

**Cost-effectiveness of minimal interventional
procedures for patients with chronic low back
pain**

Version 1.8 (Augustus 2014)

PROTOCOL TITLE: 'Cost-effectiveness of minimal interventional procedures for patients with chronic low back pain'

Protocol ID	ABR 39578 ZonMW 171202013
Short title	Minimal interventional procedures
Version	1.8
Date	Augustus 2014
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics (in Dutch: officiële productinformatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

SUMMARY

Rationale: Low back pain is a common complaint associated with high costs. Minimal interventional procedures are frequently applied in pain clinics in a subgroup of patients with chronic low back pain, namely in patients with pain resulting from single sources: facet, discus, sacroiliac joint or a combination of these. There is no general accepted definition and/or classification of these kinds of complaints. The terminology, which is used in the reimbursement system (DBC system) of the Dutch Anaesthesiology Society, is a classification of mechanical, neurologic and sympathetic. Mechanical low back pain is defined as pain resulting from single sources: facet, discus, sacroiliac joint or a combination of these. In the proposal we use the terminology in this way. These minimal interventional procedures are nowadays performed in pain clinics in a multidisciplinary setting for diagnosis and therapy. Treatment with minimal interventional procedures is used as a part of a multidisciplinary pain programme. A recent systematic review issued by the Dutch Health Insurance Council (CVZ 26/3/2011) showed that the effectiveness of minimal interventional procedures for the total group of chronic low back pain is unclear and the cost-effectiveness unknown. Based on these studies CVZ has decided not to include these procedures in our public health insurance. Despite the fact that the evidence for effectiveness of minimal interventional procedures also for specific subgroups like mechanical low back pain is limited, these procedures are, based on a risk benefit balance, recommended in the practical anaesthesiology guidelines for pain treatment and frequently applied in daily practice.

Objective: The aim of this study is to evaluate whether a multidisciplinary pain programme with minimal interventional procedures is effective and cost-effective compared with the multidisciplinary pain programme alone for patients with mechanical low back pain who did not respond to conservative primary care and were referred to a pain clinic.

Study design: We will conduct three clinical and economic evaluations from a societal perspective in which the single entities of mechanical low back pain and a mix of the single entities will be studied. Besides, we will perform an observational study of the total turnover of not eligible patients in pain clinics. Outcome measures are pain intensity, recovery, functional status and costs. Both a cost-effectiveness and cost-utility analysis will be performed.

Study population: We will include patients with mechanical low back pain who are referred by a general practitioner or medical specialist to participating pain clinics.

Intervention: In the diagnostic phase, patients will be selected by making use of diagnostic criteria as described in the Guideline low back pain (NVA, NVvN et al. 2011).

Based on signs and symptoms, patients with suspicion of a single entity, namely pain arising from the facet joints or sacroiliac joint will receive a test block with local anaesthetics.

Patients with the suspicion of pain arising from a disc will receive a provocative discography.

If patients answer yes to the question 'is there a 50% or more reduction in pain?' 30 minutes after the test block, or have a positive discography; they will be randomised to a group who receives a minimal interventional treatment + a multidisciplinary pain programme versus patients receiving the multidisciplinary pain programme alone.

Patients randomised to minimal interventional procedures will be treated according to the Guideline low back pain (NVA, NVvN et al. 2011).

Besides these three randomized trials for subgroups of patients, all patients referred to the participating pain clinics and who give informed consent will be part of an observational study. The observational data will inform us about the proportion of patients with facet joint pain, disc pain, SI pain and a combination of these, the proportion of patients with a positive block within these four groups, and the clinical outcomes of patients with a negative block.

Main study parameters/endpoints: The primary outcome measure will be measuring pain intensity with the NRS, at 3 months after the intervention.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

Participating in this trial means that difference in pain and perceived improvement in functioning will be measured at 3 and 6 weeks after the intervention; patients have to fill in web based questionnaires (see 7.1. for the questionnaires) at baseline, 3, 6, 9, and 12 months; all are referred to a multidisciplinary pain programme, and they are randomised to receive minimal interventional procedures or no additional treatment. The multidisciplinary pain program is standard care, which means that patients will not be withheld from standard care.

1. INTRODUCTION AND RATIONALE

In the Netherlands the majority of patients with low back pain is successfully treated in primary care. Approximately 20% of the patients, however, still have symptoms after 3 months and 5% after 1 year. In The Netherlands, costs of low back pain are enormous: € 3.4 billion in 2007 (Lambeek, van Mechelen et al. 2010). Patients with chronic low back pain are responsible for the majority of the high costs.

Mechanical low back pain is defined as pain resulting from single sources: facet, discus, sacroiliac joint or a combination of these. In the proposal we use the terminology in this way.

When primary care treatment has not been successful in alleviating symptoms, patients may be referred to medical specialists. Minimal interventional procedures are commonly used by anaesthesiologists in a subgroup of patients with mechanical low back pain arising from structures like facet joints, discus and sacroiliac joint or combinations of these. In The Netherlands there are more than 75 certified pain clinics that use these procedures. Indications and treatment algorithms are described in the evidence based Guideline low back pain (NVA, NVvN et al. 2011). Although these procedures are commonly used, strong evidence for their effectiveness is lacking and economic evaluations have not been performed. This multidisciplinary clinical guideline has currently been developed with support of the Dutch Society of Medical Specialists.

There is consensus among anaesthesiologists, as reflected by recommendations in this guideline, that minimal interventional procedures are effective for patients with intervertebral disc, facet joint and sacroiliac joint pain or mixed forms of these. This seems to be in contrast with recently performed systematic reviews and multidisciplinary international clinical guidelines, which concluded that there is no strong evidence that supports the effectiveness of minimal interventional procedures in patients with chronic low back pain. The main reason is that randomised controlled trials with a low risk of bias and an adequate sample size are lacking. A recent systematic review issued by the Dutch Health Insurance Council (CVZ 26/3/2011) showed that the effectiveness of minimal interventional procedures for the total group of chronic low back pain is unclear and the cost-effectiveness unknown. Based on this lack of evidence, the Dutch Health Insurance Council (CVZ) has decided to advise the Ministry of Health in The Netherlands not to reimburse minimal interventional procedures for low back pain within the Dutch public health insurance system. The anaesthesiologists claim that they are only treating a subgroup of these patients, namely patients with mechanical low back pain. It is important for care providers to evaluate the effectiveness and cost-effectiveness of minimal interventional procedures in this subgroup of patients.

Health insurance companies often have contracts with hospitals agreeing to reimburse treatment for patients with a specific health problem at specified costs without specifying the care that will be delivered. The use of diagnostic and therapeutic interventions is at the discretion of the medical specialists. For health

insurance companies it is important to know whether the care that is reimbursed is effective and cost-effective.

The aim of his project will be to provide the lacking information. The Dutch Association of Anaesthesiologists, the Dutch Spine Society, the Dutch Health Insurance Council (CVZ) and the VUmc and Erasmus MC have all explicitly acknowledged the importance of this project.

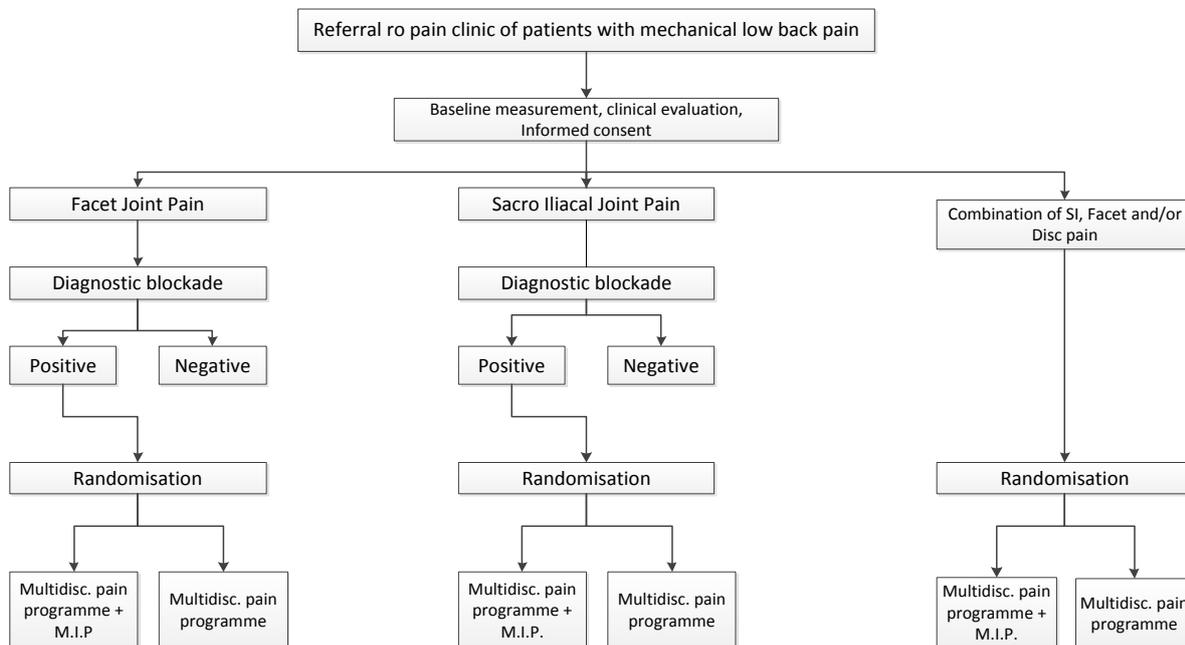
2. OBJECTIVES

Primary Objective: The main objective of this project is to evaluate the effectiveness and cost-effectiveness of minimal interventional procedures as an add-on to a multidisciplinary pain programme for patients with chronic mechanical low back pain who are referred to a pain programme/pain clinic.

The primary outcome measure will be measuring pain intensity with the NRS at 3 months after the intervention.

3. STUDY DESIGN

Economic evaluation alongside a clinical study with four subgroups for patients with mechanical low back pain who did not respond to conservative primary care and were referred to a pain clinic.



Follow – up measurements after 3 and 6 weeks: difference in pain and perceived improvement.

Follow up measurements after 3, 6, 9 and 12 months: difference in pain, perceived improvement, recovery, pain function, quality of life and patient satisfaction.

An observational study will be done alongside these trials

* Abbreviations: multidisc. pain program: multidisciplinary pain programme; M.I.P.: minimal interventional procedures

4. STUDY POPULATION

4.1 Population (base)

Patients are recruited at the departments of Anaesthesiology, i.c. the pain clinics of the participating hospitals. In this study all patients who are referred to a pain programme/pain clinic with mechanical low back pain will be invited to participate. General practitioners and medical specialists who referred patients to the pain clinics will be informed about participation of their patients in the study.

4.2 Inclusion criteria

Chronic (more than 3 months) mechanical low back pain symptoms, age between 18 and 70 years, no improvement of symptoms after at least three months of conservative treatment according to the Dutch guidelines for non-specific low back pain (GP care (advise to stay active and pain medication) and exercise therapy) in primary care. Patients must report pain on a NRS scale of 6 or higher. Patients must answer 'yes' on the question 'is there a 50% or more reduction in pain?', 30 minutes after the test block, or the disc provocation test must be positive.

4.3 Exclusion criteria

Patients with severe psychiatric or severe psychological problems, pregnant women, and patients who are not able to complete the questionnaires. Anticoagulant drug therapy and/or disturbed coagulation BMI > 35. Involved in a work related legal dispute and /or liability claim. Patients with less than 50% reduction in pain after the test block, or a negative disc provocation test. Patients that underwent instrumented surgery in the area to be investigated a laminectomy or a spondylosis.

4.4 Sample size calculation

Using a power of .9, alpha .05 and a correlation of .5 for repeated measurements, a total of 85 patients per group are needed to detect a clinically relevant mean difference of 2 points on the Numerical Rating Scale (SD 4). Anticipating potential study withdrawal (20%) 102 patients per group or 204 patients per randomized comparison are needed. In total we will need to include 612 patients in this study.

The primary outcome measure is the difference in pain intensity, measured with the numeric rating scale 3 months after the intervention. Since the intervention is directed at pain reduction, it may be expected that the effects of the minimal invasive procedures will show after a short period. A long term follow up period of 12 months is chosen to evaluate whether these effects persist, and also to create a time horizon that is long enough for the economic evaluation.

Because our primary outcome measure is the pain difference after 3 months, repeated measurements are not relevant for the sample size calculation.

The difference of 2 points in the NRS is based on a review by Ostelo et al. (Ostelo, Deyo et al. 2008), that found a Minimal Important Change of the NRS of 2 points.

Since these minimal interventional procedures have not been studied before, no SD can be found in the literature. This is in fact one of the reasons for these studies. The SD of 4 was chosen with an 'educated guess'. It may be arbitrary, but in any case it is conservative, and makes sure that we will include enough patients to find clinically relevant effects.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The selection of adequate patients in the diagnostic phase, as well as the invasive treatment of patients is usual care, as described in the Guideline low back pain (NVA, NVvN et al. 2011).

Based on signs and symptoms, patients with suspicion of a single entity, namely pain arising from the facet joints or sacroiliac joint will receive a test block with local anaesthetics. If patients answer 'yes' to the question 'is there a 50% or more reduction in pain?' 30 minutes after the test block, patients will be scheduled to receive a minimal interventional treatment.

Patients with suspicion of pain arising from the intervertebral disc will receive as test a provocative discography. If this test is positive than they will be scheduled to receive a minimal interventional treatment.

The minimal interventional procedures will take place according to a pre-specified approach:

- 1) Patients with facet joint pain will receive radiofrequency denervation of the first ramus dorsalis at L3, L4, L5 and S1.
- 2) Patients with intervertebral disc pain will receive a denervation of the involved discus.
- 3) Patients with sacroiliac joint pain will receive radiofrequency denervation of the ramus dorsalis at L5, S1, S2 and S3.
- 4) Patients with a combination of the single entities will be randomised after the clinical diagnosis to a group who receives minimal interventional treatments (i.e. a combination of the interventions mentioned under 1, 2 and 3) and a multidisciplinary pain programme.

5.2 Use of co-intervention (if applicable)

Any co intervention will be measured and included in the cost effectiveness analysis.

5.3 Escape medication (if applicable)

Not applicable

6. INVESTIGATIONAL MEDICINAL PRODUCT

Not applicable

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The primary outcome will be measuring pain intensity with the NRS at 3 months after the intervention.

7.1.2 Secondary study parameters/endpoints

Outcome measures	Follow-up						
	Baseline	3 weeks	6 weeks	3 months	6 months	9 months	12 months
Primary outcomes RCT							
Pain Intensity (NRS)	x	x	x	x	x	x	x
Secondary outcomes							
Global perceived recovery (NRS)	x	x	x	x	x	x	x
Quality of life (EQ-5D)	x	x	x	x	x	x	x
Patient satisfaction (NRS)	x			x	x	x	x
Functional Status (ODI)	x			x	x	x	x
General health (Rand-36)	x			x	x	x	x
Chronic pain experience (MPI)	x			x	x	x	x
Others							
Demographic data	x						
Pain expectation (CEQ)	x						
Pain coping strategies (PCI)	x						
Pain cognition (PCL)	x						
Depression etc. (4DSQ)	x						
Pain acceptance (CPAQ)	x						
Anxiety, depression (HADS)	x						
Economic evaluation							
Costs (diaries)					monthly		

NRS = Numeric Rating Scale; EQ-5D = EuroQol; ODI = Oswestry Disability Index; MPI = Multidimensional Pain Inventory; CEQ = Credibility/Expectancy Questionnaire; PCI = Pain Coping Inventory; PCL = Pain Cognition List; 4DSQ = Four-Dimensional Symptoms Questionnaire; CPAQ = Chronic Pain Acceptance Questionnaire; HADS = Hospital Anxiety Depression Scale

Follow-up will be 12 months. All patients participating in the trial will complete questionnaires at baseline and after 3, 6, 9, and 12 months. (The difference in pain intensity and the global- perceived improvement in functioning and quality of life will also be measured at 3 and 6 weeks after the intervention). We will ask patients to complete web-based questionnaires. If patients do not have access to the internet or prefer hard copies, we will provide these. Study subjects included in the study will receive up to two (e-mail) reminders to fill out the questionnaires. If patients still not respond the investigators will try to contact the patients by telephone once. If the patient then refuses to fill out the questionnaires the investigators will ask if by telephone they can ask the following at the **three month measure points**: Pain

Intensity (NRS), Global perceived recovery (NRS) and Patient satisfaction (NRS). Patients who refuse, will be considered lost to follow up. The core set of primary outcomes recommended for low back pain research (Bombardier 2000) will be used: global perceived recovery (7-point scale), functional status (Oswestry Disability Index (ODI)), and pain intensity (leg and back) (11-point NRS). Also general health (Rand-36), quality of life (EuroQol-5D) and patient satisfaction (NRS) are measured. The Multidimensional Pain Inventory (MPI) will be used to assess a number of dimensions of the chronic pain experience, including pain intensity, emotional distress, cognitive and functional adaptation, and social support. Patient expectation will be measured at baseline, using the CEQ. Pain cognition and coping will be measured with the Pain Cognition List and the Pain Coping Inventory. Furthermore, psychological questionnaires will be used at baseline to be able to exclude patients with severe psychiatric or psychological complaints: the 4 Dimensional Symptoms Questionnaire (4DSQ), the Chronic Pain Acceptance Questionnaire (CPAQ) and the Hospital Anxiety Depression Scale (HADS). Amongst patients that have completed the full year of follow up, dining vouchers will be distributed by means of a raffle.

7.1.3 Other study parameters

Economic evaluation: General considerations

Four economic evaluations will be performed alongside the four randomized trials. The aim of the economic evaluation is to determine and compare the total rehabilitation-related costs for patients in both trial arms, and to relate these costs to the effects of these two groups. The economic evaluations will be performed according to the intention-to-treat principle and from a societal perspective.

Economic evaluation: Costs

- Costs indicators, the following costs are considered in this study:
 - Costs of minimal interventional procedures
 - Costs of the rehabilitation programme
 - Other health care costs including the costs of physiotherapy (during follow up and in the control group), manual therapy, additional visits to other health care providers (e.g. GPs, medical specialist), prescription of medication, professional home care and hospitalisation.
 - Patient and family costs include out-of-pocket expenses (i.e., over the counter medication) and costs of paid and unpaid help.
 - Costs due to loss of production due to LBP-related work absenteeism (paid jobs and unpaid jobs).

- Measurement of volumes:
 - Number of treatment sessions during the intervention period will be registered by the therapist on standardised forms.

- All other health care costs, patient and family costs and costs due to production loss will be registered by means of cost questionnaires to be administered by the patients (Goossens, Rutten-van Molken et al. 2000). These cost questionnaires measure resources consumed on a monthly basis. Patients will receive the first questionnaire at baseline; the following diaries at the 3 weeks follow up measure, the following at the 6-week follow-up, etc. We will ask patients to complete web-based cost questionnaires. If patients do not have access to the Internet or prefer hard copies, we will provide these.

- Sources of cost prices

Costs will be valued using the guidelines published in the updated handbook for economic evaluation in the Netherlands (Hakkaart van Roijen, Tan et al. 2010). If not available then the real cost prices are calculated through the bottom-up method. Visits to other health care professionals (e.g. chiropractor) will be estimated on the basis of fees and prices charged by the professional organisation. The costs of medication will be estimated on the basis of prices charged by the Royal Society for Pharmacy. Costs of production losses due to LBP will be estimated for both paid and unpaid labour. For paid labour the costs will be calculated using both the human capital approach and the friction cost approach (Koopmanschap and Rutten 1996). For unpaid labour, the indirect costs will be estimated as the costs of production losses due to ongoing or renewed complaints in back and/or leg, e.g. voluntary work and household work, using shadow prices.

Imaging

It is standard care, in performing the minimal interventional treatments as described under 5.1, to make and save radiographic images of the needle positions. Images saved in the Facet RCT will be submitted to an expert panel to assess correct needle placement. Retrospectively we will submit all available (anonymized) images taken in the Facet RF RCT to a panel, and have them judged twice, with a 1.5 month interval. Both times we will ask the panel to judge the images as 'correct', 'incorrect' or 'unsure' - needle placement.

Out of this we want to determine an inter- and intra- observer reliability. If the reliability is high, we will determine whether 'correct placement', indeed shows a higher pain reduction (NRS) after 3 months.

7.2 Randomisation, blinding and treatment allocation

Central randomisation will be performed by a computer-generated list of random numbers. The outcome of the randomisation will be automatically reported to the local nurse who entered a positive diagnostic test in the datamanagement system. Randomisation will be stratified for clinics.

In this pragmatic trial patients and care providers will not be blinded. Because all outcome measures are self-reported, the outcome measurement is also not blinded.

Data analysis will be conducted blinded for treatment allocation and blinding will only be finished after the final analyses have been concluded.

To evaluate whether lack of blinding is associated with bias, expectations and preferences of patients will be measured before randomisation and after treatment allocation and patient satisfaction after treatment and during follow-up.

7.3 Study procedures

The selection of adequate patients in the diagnostic phase, as well as the invasive treatment of patients is usual care, described in the Guideline low back pain (NVA, NVvN et al. 2011).

On entry in the pain clinic every patient will be asked to fill the set of primary and secondary outcomes.

Eligible patients will be informed about the trial and have two weeks time to react. Patients will be included when an informed consent has been given.

Based on signs and symptoms, patients with suspicion on a single entity, namely pain arising from the facet joints or sacroiliac joint will receive a test block with local anaesthetics. If patients answer 'yes' to the question: 'is there a 50% or more reduction in pain?' 30 minutes after the test block, patients are randomized in one of the study groups. Patients with the suspicion of pain arising from the intervertebral disc will receive a provocative discography.

Patients with pain suspected to arise from multiple entities, will be randomized prior to the test block and provocative discography. The patients will follow an intention to treat protocol.

Patients will be randomised to a group who receives a multidisciplinary pain programme with a minimal interventional treatment or a group receiving a multidisciplinary pain programme alone.

All patients will receive the same standard multidisciplinary pain programme according to the guideline of the Royal Dutch Society for Physical Therapy (Bekker, Hendriks et al. 2005). Referral and coordination will take place by the anaesthesiologist; a physiotherapist will be involved, and a psychologist if necessary. The treatment will focus on activation mobilisation and consist of graded activity.

If patients in the non-interventional study groups have not improved or recovered after three months, they will not receive interventional procedures but will go back to the GP or medical specialist that had referred them to the pain clinic. We will also closely monitor and register additional care in this group.

Apart from the standard set of outcomes for low back pain research, participants in the study will fill in an economic evaluation and a monthly cost diary.

All questionnaires will be repeated at baseline, 3, 6, 9 and 12 months.

Besides these four randomized trials for subgroups of patients, all patients referred to the participating pain clinics and who give informed consent will be part of an observational study. The observational data will inform us about the proportion of patients with facet joint pain, disc pain, SI pain and a combination of these, the proportion of patients with a positive block within these four groups, and the clinical outcomes of patients with a negative block.

Participating in this trial means that difference in pain and perceived improvement in functioning will be measured at 3 and 6 weeks after the intervention; patients have to fill in web based questionnaires (see 7.1.2. for the questionnaires) at baseline, 3, 6, 9, and 12 months; all are referred to a multidisciplinary pain programme, and they are randomised to receive the minimal interventional procedures or no additional treatment.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The treating physician can decide to withdraw a subject from the study for urgent medical reasons.

7.5 Replacement of individual subjects after withdrawal

Until the sample size for the study has been reached, candidates can participate. Patients will not be replaced. No specific conditions apply for replacing an individual subject after withdrawal. When a patient withdraws him/herself (or is withdrawn by the investigator) he/she can be treated for his/her medical condition outside the study.

7.6 Follow-up of subjects withdrawn from treatment

After withdrawal patients will be asked to keep filling in the questionnaires, and an intention to treat analysis will be performed.

7.7 Premature termination of the study

Premature termination of the study is possible under the following circumstances:

- A) If no positive decision is obtained with regard to the research or if the judgement of the competent medical research ethics committee that has assessed the research is irrevocably revoked;
- B) In the event that Section 13i, clause 5 of the Medical Research Involving Human Subjects Act applies, if the Central Committee or the Minister of Health, Welfare and Sport has made an irrevocable objection to the performance of the research with medicinal products (only applicable for medicinal products);
- C) If a reasonable case can be made for terminating the research in the interests of the subjects' health;

- D) If it transpires that continuation of the research cannot serve any scientific purpose, and this is confirmed by the medical research ethics committee that has issued a positive decision on the research;
- E) If one of the two parties has been declared insolvent, or if a petition has been filed for liquidation of one of the two parties;
- F) If one of the two parties fails to comply with the obligations arising from the agreement and, provided compliance is not permanently impossible, this compliance has not taken place within thirty days after the defaulting party has received a written request to comply, unless failure to comply is out of reasonable proportion to the premature termination of the research.

8. SAFETY REPORTING

8.1 Section 10 WMO event

In accordance with section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

8.2 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / the experimental treatment]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

8.2.1 Suspected unexpected serious adverse reactions (SUSAR)

Not applicable

8.2.2 Annual safety report

Not applicable

8.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

8.4 Data Safety Monitoring Board (DSMB)

A data safety monitoring board (DSMB) will not be assembled for this study. All adverse events, serious or not, unanticipated or not, will be reported to the appropriate ethics and regulatory agencies in accordance with reporting requirements.

9. STATISTICAL ANALYSIS

9.1 Descriptive statistics

All patients will be given a distinctive number; data will be analysed anonymously. Baseline comparability was performed by descriptive statistics to examine if randomisation was successful.

9.2 Univariate analysis

An intention-to-treat analysis will be conducted for each follow-up moment. Baseline data (demographics, pain expectation and the psychological variables) will be analysed for comparing the difference between the interventiongroup and the controlgroup for each RCT. 95%-confidence intervals will be calculated for the difference of percentages (Chi-square distribution) and means (t-distribution) for dichotomous and continuous outcome variables, respectively.

9.3 Multivariate analysis

To compare changes in pain between the interventiongroup and the controlgroup for each RCT after three months multilevel analyses will be performed.

In case of unequal distributions of prognostic factors, multivariate analysis techniques will be used to correct for these between-group differences in prognosis.

Change scores for the primary and secondary outcomes will be calculated by subtracting the baseline scores from the post-treatment scores (after 3 and 6 weeks, 3, 6, 9, and 12 months) and compare those for the intervention and the controlgroup using a t-test.

Economic evaluation

For the economic evaluation of each RCT, multivariate analyses will be performed as well. Costs and QALYS will be compared for the intervention- and the controlgroup (with costs/QALYS as dependent variable and group as independent variable)

Cost-effectiveness and a cost-utility analysis will be performed. Cost-effectiveness ratios will be calculated by dividing the difference between the mean costs of the two treatment groups by the difference in the mean effects of the two treatment groups. Ratio's will include the clinical effect measures of the trial, i.e., general perceived recovery, functional status, pain intensity. Cost-utility will be based on the EuroQol and expressed in costs per QALY. Cost-effectiveness and cost-utility ratios will be estimated using bootstrapping techniques and acceptability curves and net

monetary benefit will also be estimated. Sensitivity analysis on the most important cost drivers will be performed in order to assess the robustness of the results.

- Patient outcome analysis

The primary effect measures will also be used in the economic evaluation:

1) general improvement, 2) functional status, 3) pain intensity, and 4) work absenteeism. Utilities will be measured using the EuroQol-5D. Overall utility scores for population-based quality of life can be obtained and will be expressed as QALY's. QALY's will be calculated by multiplying the utility of a health state by the time spent in this health state using the Dutch valuation tariff (Lamers, Stalmeier et al. 2005).

9.4 Interim analysis

Not applicable

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI - Ethical Principles for Medical Research Involving Human Subjects; Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, 41st WMA General Assembly, Hong Kong, September 1989, 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, 52nd WMA General Assembly, Edinburgh, Scotland, October 2000, 53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added), 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added) and 59th WMA General Assembly, Seoul, October 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

10.2 Recruitment and consent

Patients are recruited at the departments of Anaesthesiology, i.c. the pain clinics of the participating hospitals. In this pragmatic trial, all patients who are referred to a pain programme/pain clinic with mechanical low back pain will be invited to participate. General practitioners and medical specialists who referred patients to the pain clinics will be informed about participation of their patients in the study. Patients who meet the criteria are informed of the purpose and procedures of the study; each patient receives a general brochure concerning scientific research involving human subjects (in Dutch: medisch-wetenschappelijk onderzoek met mensen) and a patient information letter (section E1 of the protocol). After giving informed consent by means of an informed consent patients are enrolled in the study.

10.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

10.4 Benefits and risks assessment, group relatedness

Minimal interventional procedures provide alternatives for patients with mechanical back pain who did not improve on primary care treatment. No major complications have been reported on these procedures.

10.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.6 Incentives (if applicable)

Not applicable

11. ADMINISTRATIVE ASPECTS AND PUBLICATION

11.1 Handling and storage of data and documents

Web based questionnaires will be used to assess questionnaires, and an online data management system will be used for the management of these questionnaires. This software is installed on the computers of the Erasmus MC MGZ and VU University EMGO department, so that backup and access protection have been arranged.

The patients will receive an email notification when a questionnaire is due. The database itself is safeguarded with tokens and passwords. The trial coordinator of the Erasmus MC controls the patient tracking programme that enables her to send out emails, and check whether all questionnaires have been completed. Only the research coordinators of the VUmc and the Erasmus MC have access to all data. If the patients do not have access to the internet or prefer hard copies, we will provide these. The data from measurements and questionnaires will be stored in the Promise database.

The researchers at the VUmc and the Erasmus MC will only receive the data, and these will be processed without knowing the treatment group. The coding and randomisation will take place using a computer based list, safeguarded by the statistician of the Center for Pain Medicine of the Erasmus MC. The patient records will be coded by a code for the center that included the patient, and a number, starting with 1 for the first patient.

11.2 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

11.3 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.4 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.5 Public disclosure and publication policy

The principal investigator is free to publish.

12. REFERENCES

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