up to be nonrandom from 12 participants: those who never 10 commenced treatment (6 in MED) and those who decided to stop participation in the study after 11 they received treatment (2 in MED, 1 in SMT; 3 in HEA). We first imputed values to the missing 12 responses of these 12 participants by using the mean percentage reduction from baseline at all 13 time points specific to the group they belonged. Then we imputed the rest of the missing data 14 during treatment and the two post-treatment follow up time points using the SAS multiple 15 imputation strategy, based on the assumption that the data were missing at random. The results 16 of analyses with imputed values changed the estimates of group differences very little and all 17 statistically significant differences remained the same.

18 Non-Study Treatments

During the 12-week intervention, 4 participants reported visits to other healthcare providers for
their neck pain (MED n=3, HEA n=1). By week 52, about equal numbers of individuals in each
treatment group sought additional healthcare use following completion of the study treatment
phase (SMT n=18, MED n=14, HEA n=17).

1 Adverse Events

2 No serious adverse events were reported in the study. Expected, non-serious adverse events, 3 or side effects, typical to treatments did occur and were all transient in nature, requiring little or 4 no change to activity levels. Forty percent of the SMT group and 46% of the HEA group 5 reported adverse events, primarily musculoskeletal pain. Less frequent were paresthesia, 6 stiffness, headache, and crepitus (see Appendix Table 5). Sixty percent of individuals in the 7 MED group reported side effects, the most common being gastrointestinal symptoms and 8 drowsiness. Less commonly reported were dry mouth, cognitive disturbance, rash, congestion 9 and disturbed sleep.

10 **Discussion**

In the absence of available criteria for what constitute clinically important group differences, several factors should be considered in aggregate. This includes the statistical significance of the results of the primary efficacy analysis, as well as results of the responder analyses and the secondary outcomes analyses. Additionally, the durability of treatment effect, the safety and tolerability of the interventions, and patient's ability and willingness to comply must be taken into account. (56)

In this trial comparing spinal manipulation to medical therapy and home exercise for the treatment of acute and subacute neck pain, spinal manipulation appeared more effective than medical therapy using a variety of measures of neck pain and function. However, spinal manipulation demonstrated no apparent benefits over home exercise. Spinal manipulation and home exercise led to similar short and long term outcomes, but participants receiving medical therapy seemed to fare worse, continuing to have higher use of pain medication for neck pain

throughout the trial's entire observation period. Noteworthy is the performance of the HEA
 group, which has the potential for cost savings over spinal manipulation and medication
 interventions.

The potential for side effects is a factor that patients and clinicians consider when making treatment decisions. While the frequency of reported side effects was similar among the three groups (41-58%), the nature of the side effects differed, with patients in the SMT and HEA groups reporting predominantly musculoskeletal events, and those in the MED group reporting side effects more systemic in nature. Importantly, patients in the MED group reported higher level of medication use after the intervention phase.

Most patients had subacute neck pain lasting more than four weeks, beyond the time when pain is likely to resolve spontaneously, and there is evidence that half of nonspecific neck pain patients continue to have neck pain a year after the original complaint. (57) Although the trial did not incorporate a placebo arm, it is unlikely that the observed results are due to natural history alone.

To date, there have been very few clinical trials assessing the effectiveness of noninvasive
interventions for acute and subacute neck pain not associated with whiplash. Consequently,
there is no established and evidence-informed first line of therapy for this type of neck pain.
(12,13)

We searched MEDLINE, EMBASE, CINAHL, and The Cochrane Library (using the terms spinal
manipulation and neck pain) to identify all randomized trials published from 1960 to 2011
evaluating spinal manipulation therapy for acute or subacute neck pain. We found three trials.
(58-61) Our trial is most comparable to the trial by Hoving et al, (58,59) in which 75% of patients
had neck pain less than 12 weeks duration. Six weeks of manual therapy (mainly spinal

1 mobilization) was compared to usual medical care (advice, home exercise, and medication). 2 These authors found manual therapy to be superior to medical care, with reductions in pain and 3 disability similar to what we observed at 8 weeks but less than what we observed at 12 weeks. 4 In another study by Pool et al, (60) 6 weeks of manual therapy (up to 6 sessions) was compared to 6 weeks of a behavioral-graded activity program (maximum of 18 sessions of 30 minutes 5 6 each). At 3 months, the behavioral-graded activity program demonstrated slightly larger 7 reductions in pain and disability than manual therapy; however, the magnitude of improvements 8 in the behavioral program was similar to that found for SMT in our trial. One trial by Cleland et al 9 (61) found thrust mobilization/manipulation more effective than non-thrust manual treatment in 10 subacute neck pain patients. When considered in the context of the existing evidence, the 11 results of our trial suggest spinal manipulation/mobilization and instruction in home exercises 12 constitute viable treatment options for the management of acute and subacute mechanical neck 13 pain.

14 Strengths and Limitations

15 Our study has several strengths, including a rigorous concealed randomization procedure, use 16 of recommended reliable outcome measures, masked objective outcomes assessors, and long 17 term post-randomization follow up (6 and 12 months.) A limitation of this study is that it was not 18 possible for patients and providers to be blinded due to the nature of the treatments received 19 and delivered. Another limitation was the lack of available criteria for the definition of a clinically 20 important group difference for the different outcomes. Further, the study does not differentiate 21 between the specific effects of treatment and the contextual, or non-specific, effects including 22 patient-provider interactions and expectations. Rather, this study was intended to be pragmatic 23 in nature, answering clinical questions regarding commonly used treatment approaches 24 approximating how they are delivered in practice.

1 Conclusion

- 2 For patients with acute and subacute neck pain, spinal manipulation was more effective than
- 3 management with medication in both the short and long term; however, a few sessions of
- 4 supervised instruction in home exercises with advice resulted in outcomes similar to those of
- 5 spinal manipulation at most time points.

6 Authors' Contributions

- 7 Conception and design: Bronfort, Evans, Grimm, Bracha
- 8 Statistical Analysis: Bracha, Svendsen
- 9 interpretation of data: Bronfort, Bracha, Svendsen, Evans
- 10 Drafting of the article: Bronfort, Evans
- 11 Critical revision of the article for important intellectual content: Bronfort, Evans, Bracha,
- 12 Svendsen, Grimm, Anderson
- 13 Final approval of the article: Bronfort, Evans
- 14 Provision of study materials or patients: Bronfort, Grimm, Anderson
- 15 Statistical expertise: Bracha, Svendsen, Grimm
- 16 Obtaining of funding: Bronfort, Evans, Grimm, Bracha
- 17 Administrative, technical or logistic support: Bronfort, Evans
- 18 Collection and assembly of data: Bronfort, Evans

19 Grant Support

- 20 By the National Institutes of Health's National Center for Complementary and Alternative
- 21 Medicine (NCCAM) (grant R01 AT000707).

1 Summary of Financial Conflicts of Interest Disclosures

2 Gert Bronfort:

3 Dr. Bronfort's employer, Northwestern Health Sciences University, received funding through a 4 restricted grant provided by the National Center for Complementary and Alternative Medicine 5 (NCCAM) to perform the study described in this manuscript. Dr. Bronfort currently serves as a 6 non paid member of the National Advisory Council for Complementary and Alternative Medicine. 7 Roni Evans: 8 Dr. Evans' employer, Northwestern Health Sciences University, received funding through a 9 restricted grant provided by NCCAM to perform the study described in this manuscript. She has 10 no other financial or nonfinancial relationships, conditions, or circumstances that present 11 potential conflict of interest.

12 Al Anderson:

13 Dr. Anderson did not receive payment for the submitted work. He has no other financial or

14 nonfinancial relationships, conditions, or circumstances that present potential conflict of interest.

15 Yiscah Bracha:

16 Ms. Bracha's employer at the time, Berman Center for Outcomes and Clinical Research, at the

17 Minneapolis Medical Research Foundation, received funding through a subcontract with

18 Northwestern Health Sciences University (funding provided through NCCAM). She has no other

19 financial or nonfinancial relationships, conditions, or circumstances that present potential conflict

20 of interest.

21 Ken Svendsen:

22 Mr. Svendsen received payment as a consultant. He has no other financial or nonfinancial

23 relationships, conditions, or circumstances that present potential conflict of interest.

24 Richard Grimm:

Dr. Grimm's employer, Berman Center for Outcomes and Clinical Research at the Minneapolis
Medical Research Foundation, received funding through a subcontract with Northwestern
Health Sciences University (funding provided through NCCAM). He serves as a paid Chair of a
Data Safety and Monitoring Board for Pfizer and as a consultant for Pfizer, Merck, and Takeda.
Dr. Grimm has grants pending with Roche and the National Institutes of Aging and has
accepted honoraria from Merck and Takeda for speaking engagements.

7 Acknowledgments

- 8 We wish to thank the entire study staff for dedicating substantial time and energy to ensure
- 9 successful study completion of the trial, and for Brent Leininger, DC and Jennifer Hart, MS, for
- 10 technical assistance in the preparation of this manuscript.

11 Reproducible Research Statement

- 12 **Protocol:** Available to interested readers by contacting Dr. Bronfort at gbronfort@nwhealth.edu.
- 13 Statistical Code: Available to interested readers by contacting Dr. Bronfort at
- 14 gbronfort@nwhealth.edu.
- 15 Data: Not available

1 Current postal addresses for all authors

- 2 Gert Bronfort, DC, PhD 3 Wolfe-Harris Center for Clinical Studies 4 Northwestern Health Sciences University 2501 W 84th St 5 6 Bloomington MN 55431 7 8 Roni Evans, DC, MS 9 Wolfe-Harris Center for Clinical Studies 10 Northwestern Health Sciences University 2501 W 84th St 11 12 Bloomington MN 55431 13 14 Alfred V. Anderson, DC, MD 15 Medical Pain Management 5775 Wayzata Blvd, Suite 110 16 Saint Louis Park, MN 17 18 55416 19 20 Kenneth H. Svendsen, MS
- 21 900 Forest Ave
- 22 Birmingham, MI 48009
- 23
- 24 Yiscah Bracha, MS
- 25 Division of Health Policy and Clinical Effectiveness
- 26 Cincinnati Children's Hospital
- 27 3333 Burnet Ave, MLC 5040
- 28 Cincinnati, OH 45229
- 29
- 30 Richard H. Grimm, MD, MPH, PhD
- 31 Berman Center for Outcomes & Clinical Research
- 32 825 S 8th St, Suite 440
- 33 Minneapolis MN 55404
- 34

References

2	1.	Cote P, Cassidy JD, Carroll L. The Saskatchewan Health and Back Pain Survey. The
3		prevalence of neck pain and related disability in Saskatchewan adults. Spine 1998;
4		23(15):1689-98. [PMID: PM:9704377]
5	2.	Fejer R, Kyvik KO, Hartvigsen J. The prevalence of neck pain in the world population:
6		a systematic critical review of the literature. Eur Spine J 2005; 15(6):834-48. [PMID:
7		PM:15999284]
8	3.	Hogg-Johnson S, van der Velde GM, Carroll LJ, Holm L, Cassidy D, Guzman J et
9		al. The burden and determinants of neck pain in the general population: results of the
10		Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated
11		Disorders. Spine 2008; 33(4S):S39-S51.
12	4.	Guzman J, Haldeman S, Carroll LJ, Carragee EJ, Hurwitz EL, Peloso P et al. Clinical
13		practice implications of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain
14		and Its Associated Disorders: from concepts and findings to recommendations. Spine
15		2008; 33(4S):S199-S213.
16	5.	Riddle DL, Schappert SM. Volume and characteristics of inpatient and ambulatory
17		medical care for neck pain in the United States: data from three national surveys. Spine

2007; 32(1):132-40. [PMID: PM:17202904]

1	6.	Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative
2		medicine use among adults: United States, 2002. Adv Data 2004;(343):1-19. [PMID:
3		PM:15188733]
4	7.	Coulter ID, Hurwitz EL, Adams AH, Genovese BJ, Hays R, Shekelle PG. Patients
5		using chiropractors in North America: who are they, and why are they in chiropractic
6		care? Spine 2002; 27(3):291-6. [PMID: PM:11805694]
7	8.	Martin BI, Deyo RA, Mirza SK, Turner JA, Comstock BA, Hollingworth W et al.
8		Expenditures and health status among adults with back and neck problems. JAMA 2008;
9		299(6):656-64. [PMID: PM:18270354]
10	9.	Cote P, van der Velde GM, Cassidy D, Carroll LJ, Hogg-Johnson S, Holm L et al.
11		The burden and determinants of neck pain in workers: results of the Bone and Joint
12		Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine 2008;
13		33(4S):S60-S74.
14	10.	Cote P, Kristman V, Vidmar M, Van Eerd D, Hogg-Johnson S, Beaton D et al. The
15		prevalence and incidence of work absenteeism involving neck pain: a cohort of Ontario
16		lost-time claimants. Spine 2008; 33(4S):S192-S198.
17	11.	Linton SJ, Hellsing AL, Hallden K. A population-based study of spinal pain among 35-
18		45-year-old individuals. Prevalence, sick leave, and health care use. Spine 1998;
19		23(13):1457-63.

1	12.	Gross A, Hoving JL, Haines T, Goldsmith CH, Kay TM, Aker P et al. Manipulation
2		and mobilisation for mechanical neck disorders (review). Cochrane Database Syst Rev
3		2009;(4):1-91.
4	13.	Kay TM, Gross A, Goldsmith CH, Hoving JL, Bronfort G. Exercises for mechanical
5		neck disorders (Review). Cochrane Database Syst Rev 2009;(4):1-107.
6	14.	Peloso P, Gross A, Haines T, Trinh K, Goldsmith CH, Burnie S. Medicinal and
7		injection therapies for mechanical neck disorders. Cochrane Database Syst Rev
8		2007;(3):CD000319. [PMID: PM:17636629]
9	15.	Gross A, Miller J, D'Sylva J, Burnie SJ, Goldsmith CH, Graham N et al. Manipulation
10		or mobilisation for neck pain. Cochrane Database Syst Rev 2010;(1):CD004249. [PMID:
11		PM:20091561]
12	16.	Spitzer WO, Skovron ML, Salmi LR, Cassidy JD, Duranceau J, Suissa S et al.
13		Scientific monograph of the Quebec Task Force on Whiplash-Associated Disorders:
14		redefining "whiplash" and its management. Spine 1995; 20(8 Suppl):S1-73.
15	17.	Guzman J, Hurwitz EL, Carroll LJ, Haldeman S, Cote P, Carragee EJ et al. A new
16		conceptual model of neck pain: linking onset, course, and care: the Bone and Joint
17		Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine 2008;
18		3(4S):S14-S23.
19	18.	Pocock SJ. Clinical Trials. A Practical Approach. Chichester, West Sussex, UK: John
20		Wiley and Sons; 1986.

1	19.	Evans R, Bronfort G, Bittell S, Anderson AV. A pilot study for a randomized clinical
2		trial assessing chiropractic care, medical care, and self-care education for acute and
3		subacute neck pain patients. J Manipulative Physiol Ther 2003; 26(7):403-11. [PMID:
4		PM:12975626]
F	00	Deserve TE Deterson DU Chinese stie Technissee Drinsiples and Dress dures and
5	20.	Bergmann IF, Peterson DH. Chiropractic Technique: Principles and Procedures. 3rd
6		ed. St. Louis: Mosby; 2011.
7	21.	Seffinger MA, Najm WI, Mishra SI, Adams A, Dickerson VM, Murphy LS et al.
8		Reliability of spinal palpation for diagnosis of back and neck pain: a systematic review of
9		the literature. Spine 2004; 29(19):E413-E425. [PMID: PM:15454722]
10	00	Tierney I.M. McDhee S.I. Dependelsie MA. Current medical diagnosis and tractment
10	ΖΖ.	nemey LM, MCFnee SJ, Fapadakis MA. Current medical diagnosis and treatment.
11		36th ed. Stamford: Appleton & Lange; 1997.
12	23.	Scholten-Peeters GG, Bekkering GE, Verhagen AP, van der Windt DA, Lanser K,
13		Hendriks EJ et al. Clinical practice guideline for the physiotherapy of patients with
14		whiplash-associated disorders. Spine 2002; 27(4):412-22. [PMID: PM:11840109]
15	24	McKenzie R. Treat Your Own Neck, Third Edition ed Waikanae, New Zealand: Spinal
10	Δ-Τ.	
16		Publications; 2002.
17	25.	Bronfort G, Evans R, Nelson B, Aker P, Goldsmith C, Vernon H. A randomized
18		clinical trial of exercise and spinal manipulation for patients with chronic neck pain. Spine
19		2001; 26(7):788-99.

1	26.	Jaeschke R, Singer J, Guyatt GH. A comparison of seven-point and visual analogue
2		scales. Data from a randomized trial. Controlled Clin Trials 1990; 11(1):43-51.
3	27.	Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a
4		comparison of six methods. Pain 1986; 27:117-26.
5	28.	Huskisson EC. Measurement of pain. Lancet 1974; 2:1127-31.
6	29.	Carlsson AM. Assessment of chronic pain. I: Aspects of the reliability and validity of the
7		visual analogue scale. Pain 1983; 16(1):87-101.
8	30.	Vernon H, Mior S. The Neck Disability Index: a study of reliability and validity. J
9		Manipulative Physiol Ther 1991; 14(7):409-15.
10	31.	Koes BW, Bouter LM, van Mameren H, Essers AH, Verstegen GM, Hofhuizen DM et
10 11	31.	Koes BW, Bouter LM, van Mameren H, Essers AH, Verstegen GM, Hofhuizen DM et al. A blinded randomized clinical trial of manual therapy and physiotherapy for chronic
10 11 12	31.	Koes BW, Bouter LM, van Mameren H, Essers AH, Verstegen GM, Hofhuizen DM et al. A blinded randomized clinical trial of manual therapy and physiotherapy for chronic back and neck complaints: physical outcome measures. J Manipulative Physiol Ther
10 11 12 13	31.	Koes BW, Bouter LM, van Mameren H, Essers AH, Verstegen GM, Hofhuizen DM et al. A blinded randomized clinical trial of manual therapy and physiotherapy for chronic back and neck complaints: physical outcome measures. J Manipulative Physiol Ther 1992; 15(1):16-23.
10 11 12 13 14	31. 32.	Koes BW, Bouter LM, van Mameren H, Essers AH, Verstegen GM, Hofhuizen DM et al. A blinded randomized clinical trial of manual therapy and physiotherapy for chronic back and neck complaints: physical outcome measures. J Manipulative Physiol Ther 1992; 15(1):16-23. Deyo RA, Walsh NE, Martin DC, Schoenfeld LS, Ramamurthy S. A controlled trial of
10 11 12 13 14 15	31. 32.	Koes BW, Bouter LM, van Mameren H, Essers AH, Verstegen GM, Hofhuizen DM et al. A blinded randomized clinical trial of manual therapy and physiotherapy for chronic back and neck complaints: physical outcome measures. J Manipulative Physiol Ther 1992; 15(1):16-23. Deyo RA, Walsh NE, Martin DC, Schoenfeld LS, Ramamurthy S. A controlled trial of transcutaneous electrical nerve stimulation (TENS) and exercise for chronic low back
10 11 12 13 14 15 16	31. 32.	 Koes BW, Bouter LM, van Mameren H, Essers AH, Verstegen GM, Hofhuizen DM et al. A blinded randomized clinical trial of manual therapy and physiotherapy for chronic back and neck complaints: physical outcome measures. J Manipulative Physiol Ther 1992; 15(1):16-23. Deyo RA, Walsh NE, Martin DC, Schoenfeld LS, Ramamurthy S. A controlled trial of transcutaneous electrical nerve stimulation (TENS) and exercise for chronic low back pain. N Engl J Med 1990; 322(23):1627-34.
10 11 12 13 14 15 16 17	31. 32. 33.	Koes BW, Bouter LM, van Mameren H, Essers AH, Verstegen GM, Hofhuizen DM et al. A blinded randomized clinical trial of manual therapy and physiotherapy for chronic back and neck complaints: physical outcome measures. J Manipulative Physiol Ther 1992; 15(1):16-23. Deyo RA, Walsh NE, Martin DC, Schoenfeld LS, Ramamurthy S. A controlled trial of transcutaneous electrical nerve stimulation (TENS) and exercise for chronic low back pain. N Engl J Med 1990; 322(23):1627-34. Hansen FR, Bendix T, Skov P, Jensen CV, Kristensen JH, Krohn L et al. Intensive,
10 11 12 13 14 15 16 17 18	31. 32. 33.	Koes BW, Bouter LM, van Mameren H, Essers AH, Verstegen GM, Hofhuizen DM et al. A blinded randomized clinical trial of manual therapy and physiotherapy for chronic back and neck complaints: physical outcome measures. J Manipulative Physiol Ther 1992; 15(1):16-23. Deyo RA, Walsh NE, Martin DC, Schoenfeld LS, Ramamurthy S. A controlled trial of transcutaneous electrical nerve stimulation (TENS) and exercise for chronic low back pain. N Engl J Med 1990; 322(23):1627-34. Hansen FR, Bendix T, Skov P, Jensen CV, Kristensen JH, Krohn L et al. Intensive, dynamic back-muscle exercises, conventional physiotherapy, or placebo-control
10 11 12 13 14 15 16 17 18 19	31. 32. 33.	Koes BW, Bouter LM, van Mameren H, Essers AH, Verstegen GM, Hofhuizen DM et al. A blinded randomized clinical trial of manual therapy and physiotherapy for chronic back and neck complaints: physical outcome measures. J Manipulative Physiol Ther 1992; 15(1):16-23. Deyo RA, Walsh NE, Martin DC, Schoenfeld LS, Ramamurthy S. A controlled trial of transcutaneous electrical nerve stimulation (TENS) and exercise for chronic low back pain. N Engl J Med 1990; 322(23):1627-34. Hansen FR, Bendix T, Skov P, Jensen CV, Kristensen JH, Krohn L et al. Intensive, dynamic back-muscle exercises, conventional physiotherapy, or placebo-control treatment of low-back pain. A randomized, observer-blind trial. Spine 1993; 18(1):98-

34.	Bronfort G, Goldsmith CH, Nelson CF, Boline PD, Anderson AV. Trunk exercise
	combined with spinal manipulative or NSAID therapy for chronic low back pain: a
	randomized, observer-blinded clinical trial. J Manipulative Physiol Ther 1996; 19(9):570-
	82.
35.	Daffner SD, Hilibrand AS, Hanscom BS, Brislin BT, Vaccaro AR, Albert TJ. Impact
	of neck and arm pain on overall health status. Spine 2003; 28(17):2030-5. [PMID:
	PM:12973155]
36.	Dvorak J, Antinnes JA, Panjabi M, Loustalot D, Bonomo M. Age and gender related
	normal motion of the cervical spine. Spine 1992; 17(10 Suppl):S393-8.
37.	Petersen CM, Johnson RD, Schuit D. Reliability of cervical range of motion using the
	OSI CA 6000 spine motion analyser on asymptomatic and symptomatic subjects. Man
	Ther 2000; 5(2):82-8. [PMID: PM:10903583]
38.	Evans R, Bronfort G, Nelson B, Goldsmith CH. Two-year follow-up of a randomized
	clinical trial of spinal manipulation and two types of exercise for patients with chronic
	neck pain. Spine 2002; 27(21):2383-9. [PMID: PM:12438988]
39.	Littell RC, Milliken GA, Stroup WW, Wolfinger RD. SAS System for Mixed Models.
	Cary, NC: SAS Publications; 1996.
40.	Linear Mixed Models in Practice: A SAS-Oriented Approach. New York: Springer; 1997.
41.	Brown H, Prescott R. Applied mixed models in medicine. New York: John Wiley &
	Sons, Inc.; 1999.
	 34. 35. 36. 37. 38. 39. 40. 41.

1	42.	Jennrich RI, Schluchter MD. Unbalanced repeated-measures models with structured
2		covariance matrices. Biometrics 1986; 42(4):805-20. [PMID: PM:3814725]
3	43.	Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate
4		adjustment and baseline comparisons in clinical trial reporting: current practice and
5		problems. Stat Med 2002; 21(19):2917-30. [PMID: PM:12325108]
6	44.	Yu LM, Chan AW, Hopewell S, Deeks JJ, Altman DG. Reporting on covariate
7		adjustment in randomised controlled trials before and after revision of the 2001
8		CONSORT statement: a literature review. Trials 2010; 11:59. [PMID: PM:20482769]
9	45.	Sherman KJ, Cherkin DC, Erro J, Miglioretti DL, Deyo RA. Comparing yoga,
10		exercise, and a self-care book for chronic low back pain: a randomized, controlled trial.
11		Ann Intern Med 2005; 143(12):849-56. [PMID: PM:16365466]
12	46.	Levin J, Serlin R, Seaman M. A controlled, powerful multiple-comparison strategy for
13		several situations. Psychol Bull 1994; 115(1):153-9.
14	47.	Little RJA, Rubin DB. Statistical Analysis with Missing Data. 2nd ed. New York: John
15		Wiley & Sons, Inc.; 2002.
16	48.	Rubin DB. Inference and missing data. Biometrika 1976; 63:581-92.
17	49.	Ostelo RW, de Vet HC. Clinically important outcomes in low back pain. Best Pract Res
18		Clin Rheumatol 2005; 19(4):593-607. [PMID: PM:15949778]

1	50.	Pool JJ, Ostelo RW, Hoving JL, Bouter LM, de Vet HC. Minimal clinically important
2		change of the Neck Disability Index and the Numerical Rating Scale for patients with
3		neck pain. Spine 2007; 32(26):3047-51. [PMID: PM:18091500]
4	51.	Sherman KJ, Cherkin DC, Hawkes RJ, Miglioretti DL, Deyo RA. Randomized trial of
5		therapeutic massage for chronic neck pain. Clin J Pain 2009; 25(3):233-8. [PMID:
6		PM:19333174]
7	52.	Fritz JM, Hebert J, Koppenhaver S, Parent E. Beyond minimally important change:
8		defining a successful outcome of physical therapy for patients with low back pain. Spine
9		(Phila Pa 1976) 2009; 34(25):2803-9. [PMID: PM:19910868]
10	53.	Bendtsen L, Bigal ME, Cerbo R, Diener HC, Holroyd K, Lampl C et al. Guidelines for
11		controlled trials of drugs in tension-type headache: second edition. Cephalalgia 2010;
12		30(1):1-16. [PMID: PM:19614696]
13	54.	Ostelo RW, Deyo RA, Stratford P, Waddell G, Croft P, Von Korff M et al. Interpreting
14		change scores for pain and functional status in low back pain: towards international
15		consensus regarding minimal important change. Spine 2008; 33(1):90-4. [PMID:
16		PM:18165753]
17	55.	Guyatt GH, Juniper EF, Walter SD, Griffith LE, Goldstein RS. Interpreting treatment
18		effects in randomised trials. BMJ 1998; 316(7132):690-3. [PMID: PM:0009522799]
19	56.	Dworkin RH, Turk DC, McDermott MP, Peirce-Sandner S, Burke LB, Cowan P et al.
20		Interpreting the clinical importance of group differences in chronic pain clinical trials:
21		IMMPACT recommendations. Pain 2009; 146(3):238-44. [PMID: PM:19836888]

1	57.	Hill J, Lewis M, Papageorgiou AC, Dziedzic K, Croft P. Predicting persistent neck
2		pain: a 1-year follow-up of a population cohort. Spine 2004; 29(15):1648-54. [PMID:
3		PM:15284511]
4	58.	Hoving JL, Koes BW, de Vet HC, van der Windt DA, Assendelft WJ, van Mameren
5		H et al. Manual therapy, physical therapy, or continued care by a general practitioner for
6		patients with neck pain. A randomized, controlled trial. Ann Intern Med 2002;
7		136(10):713-22. [PMID: PM:12020139]
8	59.	Hoving JL, de Vet HC, Koes BW, Mameren H, Deville WL, van der Windt DA et al.
9		Manual therapy, physical therapy, or continued care by the general practitioner for
10		patients with neck pain: long-term results from a pragmatic randomized clinical trial. Clin
11		J Pain 2006; 22(4):370-7. [PMID: PM:16691091]
12	60.	Pool JJ, Ostelo RW, Koke AJ, Bouter LM, de Vet HC. Comparison of the
13		effectiveness of a behavioural graded activity program and manual therapy in patients
14		with sub-acute neck pain: design of a randomized clinical trial. Man Ther 2006;
15		11(4):297-305. [PMID: PM:16380288]
16	61.	Cleland JA, Glynn P, Whitman JM, Eberhart SL, MacDonald C, Childs JD. Short-term
17		effects of thrust versus nonthrust mobilization/manipulation directed at the thoracic spine
18		in patients with neck pain: a randomized clinical trial. Phys Ther 2007; 87(4):431-40.
19		[PMID: PM:17341509]

	SMT	MED	HEA
Number of participants	91	90	91
Age (years)	48.3 (15.2)	46.8 (12.2)	48.6 (12.5)
Gender (% female)	58.2	72.2	65.9
Married/living with someone (%)	60.4	73.3	60.4
College graduate (%)	55.0	48.9	52.8
Current smoker (%)	13.2	14.4	17.6
BMI (kg/m ²)	27.6 (5.8)	27.9 (6.6)	26.4 (6.1)
Duration of neck pain (weeks)	7.0 (3.2)	7.4 (3.0)	6.8 (3.2)
Frequency of neck pain (0=none of the time; 5=all of the time)	3.5 (0.9)	3.3 (0.9)	3.7 (0.9)
Pain radiation to upper extremity (%)	24.2	20.0	23.3
Awake at night because of neck pain (%)	49.5	65.6	61.5
Reported cause of neck pain:			
-Trauma	29.7	22.2	16.5
Auto accident (%)	8.8	7.8	8.8
Leisure time accident (%)	16.5	12.2	5.5
Job accident (%)	4.4	2.2	2.2
-No apparent cause (%)	45.1	48.9	50.5
-Did not recall (%)	5.5	8.9	6.6
-Other (e.g., repetitive motion, stress, sleep position) (%)	19.8	20.0	26.4
Depression (CES-D) score (0-100)	14.3 (12.7)	15.3 (11.0)	12.7 (9.6)
Expectation of change in pain (1=much better; 5=much worse)	1.5 (0.7)	1.8 (.6)	1.9 (0.6)

Table 1. Baseline demographic and clinical characteristics (SD)

SMT=Spinal Manipulation Therapy; MED=Medication; HEA=Home Exercise with Advice

Treatment group (number of patients who. received treatment)	Mean number of visits (range)	Specific aspects of intervention	Number of patients (%)
		Cervical SMT	90 (99%)
		Thoracic SMT	56 (62%)
		Soft tissue	79 (87%)
SMT (91)	15.3 (2-23)	Assisted stretch	61 (67%)
		Hot packs	38 (42%)
		Cold packs	61 (67%)
		Prescription medication	0
		NSAID, opioid analgesic, and muscle relaxant	76 (90%)
		NSAID and opioid analgesic	3 (4%)
MED (84)	4.8 (1-8)	NSAID and muscle relaxant	2 (2%)
		Opioid analgesic and muscle relaxant	1 (1%)
		Muscle relaxant only	1 (1%)
		Exercise instruction	91 (100%)
		Education (spinal anatomy, etc)	91 (100%)
HEA (91)	2 (1-2)	Self care advice (pain management, etc)	91 (100%)
. ,	- /	Instructions for ADLs (lifting, etc)	88 (97%)
		Prescription medication	0

Table 2. Details of treatment interventions

SMT=Spinal Manipulation Therapy; MED=Medication; HEA=Home Exercise with Advice; NSAID=nonsteroidal anti-inflammatory drug; ADLs=activities of daily living

Table 3. Between-group diff	erences for changes	from baseline in	patient-rated pain
-----------------------------	---------------------	------------------	--------------------

	SMT (n=91)	MED (n=90)	HEA (n=91)	Change in SMT minus change in MED	P value	Change in SMT minus change in HEA	P value	Change in HEA minus change in MED	P value
Week 0	5.27 (1.57)	4.93 (1.49)	5.05 (1.64)						
Week 2	3.77 (1.86)	3.62 (1.97)	3.47 (2.12)						
Week 2 – Week 0	1.51 (1.15 to 1.86)	1.28 (0.92 to 1.65)	1.57 (1.22 to 1.93)	0.22 (-0.35 to 0.79)	0.44	-0.07 (-0.63 to 0.50)	0.82	0.29 (-0.28 to 0.86)	0.32
Week 4	2.93 (2.02)	2.89 (1.83)	2.80 (2.15)						
Week 4 – Week 0	2.31 (1.90 to 2.73)	2.01 (1.68 to 2.35)	2.27 (1.85 to 2.69)	0.30 (-0.27 to 0.87)	0.30	0.05 (-0.52 to 0.61)	0.87	0.25 (-0.32 to 0.83)	0.39
Week 8	2.01 (1.88)	2.39 (1.80)	2.22 (2.22)						
Week 8 – Week 0	3.24 (2.80 to 3.67)	2.50 (2.13 to 2.88)	2.85 (2.37 to 3.33)	0.73 (0.16 to 1.30)	0.012	0.38 (-0.18 to 0.95)	0.185	0.35 (-0.22 to 0.92)	0.23
Week 12	1.50 (1.70)	2.08 (1.65)	1.74 (1.84)						
Week 12 – Week 0	3.75 (3.34 to 4.16)	2.81 (2.41 to 3.20)	3.31 (2.88 to 3.74)	0.94 (0.37 to 1.51)	0.001	0.44 (-0.13 to 1.00)	0.130	0.50 (-0.07 to 1.08)	0.087
Short Term*				0.55 (0.10 to 1.00)	0.017	0.20 (-0.25 to 0.65)	0.38	0.35 (-0.10 to 0.80)	0.129
Week 26	1.90 (2.24)	2.33 (1.86)	1.77 (2.09)						
Week 26 – Week 0	3.30 (2.83 to 3.77)	2.52 (2.06 to 2.98)	3.21 (2.73 to 3.69)	0.78 (0.20 to 1.36)	0.009	0.09 (-0.49 to 0.67)	0.76	0.69 (0.10 to 1.28)	0.021
Week 52	1.60 (1.53)	2.14 (1.85)	1.92 (2.34)						
Week 52 – Week 0	3.57 (3.13 to 4.00)	2.70 (2.20 to 3.20)	3.07 (2.46 to 3.69)	0.87 (0.27 to 1.47)	0.005	0.49 (-0.10 to 1.08)	0.101	0.37 (-0.22 to 0.97)	0.22
Long Term [†]				0.64 (0.21 to 1.08)	0.004	0.23 (-0.20 to 0.66)	0.30	0.41 (-0.03 to 0.85)	0.066
Absolute reduction in pain									
Week 12									
≥ 50%	82.2%	69.0%	77.0%	13.2% (0.5% to 25.8%)		5.2% (-6.7% to 17.1%)		8.0% (-5.3% to 21.2%)	
≥ 75%	56.7%	33.3%	48.3%	23.3% (9.0% to 37.7%)		8.4% (-6.3% to 23.1%)		14.9% (0.4% to 29.5%)	
100%	32.2%	13.1%	29.9%	19.1% (7.1% to 31.2%)		2.3% (-11.3% to 16.0%)		16.8% (4.8% to 28.8%)	
Week 26									
≥ 50%	75.0%	59.0%	71.6%	16.0% (1.7% to 30.3%)		3.4% (-10.1% to 16.9%)		12.6% (-2.1% to 27.3%)	
≥ 75%	53.6%	30.8%	49.4%	22.8% (8.0% to 37.6%)		4.2% (-11.1% to 19.4%)		18.6% (3.7% to 33.6%)	
100%	36.9%	19.2%	34.6%	17.7% (4.2% to 31.2%)		2.3% (-12.3% to 17.0%)		15.3% (1.8% to 28.9%)	
Week 52									
≥ 50%	81.8%	69.0%	69.6%	12.8% (-1.0% to 26.6%)		12.2% (-1.1% to 25.5%)		0.6% (-14.2% to 15.4%)	
≥ 75%	53.2%	38.0%	49.4%	15.2% (-0.7% to 31.1%)		3.9% (-11.8% to 19.6%)		11.3% (-4.4% to 27.1%)	
100%	27.3%	16.9%	36.7%	10.4% (-2.9% to 23.6%)		-9.4% (-24.0% to 5.1%)		19.8% (6.1% to 33.6%)	

Values are means (standard deviations) for individual time point data and means (95% Confidence Interval) for both within group change from baseline and between group comparisons.

*Group differences based on weeks 2, 4, 8, and 12 data; [†]Group differences based on weeks 2, 4, 8, 12, 26, and 52 data

SMT=Spinal Manipulation Therapy; MED=Medication; HEA=Home Exercise with Advice

Pain: 0-10 scale (0=no neck pain, 10=the worst neck pain possible)

	Harris to helpful composition of the second	former (* 10) Andre Franker (* 10) Handelsen (* 10) Handelsen (* 10) Andre Franker (* 10) Handelsen (* 10) Handelsen (* 10) Handelsen (* 10)	
1			
Sand Research Property (1971)	Teamater (ME)	These even and Assessment	
Annuari scriff (scrift) Annuari 1997 (scrift) Direct scrift (scrift)	The second secon	Manager (GLAND) Noted (GLAND) Diversity (GLAND) Diversity (GLAND)	
Description of the sector Reserves Reserves and sector Reserves and sector	Paganta Milanii Roman Paganti (mil) Refere La prisane (mil)	Annual di sub Manual annual (CA)	
Part later and later familie families families man de prim man de prim man de prim	Test Discount of page Test Discount of the second of the	Part State of State	
Analyzad (1997)	Analysis (1-10)	Analysis (1997)	
The subtract local billion of our fit	where the states are left and provide	No. 4 and colored the part	

Wk 12 Chanza in Nack Bearson Correlation	Wk 12					BL1 Q(2)		BL1 Q(17) Pain	Neck pain			BL1 Q(4)	Expectation in
Wk 12 Change in Neck Dearson Correlation	Crange in Neck Pain	Pxw26bl	Pxw52bl	Mean CESD	UUKATION IN weeks	Gender	BL1 Q(3) Marital Status	worse with coughing or sn	wake you up at night	BL1and2Freg	trauma	How much schooling	Group
	-	616(**)	602(**)	101	.202(**)	.027	015	192(**)	202(**)	267(**)	033	.010	.129(*)
Pain Sig. (2-tailed)		000	000	.103	.001	.662	.810	.002	.001	000	.598	.875	.037
Z	261	241	226	261	260	261	261	261	261	261	261	261	261
Pxw26bl Pearson Correlation	616(**)	-	.577(**)	055	109	001	.015	.154(*)	.137(*)	.126(*)	.027	114	135(*)
Sig. (2-tailed)	000.		000	.391	.091	.992	.819	.016	.032	.050	.678	.076	.035
Z	241	243	220	243	242	243	243	243	243	243	243	243	243
Pxw52bl Pearson Correlation	602(**)	.577(**)	-	.119	.018	.102	093	.162(*)	.139(*)	.215(**)	056	076	147(*)
Sig. (2-tailed)	000.	000.		.074	.783	.124	.164	.015	.036	.001	.402	.257	.027
Z	226	220	227	227	226	227	227	227	227	227	227	227	227

Correlations

Correlations

Expectation in Assigned Group	.150(*)	.016	261	161(*)	.012	243	128	.055	227		
BL1 Q(4) How much schooling	.036	.564	261	113	620.	243	101	.127	227		
trauma	016	.792	261	900.	.920	243	056	.398	227		
BL1 and2Freq	232(**)	000.	261	.150(*)	.020	243	.235(**)	000.	227		
BL1 Q(23) Neck pain wake you up at night	200(**)	.001	261	.140(*)	.029	243	.147(*)	.027	227		
BL1 Q(17) Pain worse with coughing or sn	189(**)	.002	261	.149(*)	.020	243	.176(**)	.008	227		
BL1 Q(3) Marital Status	016	.795	261	.034	.594	243	047	.483	227		
BL1 Q(2) Patient's Gender	.023	.710	261	008	.901	243	.106	.110	227		
DURATION in weeks	.205(**)	.001	260	120	.063	242	.028	.670	226		
BL1 and BL2 Mean CESD	141(*)	.023	261	000 [.]	766.	243	.140(*)	.035	227		
Pxw52bl	611(**)	000	226	.635(**)	000.	220	1.000	•	227		
Pxw26bl	647(**)	000.	241	1.000		243	.635(**)	000.	220		
Wk 12 Change in Neck Pain	1.000		261	647(**)	000 [.]	241	611(**)	000	226		
	Correlation Coefficient	Sig. (2-tailed)	z	Correlation Coefficient	Sig. (2-tailed)	z	Correlation Coefficient	Sig. (2-tailed)	z		
	Wk 12 Change in Neck Pain			Pxw26bl			Pxw52bl				
	Spearman's rho										

** Correlation is significant at the 0.01 level (2-tailed).
 * Correlation is significant at the 0.05 level (2-tailed).



Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



Section 1.	Identifying Infor	mation	
1. Given Name (Fi Gert	irst Name)	2. Surname (Last Name) Bronfort	3. Effective Date (07-August-2008) 25-October-2011
4. Are you the cor	responding author?	✓ Yes No	
E Manuscript Titl	•		

5. Manuscript Title

Spinal manipulation, medication, or home exercise with advice for acute and subacute neck pain: A randomized controlled trial

6. Manuscript Identifying Number (if you know it)

M11-0299

Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

The Work Under Consideration f	or Pub	lication				
Туре	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant			\checkmark	NWHSU		×
						ADD
3. Support for travel to meetings for the study or other purposes			\checkmark	NWHSU		×
						ADD

* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.



Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities out	side the	submit	ted work			
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	

* This means money that your institution received for your efforts.

** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section 4.

Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

✓ No other relationships/conditions/circumstances that present a potential conflict of interest

Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Show All Table Rows

CAVE	
SAVE	

Evaluation and Feedback

Please visit <u>http://www.icmje.org/cgi-bin/feedback</u> to provide feedback on your experience with completing this form.



INSTRUCTIONS:

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form has five parts.

1. Identifying information.

Each author should submit a separate form. Provide complete information and double-check the manuscript number. If you are NOT the corresponding author please insert his or her name.

2. The work under consideration for publication.

Please provide information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The idea is to provide for the reader information about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. If you check the "No" box it means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds to pay you. If you or your institution did receive funds from a third party to support the work, check "Yes" along with the appropriate boxes to indicate the type of support and whether you or your institution received it.

3. Relevant financial activities outside the submitted work.

Please report all sources of revenue relevant to the submitted work that accrued either directly to you or were paid to your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. If there is any question, it is usually better to disclose a relationship than not to do so. Please note that your interactions with the work's sponsor outside the submitted work should be listed here. For each category list each entity on a separate line. Use as many lines as necessary to provide complete information. In addition, please disclose relationships that fall outside the 36-month window that readers may want to know about and could reasonably criticize you for not disclosing (for example, long-term financial relationships that are now ended).

The goal of this section is to provide information for our reviewers and readers about your interactions with entities in the biomedical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer. For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to benefit financially from the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as the NIH or the MRC, need not be disclosed. For example, if the NIH sponsored a piece of work you have been involved in but drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Financial relationships involving your spouse or partner or your children (under 18 years of age).

If monies from the types of relationships listed in Section 3 were paid to your spouse or partner or dependent children, please list the type of activity and source of the money.

5. Nonfinancial associations.

Please report any personal, professional, political, institutional, religious, or other associations that a reasonable reader would want to know about in relation to the submitted work.



Section 1. Identifying Information.

Given Name: (or first)	Roni	Surname: (or last)	Evans	Effective Date: 21-October-2011
Are you the	corresponding author?	Yes X N	Ňo	Format example: 07-August-2008
Corresponding	author's name: Gert I	Bronfort		
Manuscript Tit	tle: Spinal manipulation randomized control	, medication, o led trial	r home exercise with advice for a	icute and subacute neck pain: A
Manuscript Ide	entifying Number (if y	ou know it):	M11-0299	

Section 2. Information about the support of the work under consideration for publication.

Did you or your institution at any time receive payment or support in kind for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

🗌 No

Yes, specify nature of compensation

Section 3. Information about relevant financial relationships outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with any entities that have an interest related to the submitted work. Use one line for each entity; add as many lines as you need. Use the comments column to indicate any additional information that you think a reader or editor would want to know about the compensation. Report relationships that were present during the 36 months prior to submission. In addition please disclose relationships that fall outside the 36-month window that readers may want to know about and could reasonably criticize you for not disclosing (for example, long-term financial relationships that are now ended).

If you have more than one relationship, click "Add +" to add a row. Click "Del ×" to delete an extra row.

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your institution	Entity	Comments	
Board membership	\boxtimes					Del ×
						Add +
Consultancy	\mathbf{X}					Del ×
	•	•				Add +
Employment	\boxtimes					$\text{Del} \times$
					•	Add +



Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your institution	Entity	Comments	
Expert testimony	\boxtimes					Del ×
						Add +
Gifts	\boxtimes					Del ×
						Add +
Grants/grants pending	\boxtimes					$\text{Del} \times$
	1	1	1	1		Add +
Honoraria	\square					Del ×
	1	1	1	I	1	Add +
Payment for manuscript preparation	\boxtimes					$Del \times$
		1				Add +
Patents (planned, pending or issued)	\boxtimes					Del ×
						Add +
Royalties	\boxtimes					$\text{Del} \times$
						Add +
Payment for development of educational presentations including service on speakers' bureaus	\boxtimes					Del ×
						Add +
Stock/stock options	\boxtimes					$\text{Del} \times$
						Add +
Travel/accommodations expenses covered or reimbursed	\boxtimes					Del ×
						Add +
Other (err on the side of full disclosure)	\boxtimes					Del ×
						Add +



Section 4. Information about financial relationships involving your spouse or partner or your children (under 18 years of age).

Do your children or your spouse or partner have financial relationships with entities that have an interest in the content of the submitted work?

No other relationships/conditions/circumstances that present potential conflict of interest

Yes, the following relationships/conditions/circumstances are present (explain below):

Section 5. Information about relevant nonfinancial associations.

Do you have any relevant nonfinancial associations or interests (personal, professional, political, institutional, religious, or other) that a reasonable reader would want to know about in relation to the submitted work?

No relevant nonfinancial relationships/conditions/circumstances to report.

Yes, the following relevant nonfinancial relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Save Form



Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.

Enter your full name. If you are NOT the corresponding author please check the box "no" and a space to enter the name of the corresponding author in the space that appears. Provide the requested manuscript information. Double-check the manuscript number and enter it.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work. For example, if your article is about testing an epidermal growth factor receptor (EGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

Other relationships.

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.



Section 1.	Identifying Inform	nation		
1. Given Name (Fi Yiscah	rst Name)	2. Surname (Last Name) Bracha		3. Effective Date (07-August-2008) 27-October-2011
4. Are you the cor	responding author?	Yes 🖌 No	Corresponding Author's Nam Gert Bronfort	e
5. Manuscript Title Spinal manipula trial	e tion, medication, or ho	me exercise with advice	or acute and subacute neck p	ain: A randomized controlled
6. Manuscript Idei	ntifying Number (if you k	now it)		

M11-0299

Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

The Work Under Consideration f	for Pub	lication				
Туре	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
1. Grant			\checkmark	Minneapolis Medical Research Foundation		×
						ADD
2. Consulting fee or honorarium	\checkmark					×
						ADD
3. Support for travel to meetings for the study or other purposes	\checkmark					×
						ADD
 Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like 	\checkmark					×
						ADD
5. Payment for writing or reviewing the manuscript			\checkmark	Minneapolis Medical Research Foundation		×
						ADD



The Work Under Consideration f	or Publ	lication				
Туре	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**	
 Provision of writing assistance, medicines, equipment, or administrative support 	\checkmark					×
						ADD
7. Other	\checkmark					×
						ADD

* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.

Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship click the "Add" button to add a row. Excess rows can be removed by clicking the "X" button.

Relevant financial activities outside the submitted work								
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments			
1. Board membership	\checkmark					×		
						ADD		
2. Consultancy	\checkmark					×		
						ADD		
3. Employment	\checkmark					×		
						ADD		
4. Expert testimony	\checkmark					×		
						ADD		
5. Grants/grants pending	\checkmark					×		
						ADD		
Payment for lectures including service on speakers bureaus	\checkmark					×		



Relevant financial activities outs	ide the	submit	ted work			
Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Entity	Comments	
						ADD
7. Payment for manuscript preparation	\checkmark					×
						ADD
 Patents (planned, pending or issued) 	\checkmark					×
						ADD
9. Royalties	\checkmark					×
						ADD
10. Payment for development of educational presentations	\checkmark					×
						ADD
11. Stock/stock options	\checkmark					×
						ADD
 Travel/accommodations/ meeting expenses unrelated to activities listed** 	\checkmark					×
						ADD
13. Other (err on the side of full disclosure)	\checkmark					×
						ADD

* This means money that your institution received for your efforts.

** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section 4. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

✓ No other relationships/conditions/circumstances that present a potential conflict of interest

Yes, the following relationships/conditions/circumstances are present (explain below):



At the time of manuscript acceptance, journals will ask authors to confirm and, if necessary, update their disclosure statements. On occasion, journals may ask authors to disclose further information about reported relationships.

Hide All Table Rows Checked 'No'

C		V	
P .	F 1	11	

Evaluation and Feedback

Please visit <u>http://www.icmje.org/cgi-bin/feedback</u> to provide feedback on your experience with completing this form.