BMJ Open

Effectiveness and cost-effectiveness of dynamic bracing versus standard care alone in patients suffering from osteoporotic vertebral compression fractures: protocol for a multicentre, two-armed, parallel-group randomised controlled trial with 12 months of follow-up

Annemarijn Weber ®,[1] Stephanie M D Huysmans,[1] Sander M J van Kuijk ®,[2] Silvia M A A Evers,[3,4] Elisabeth M C Jutten,[1] Rachel Senden,[5] Aggie T G Paulus,[6,7] Joop P W van den Bergh,[8,9] Rob A de Bie,[10] Johannes M R Merk,[11] Sandrine P G Bours,[12] Mark Hulsbosch,[13] Esther R C Janssen,[1,13] Inez Curfs,[14] Wouter L W van Hemert,[14] Martijn G M Schotanus,[1,14] Paul de Baat,[15] Niek C Schepel,[15] Willem A den Boer,[16] Johannes G E Hendriks,[16] Wai-Yan Liu,[15,16] Marinus de Kleuver,[17] Martin H Pouw,[17] Miranda L van Hooff,[17] Eva Jacobs,[1] Paul C P H Willems[1]

For numbered affiliations see end of article.

Correspondence to
Annemarijn Weber;
a.weber@maastrichtuniversity.nl

ABSTRACT

Introduction Patients with osteoporosis may suffer from a fracture after minimal trauma. Osteoporotic vertebral compression fractures (OVCFs) are among the most common fractures, often leading to substantial pain. There is a need for evidence-based conservative treatment to aid in the management of OVCFs. The objective of this randomised controlled trial (RCT) is to evaluate the effectiveness and cost-effectiveness of dynamic bracing in addition to standard care for improving quality of life (QoL) in patients suffering from an OVCF.

Methods and analysis Ninety-eight postmenopausal women from two academic and four community hospitals with a recent symptomatic thoracolumbar OVCF will be randomised into either the standard care or dynamic bracing group. In the dynamic bracing group, the Spinova Osteo orthosis will be used in addition to standard care. Standard care comprises pain control with analgesics, physical therapy and osteoporosis medication. The primary outcome parameter is QoL 1 year after inclusion, as measured by the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO-41). Secondary outcome parameters are pain, pain medication used, functional disability, sagittal spinal alignment, recurrence rate of OVCFs and physical activity in daily life. A trial-based economic evaluation consisting of both cost-effectiveness analysis and cost-utility analysis will be performed based on empirical data obtained in the RCT. A process evaluation will assess the feasibility of dynamic bracing. All outcomes will be assessed at baseline, 6 weeks, 3 months, 6 months, 9 months and 12 months.

Ethics and dissemination Ethical approval has been granted by the Medical Ethics Committee, University Hospital Maastricht and Maastricht University (METC azM/UM) (NL74552.068.20/METC 20-055). Patients will be included only after verification of eligibility and obtaining written informed consent. Results will be disseminated via the Dutch National Osteoporosis Patient Society and via publications and conferences.

Trial registration number NL8746.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study addresses the need for evidence-based conservative treatment options for osteoporotic vertebral compression fractures.
⇒ The multicentre design with participating regional and academic centres will aid with external validation and simulate real-life experience.
⇒ Combination of effect, economic and process evaluation explores and determines whether implementation of dynamic bracing in addition to current standard care is favourable.
⇒ Blinding to the treatment allocation for patients and medical staff is not possible.
⇒ The use of temperature sensors will provide good insight in the level of compliance in wearing the brace.

INTRODUCTION

Osteoporosis is a major public health issue which is highly prevalent in the ageing population, affecting predominantly postmenopausal women. This condition often leads to substantial pain, suffering and disability for the individual and carries significant costs for society.[1] In 2010, it was estimated that 10% of women and 3% of men in the European Union suffered from osteoporosis.[1] Worldwide, these numbers add up to a staggering 200 million[2] and these numbers will only continue to rise over the upcoming years due to an increasingly elderly population.[3] With a complex and multifactorial pathogenesis, osteoporosis results in reduced bone mineral density (BMD) and a disruption of the architecture of the trabecular bone resulting in decreased bone strength.[4] Pathognomonic of this skeletal fragility, patients may suffer from a fracture after minimal trauma.[1] Osteoporotic fractures accounted for the loss of 1 165 000 quality-adjusted life-years (QALYs) in the European Union in 2010.[1] Valuing a QALY at 2 × gross domestic product per capita, this amounts to a total value of €60 billion lost due to osteoporotic fractures in Europe alone.[1]

Among the most common fragility fractures are osteoporotic vertebral compression fractures (OVCFs) with approximately 500 000 new fractures per year in Europe.[5 6] The majority of these patients experience substantial pain and functional disability, leading to a decrease in quality of life (QoL) with substantial morbidity, and even mortality.[6–8] In OVCFs, the vertebra is commonly deformed by disproportionate height loss from the anterior vertebral body resulting in wedging.[8 9] Wedge accumulation over multiple thoracolumbar levels may lead to progressive spinal deformity, that is, an increased thoracolumbar kyphosis and decreased lumbar lordosis.[10] The increased anterior spinal loading in degenerative thoracolumbar hyperkyphosis is an independent risk factor for vertebral fractures,[11] and has been associated with a downward spiral of additional OVCFs, also known as the 'vertebral fracture cascade'.[7] Of those with an incident vertebral fracture, 20% will have an additional fracture within 1 year.[12] Thoracolumbar hyperkyphosis may also negatively affect physical function, postural control during walking and pulmonary function.[7 13]

Unfortunately, therapeutic recommendations for both invasive and conservative treatment are inconsistent.[14–23] Percutaneous vertebroplasty and balloon kyphoplasty, the minimally invasive cement augmentation techniques available for treatment of symptomatic OVCFs, have shown variable clinical results.[24–27] Contradicting results over the course of multiple studies have fuelled discussions and endless dispute on the effectiveness and medical appropriateness of these techniques.[28 29] The results have polarised opinions leaving conservative management as the preferred or even sole available treatment option for some patients. Current conservative management of symptomatic OVCFs generally comprises a mixture of analgesics, physical therapy and osteoporosis medication.[13 14] Although this treatment strategy may reduce acute pain, improve flexibility and strength and increase BMD or slow bone loss, it does not decrease the anterior loading of the spine and thus cannot prevent the risk of the subsequent vertebral fracture cascade. With an overall ageing population and no decline in the high number of repeated OVCFs, it stands to reason that the frequency of OVCFs and resultant hyperkyphotic deformity in Western society will not abate. Instead, it will only increase under current conservative management.[1 5 7]

Rationale

Bracing may offer a solution to the vertebral fracture cascade as orthoses have been reported to prevent or slow down the progression of thoracolumbar hyperkyphosis and the subsequent decline in postural control.[30–35] The use of conventional, rigid spinal orthoses is generally not recommended in patients suffering from osteoporosis due to the suspected atrophy of the trunk muscles as a result of inactivity and restricted respiration leading to low patient compliance.[31] Dynamic braces are semi-rigid thoracolumbar orthoses that provide biomechanical support, similar to conventional three-point rigid braces, while also allowing for dorsal lumbar musculature biofeedback. This allows for improved trunk muscle strength[36 37] and encourages improved compliance through increased comfort. Originally designed for high energy traumatic vertebral fractures,[13 14] positive effects have been shown on QoL, respiratory function and postural control in patients suffering from an OVCF.[30] In a previous study, 6 weeks of continuous bracing with dynamic braces resulted in a more upright posture (ie, decrease in anterior bending moment) which seemed to have a positive effect on gait and stability. Due to the single-armed study set-up, results were interpreted with caution and higher level evidence is necessary to analyse whether these effects are due to dynamic bracing or to natural recovery following OVCF.

This protocol describes a multicentre randomised controlled trial (RCT) evaluating the effectiveness and cost-effectiveness of dynamic bracing compared with standard care alone. We hypothesise that in patients suffering from an OVCF, dynamic bracing will improve QoL with a positive effect on pain and sagittal spinal alignment. Dynamic bracing improves gait quality and balance, as well as physical activity, and decreases the recurrence rate of OVCFs. As such, dynamic bracing is a cost-effective treatment for patients suffering from an OVCF.

Objectives

The primary objective of the effect evaluation is to investigate whether supplementing standard care with dynamic bracing will improve QoL in patients suffering from OVCFs as compared with standard care alone. Secondary objectives include evaluating the effects of dynamic bracing on pain, pain medication used, functional disability, static sagittal spinal alignment, the recurrence rate of vertebral fractures and physical activity in daily life. The effect of dynamic bracing on gait, expressed as

3D joint kinematics, spatiotemporal parameters, dynamic sagittal spinal alignment and daily physical activity, will be investigated in a subgroup of patients. Concurrent to the effect evaluation, a trial-based cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) will be carried out with the primary objective to examine whether dynamic bracing and standard care compared with standard care alone in patients suffering from OVCFs is preferable in terms of costs, effects and utilities from a societal perspective. A budget impact analysis will also be conducted to inform decision-makers about the financial consequences of implementing dynamic bracing in patients suffering from OVCFs on a national level. Alongside the clinical effect and economic evaluations, a process evaluation will assess the feasibility of dynamic bracing. Here, the main objective is to analyse the extent to which treatment is performed according to the protocol, the attendance and adherence of patients and the opinion of patients and care professionals regarding the treatment and implementation thereof.

The main research question for the effect evaluation is:

> What is the effectiveness on quality of life of dynamic bracing in patients suffering from an OVCF?

For the economic evaluation the main research question is:

> From the viewpoint of society, is the additional delivery of dynamic bracing to standard care in patients suffering from OVCFs preferable in terms of costs, effects and utilities?

The main research question for the process evaluation is:

> What are the experiences and opinions of patients, caregivers and professionals regarding dynamic bracing?

Additionally, the process evaluation will look at the following research question:

> Has the dynamic bracing multicomponent intervention been delivered according to protocol? And if not, what are the reasons for protocol deviation?

METHODS AND ANALYSIS
Trial design
This is a multicentre, two-armed, parallel-group RCT with a 1:1 allocation ratio (figure 1) consisting of an effect, economic and process evaluation. Patients will be allocated to groups as per a computer-generated randomisation schedule stratified by site with non-disclosed block sizes. Blinding to the treatment allocation for patients and medical staff is not possible. This study will be conducted in two academic hospitals and four community hospitals in the Netherlands. Recruitment started on 21 December 2020, and the first patient was included on 21 January 2021. At the time of submission, 37 of the 98 patients have been included in the study. The inclusion period is expected to last onto December 2022, and the total

follow-up period is planned to be completed in January 2023.

Trial registries (http://clinicaltrials.gov and http://trialregister.nl) were checked to identify any planned or ongoing trials with a similar aim as the study described in this protocol. No similar trials were identified.

Trial population
Postmenopausal women with a first or second symptomatic thoracolumbar (Th8–L5) OVCF present for less than 6 weeks will be eligible to participate in this study. Patients meeting any of the following criteria will be excluded: unstable vertebral fractures amenable for operative treatment, neurological deficit, severe spinal deformity (scoliosis with a Cobb angle larger than 30°), infection, malignancy requiring current treatment, psychiatric or mental disease and insufficient cognitive or language skills to complete the questionnaires.

Intervention
Standard care will consist of analgesics, antiosteoporosis medication and optionally physical therapy at the discretion of the treating physician and according to current and local clinical guidelines.[14–17] Antiosteoporosis medication in the Netherlands is patient tailored and depends on the degree of osteoporosis as well as other patient-specific factors. Medication is therefore not standardised in this study. To ensure adequate intake of vitamin D and calcium, supplementation is always advised in conjunction to antiosteoporosis medication.[14 38] Patients allocated to the intervention group will receive a dynamic thoracolumbar brace, the Spinova Osteo (Bauerfeind Benelux) (figure 2), in addition to standard care. Patients will be instructed to wear the brace for at least 8 hours per day during all regular daily activities. This includes all forms of activities of daily living, including lying down or afternoon sleeping should this be part of a patient's normal daily schedule. The Spinova Osteo brace will be fitted by the local orthopaedic technician on the day of or within a few days after inclusion. To ensure patients are comfortable using the brace in all facets of their lives, they receive a thorough instruction on how to wear and use it during their appointment with the orthopaedic technician. This includes, but is not limited to, how to put on the brace when alone or with the help of a partner, (re)adjusting during daily activities and sitting down in chairs.

Participants will be assessed at baseline, 6 weeks, 3 months, 6 months, 9 months and 1 year after randomisation (tables 1 and 2). As in routine clinical practice, all patients will be treated according to standard care. Full-spine radiographs will be obtained and relevant patient-reported outcome measures (PROMs) will be collected at baseline and all follow-up visits. An overview is provided in table 2. Safety event reporting will also be done at all follow-up moments. Adverse events meeting the criteria for serious adverse event will be reported according to the guidelines provided by the Central Committee on Research Involving Human Subjects. In the Maastricht
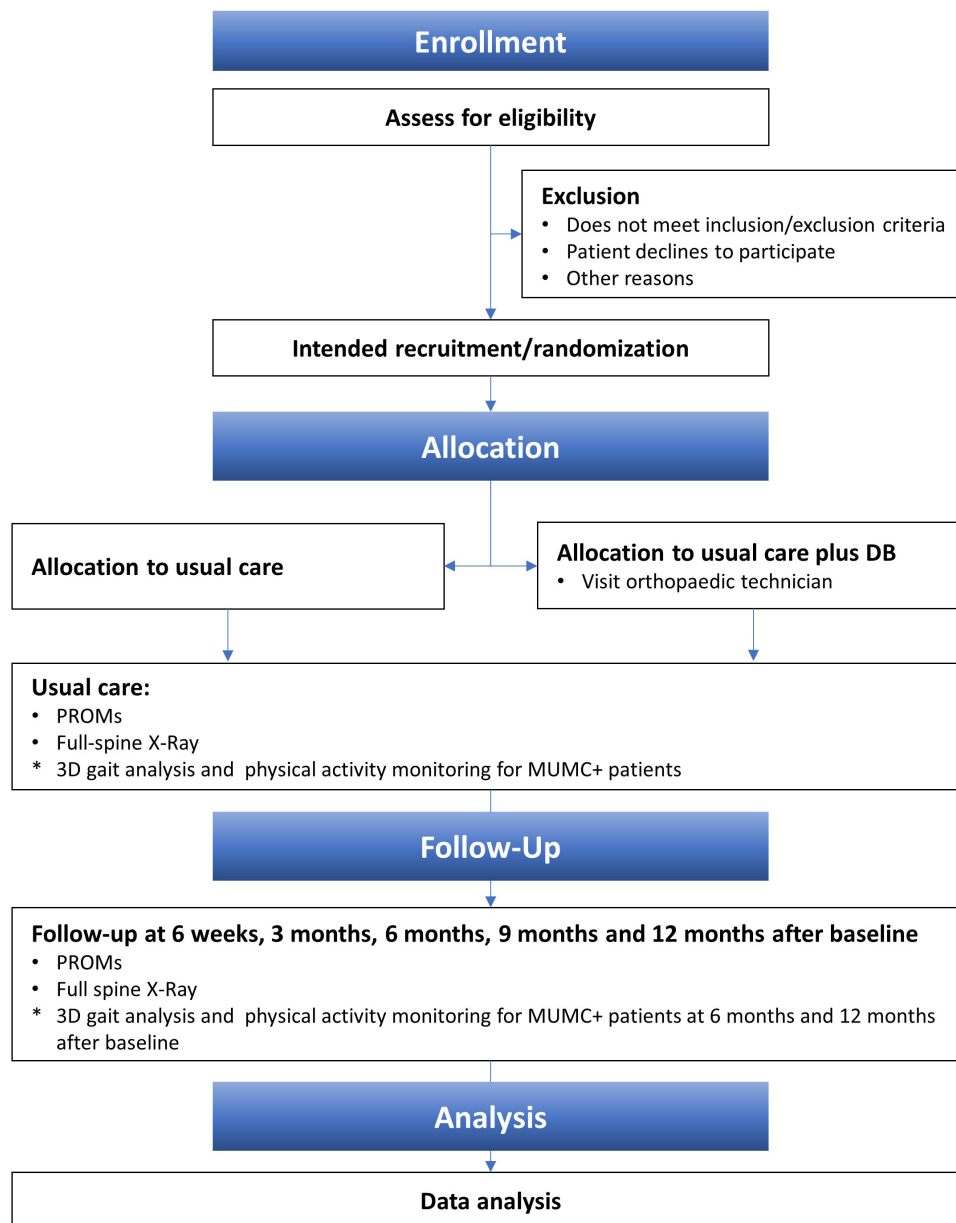
Enrollment

Assess for eligibility

Exclusion
- Does not meet inclusion/exclusion criteria
- Patient declines to participate
- Other reasons

Intended recruitment/randomization

Allocation

Allocation to usual care

Allocation to usual care plus DB
- Visit orthopaedic technician

Usual care:
- PROMs
- Full-spine X-Ray
* 3D gait analysis and physical activity monitoring for MUMC+ patients

Follow-Up

Follow-up at 6 weeks, 3 months, 6 months, 9 months and 12 months after baseline
- PROMs
- Full spine X-Ray
* 3D gait analysis and physical activity monitoring for MUMC+ patients at 6 months and 12 months after baseline

Analysis

Data analysis

Figure 1 Diagram showing study design with enrolment, 1:1 allocation using block randomisation, follow-up moments and data analysis. MUMC+, Maastricht University Medical Center+; PROMs, patient-reported outcome measures.

University Medical Center+ (MUMC+) patient population, gait and balance will be assessed using the Computer-Assisted Rehabilitation Environment system (CAREN, Motekforce Link, Amsterdam, The Netherlands). Gait and balance will be determined using 3D joint kinematics, spatiotemporal parameters and dynamic sagittal alignment parameters during walking at baseline and 6 and 12 months after baseline. In this subgroup, daily physical activity will also be assessed during seven successive days in daily life using the MOX activity monitor (3D accelerometer, Maastricht Instruments, Maastricht, The Netherlands).

Sample size
A sample size of 98 patients was determined to yield sufficient statistical power (80%) to detect a medium effect size at 12 months after inclusion using an independent t-test as calculated using the Cochran formula.[39] Sample size was computed using R software V.4.0.4. Based on previous research in a similar patient population, the SD of the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO-41) score is assumed to be about 15.6.[40] No minimally clinically important difference is known to have been suggested for the QUALEFFO-41 score.[41 42] To be able to detect a medium effect size (defined as a Cohen's d of 0.6), at least 44 patients will need to be included per group. To account for a dropout rate of 10%, 49 patients per group will be included. Thus, 98 patients in total should result in both sufficient data for the primary outcome measure at 12 months, as well as for the longitudinal analysis over

Figure 2 The Spinova Osteo—actively straightening back orthosis for stabilisation of the spine in case of osteoporosis (Bauerfeind Benelux).

the entire follow-up period. The latter will include up to 588 follow-up moments with six observations per patient. Based on the number of annual patients presenting with an OVCF at participating centres (table 3), it should be possible to recruit the required number of patients within 2 years.

Outcomes

Clinical effect evaluation

To assess the effectiveness of dynamic bracing, outcome assessments will be completed at baseline, 6 weeks, 3 months, 6 months, 9 months and 12 months. Please refer to tables 1 and 2 for a detailed overview of the outcome assessments and their timing.

The primary outcome parameter for the effect evaluation is QoL at 1 year after inclusion. This will be quantified with the QUALEFFO-41 score.[41] Secondary outcome

parameters are pain, pain medication use, functional disability, radiographic sagittal alignment, recurrent fractures and physical activity. The change in pain level will be assessed by an 11-point Numeric (pain) Rating Scale where level 10 implies extreme pain and level 0 no pain at all. The use of pain medication will be assessed over the course of the study using patient diaries and current medication lists. Pain medication use will be quantified using the Medication Quantification Scale III.[43] Functional disability will be assessed using the Oswestry Disability Index.[44] Static sagittal alignment and recurrence fracture rate will be analysed on standard full-spine lateral and anteroposterior (AP) radiographs. On the standing full-spine radiographs, wedge height of the fractured vertebra, sagittal balance and eventual secondary fractures will be assessed. Pelvic parameters that will be measured are the pelvic incidence, pelvic tilt and sacral slope. Regional spinal parameters include PI-LL mismatch, L1-S1 lumbar lordosis, L4-S1 lumbar lordosis and thoracic kyphosis (T4–T12). Sagittal alignment will be assessed linearly by T1 spinopelvic inclination, T1 pelvic angle, global tilt and global sagittal alignment. Physical activity will be assessed with the International Physical Activity Questionnaire-Short Form[45] in the entire patient population, as well as with the MOX activity monitor in the MUMC+ population. Compliance to brace treatment will be recorded using Orthotimer temperature sensors embedded in the brace. The Orthotimer system is a microsensor (9×13×4.5 mm) which can easily be integrated into the brace using a Velcro pouch placed on the pelvic support directly underneath the reclinator. Every sensor features a unique ID number and makes use of continuous measurement. Temperatures between 29°C and 37.8°C correspond to patients wearing the brace. Temperatures above or below this range indicate that the brace was not worn at that time.

Furthermore, patient diaries will be used to check adherence to the treatment. Participants will be asked to complete these on a daily basis up to 6 weeks and thereafter on a weekly basis up to 3 months. Hereafter, the patient diaries will be included with the other PROMs at all follow-up visits. In order to determine baseline characteristics, the following parameters will be assessed: age, body mass index, BMD, concomitant diseases and medication, falls within the previous 6 months as reported by study participants' use of corticosteroids and tobacco and alcohol consumption. In the MUMC+ patient population, gait measurements will be performed at baseline, and 6 and 12 months after baseline, using a CAREN (Motek-force Link). The CAREN system combines a dual-belt treadmill with instrumented force plates (1000 Hz), 12 infrared cameras (100 Hz, Bonita, Vicon Motion Systems, Oxford, UK), three 2D cameras for motion capturing and a virtual environment (industrial environment with passing objects and structures) projected on a 180° curved screen which provides optic flow. Retroreflective markers are attached to anatomical landmarks according to the human body model II for lower limbs

Table 1 Patient follow-up schedule

Event or examination	Visit Emergency Department	Baseline	6 weeks	3 months	6 months	9 months	1 year
Assessment of eligibility	✓						
Provide patient information	✓		✓				
Inclusion or exclusion		✓					
Informed consent		✓					
Randomisation		✓					
Orthosis (orthopaedic technician)		✓					
PROMs							
QUALEFFO-41		✓	✓	✓	✓	✓	✓
NRS		✓	✓	✓	✓	✓	✓
ODI		✓	✓	✓	✓	✓	✓
EQ-5D-5L		✓	✓	✓	✓	✓	✓
IPAQ-SF		✓	✓	✓	✓	✓	✓
iMCQ		✓		✓	✓	✓	✓
iPCQ		✓		✓	✓	✓	✓
Pain medication used		✓	✓	✓	✓	✓	✓
Radiographic assessment		✓	✓	✓	✓	✓	✓
Gait analysis*		✓			✓		✓
Activity monitoring*		✓			✓		✓
Safety event reporting		✓	✓	✓	✓	✓	✓

Visits should take place at 6 (±1 week) weeks and 3 (±2 weeks), 6 (±2 weeks), 9 (±2 weeks) and 12 (±2 weeks) months.
*Only applicable for Maastricht University Medical Center+ (MUMC+) subpopulation.
EQ-5D-5L, 5-level EuroQoL-5 dimension; iMCQ, iMTA Medical Consumption Questionnaire; IPAQ-SF, International Physical Activity Questionnaire-Short Form; iPCQ, iMTA Productivity Cost Questionnaire; NRS, Numeric (pain) Rating Scale; ODI, Oswestry Disability Index; PROMs, patient-reported outcome measures; QUALEFFO-41, Quality of Life Questionnaire of the European Foundation for Osteoporosis.

with additional trunk and shoulder markers, which will be tracked by the 3D motion capture system. The following parameters are calculated: spatiotemporal parameters such as walking speed; step length and step width; 3D kinematics of ankle, knee, hip, trunk and pelvis; dynamic sagittal alignment parameters such as sagittal vertical axis; and sagittal angles between C7-S1 and T12-S1.[46] During the gait measurement, participants wear a safety harness connected to an overhead frame to prevent falling. All participants walk on turning shoes to eliminate the effect of shoe wear. Daily physical activity will be assessed during seven successive days from baseline with the MOX activity monitor secured to the front of the upper right leg of the patient.[47 48]

Table 2 The numbers of all female patients older than 50 who presented themselves at one of the participating hospitals with a symptomatic osteoporotic vertebral compression fracture in 2018 and 2019 according to the Dutch Coding System ('DBC' number 1395)

	2018	2019	Total
MUMC+	62	97	159
Zuyderland MC	88	72	160
VieCuri MC	72	84	156
Máxima MC	31	36	67
Catharina Hospital	44	23	67
Radboud UMC	6	9	15
Total	303	321	624

MUMC+, Maastricht University Medical Center+.

Economic evaluation

The trial-based economic evaluation will be performed according to the Dutch Guidelines of the National Health Care Institute[49] and will be based on empirical data obtained with the iMTA Medical Consumption Questionnaire and iMTA Productivity Cost Questionnaire. Within the economic evaluation, the primary outcome parameters are cost-effectiveness and cost-utility. The primary outcome measure for the CUA will be QALYs based on the 5-level EuroQoL-5 dimension (EQ-5D-5L) utility scores.[50] In the CUA, the incremental cost-effectiveness ratio (ICER) will be expressed as the incremental costs per QALY. The primary outcome measure for the CEA will be improvement in QoL as measured by QUALEFFO-41.[41] Within the CUA, outcomes will be measured by means of

Table 3 Patient-reported outcome measures

Patient-completed measures	Description
Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO-41)	The QUALEFFO-41 is a specific questionnaire for patients with vertebral fractures. This questionnaire includes 41 questions in the domains of pain, physical function, social function, general health perception and mental function. The QUALEFFO-41 is repeatable, coherent and discriminates well between patients with vertebral fractures and matched control subjects.[41] A scoring algorithm is used to determine the total score.
Numeric (pain) Rating Scale (NRS)	A segmented numeric subjective measure in which individuals rate their pain on an 11-point numerical scale.[57] The scale is composed of 0 (no pain at all) to 10 (worst imaginable pain). Scores range from 0 to 10 points with higher scores indicating greater pain intensity.
Oswestry Disability Index (ODI)	Gives a subjective score of level of function/disability in daily activities in patients rehabilitating from (lower) back pain.[44] This questionnaire consists of 10 sections with a total possible score of 5 per section. Scoring is done by dividing the total score by the total possible score. Interpretation of scores: 0%–20% (minimal disability), 21%–40% (moderate disability), 41%–60% (severe disability), 61%–80% (crippled), 81%–100% (bed bound or exaggerating symptoms).
EQ-5D-5L	Health utility index with five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and five levels.[58] Patients are asked to indicate their health state in each of the five dimensions which results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. These are then converted to a single utility index for the entire EQ-5D. The evaluation component has patients who record their overall health status using a visual analogue scale (EQ-VAS).
International Physical Activity Questionnaire–Short Form (IPAQ-SF)	Assesses the types and intensity of physical activity and sitting time people engage in as part of their daily lives.[45] Results are either reported in categories (low, moderate or high activity levels) or as a continuous variable (MET min/week). MET minutes represent the amount of energy expended during physical activity.
Health-Related Resource Use Measurement (RUM) Questionnaire consisting of the iMCQ and iPCQ	A healthcare cost questionnaire developed specifically for this, based on existing questionnaires, which will measure all relevant costs aspects.[59]
Patient diary	Pain medication used will be assessed daily for the first 6 weeks and then weekly up to the 3-month follow-up by using a patient diary and quantified using the Medication Quantification Scale (MQS III). The questions asked in the patient diary will then be included in the questionnaire package for the later follow-up moments.

All patient-related outcome measures (PROMs) are completed by all patients at all follow-up moments except for the Health-Related RUM Questionnaire which is completed at baseline, and 3, 6, 9 and 12 months.
EQ-5D-5L, 5-level EuroQoL-5 dimension; iMCQ, iMTA Medical Consumption Questionnaire; iPCQ, iMTA Productivity Cost Questionnaire; MET, metabolic equivalent of task.

the standard Dutch version of the EQ-5D-5L.[50] Resource use (costs) will be measured continuously and outcomes for the economic evaluation will be measured at baseline and subsequently every 3 months until 12 months after intervention.

Process evaluation

The process evaluation will be performed according to the framework provided by Saunders et al[51] in which important characteristics for a process evaluation plan are identified along seven basic components, namely fidelity (quality, dose delivered), dose received (exposure, satisfaction), reach (participation rate), recruitment and context. In following this set-up, it will be possible to determine the underlying factors responsible for results seen in the effect evaluation. The process being evaluated will be split into two phases: 'pre-treatment' and 'treatment' in order to gain a thorough understanding of the patient journey and experiences. 'Pre-treatment' will cover all relevant events and experiences from first presentation up to inclusion and randomisation. 'Treatment' will cover baseline and all follow-up moments. Qualitative and quantitative data will be collected through a mixed methods design. A random selection of 12 patients allocated to standard care and 12 patients allocated to the intervention group will be asked to participate in two semistructured face-to-face interviews in which they will be asked to reflect on their opinions and expectations regarding the (pre)treatment and their overall experience with the care provided in either arm of the trial. The first interview will focus on experiences and opinions concerning 'pre-treatment' and take place during the 6-week follow-up visit. The second interview will focus on experiences and opinions concerning the 'treatment' period and take place during the 9-month

follow-up visit. The 24 randomly selected patients will be evenly spread across all sites. During the final visit, a short evaluation form questions covering the topics identified through the framework by Saunders *et al* will be provided to all patients.[51] Physicians and orthopaedic technicians involved in the study will also be approached 1 year after site initiation for a semistructured interview with predetermined open-ended questions to investigate their (previous) experiences with and beliefs about treatment with dynamic bracing, the process and factors influencing this. Semistructured interview guides will be developed based on study objectives.

Data analysis

Patient baseline characteristics will be described as stratified by group allocation. Continuous variables will be presented as mean and SD or, in case of skewness, as median and IQR. Categorical variables will be presented as count and proportion. In case 5% or more of records are incomplete due to missing values on the variables of interest, an imputation method will be used to produce a synthetic part of the data to allow analysis of all included patients. An imputation method will be selected after careful consideration of the missing data mechanism and the proportion of incomplete cases. In case imputation will be used, a sensitivity analysis for the primary study parameter will be performed by using only complete cases. Patients randomised into the brace group are allowed to refuse the brace and will thereby cross over to the control group. This is solely possible on randomisation and has not occurred as of yet. Should a patient indicate after receiving the brace that they are no longer wearing the brace or refuse to meet the wearing advice this will be considered a matter of compliance and not ground for crossover. In some cases, crossover is possible for patients initially randomised into the standard care group if they develop a strong preference for a brace, or if the attending physician thinks this would be in the best interest for the patient. Patients who indicate before inclusion and randomisation that they have a strong preference for either treatment arm will not be included. All analyses on primary and secondary study parameters will be performed according to intention to treat (ITT). In addition to the ITT analysis, a per-protocol analysis will be performed for the primary outcome.

Effect evaluation
Primary study parameter(s)

The primary outcome within the effect evaluation, QoL 12 months after inclusion, will be compared between the intervention and standard care group using the independent samples t-test where $p<0.05$ will be considered significant. If data are not normally distributed, a non-parametric Mann-Whitney U test will be used to compare the intervention and standard care group. In addition, QoL changes over the course of follow-up will be compared between groups using a linear mixed-effects model with random intercept and random slope with

time. Should a positive correlation be found between dynamic bracing and QoL, a post hoc analysis will be considered to determine whether this correlation is more profound in patients with a positive sagittal balance.

Secondary study parameter(s)

Secondary outcome parameters such as pain, pain medication use, functional disability and physical activity, as reported in the PROMs (table 3), will be compared between standard care and intervention groups using a linear mixed-effects model. The standardised lateral and AP full-spine radiography used to assess static sagittal spinal alignment will be analysed using validated software (Surgimap; Nemaris, New York, New York, USA). Depending on whether the data are distributed normally, an independent t-test or non-parametric tests will be used to investigate joint kinematics, spatiotemporal parameters, dynamic sagittal alignment parameters and daily physical activity. The interval-censored fracture recurrence data will be compared between groups using a model for discrete-time survival analysis. Compliance will be described using descriptive summary statistics.

Economic evaluation

Total costs will be estimated using a bottom-up approach.[50] To measure the actual use of resources, data will be obtained using combined sources over the same time horizon as the follow-up period of the effect evaluation. Resources used related to the interventions will be based on the time professionals register. Intervention costs will include all costs contributing to the administration of dynamic braces. All use of resources by the patient and their family inside and outside the healthcare sector will be measured by means of a cost questionnaire. Costs will be calculated by multiplying resource use with unit costs based on 2022 Dutch costing guidelines.[50 52] Generic QoL and utilities will be calculated using the EQ-5D-5L. The utilities will be used to compute a QALY score by means of the area under the curve method.

Due to the short-term nature of follow-up, namely 1 year, discounting is not necessary.[40] The primary analysis will be performed according to the ITT principle. A baseline analysis will be performed to examine the comparability of groups at baseline for both costs and outcomes. If necessary, methods will be applied to control for differences in baseline.[53] To investigate whether data are normally distributed, a Kolmogorov-Smirnov test will be performed. In case of skewness of the cost data, non-parametric bootstrapping will be used to test for statistical differences in costs between the intervention and standard care group. The bootstrap replications will be used to calculate 95% CIs around the costs based on the 2.5th and 97.5th percentiles. The ICER will be determined on the basis of incremental costs and effects of dynamic bracing and standard care. The cost-effectiveness ratio will be stated in terms of costs per outcome rate, the cost-utility ratio will focus on the net cost per QALY gained. The ICER will be calculated as follows: $ICER = (C_i - C_c)/$

(Ei–Ec), where Ci is the annual total cost of the dynamic bracing and standard care group, Cc is the annual total cost of the standard care group, Ei is the effect at 1-year follow-up for the dynamic bracing and standard care group and Ec is the effect at the last follow-up for the standard care group. The robustness of the ICER will be checked by non-parametric bootstrapping. Bootstrap simulations will also be conducted to quantify the uncertainty around the ICER, yielding information about the joint distribution of cost and effect differences.

Since choice of treatment depends on the ceiling ratio, the bootstrapped ICER will also be depicted in a cost-effectiveness acceptability curve to the probability that dynamic bracing is cost-effective using a range of ceiling ratios. In the Netherlands, ceiling ratios of €20 000, €50 000 and €80 000 per QALY exist depending on the burden of disease.[54] Additionally, a multiway sensitivity analysis will demonstrate the robustness of base case findings. In the sensitivity analysis, uncertain factors of assumptions in the base case analysis will be recalculated in order to assess whether the assumptions have influenced the ICER.[55]

Process evaluation

To understand the perspectives of patients and healthcare professionals regarding dynamic bracing and standard care, in-depth face-to-face interviews will be carried out according to predetermined semistructured interview guides. To ensure credibility, all interviews will be audio recorded and transcribed verbatim. Additionally, participants will be asked for feedback to confirm the interpretation of the data. In total, approximately 60 interviews will be conducted with one to two healthcare professionals and two to six patients per site. The final number of interviews will depend on the saturation of themes. Thematic analysis will be carried out using a software for qualitative analysis (eg, NVivo) to identify themes within the various subheadings of the process evaluation framework (Saunders). Constant comparison between sources will be carried out to ensure all common and distinctive themes are identified. Triangulation between observations, interviews and PROMs will be used to increase the credibility and reliability of research findings.

To determine whether the dynamic bracing intervention has been delivered according to protocol, data collected through the PROMs, patient diaries and heat sensors will be analysed. Quantitative data will be analysed using descriptive statistics, χ^2 tests and through analysis of variance.

Patient and public involvement

Two patients from a previous study,[30] two independent patients with OVCF, the patient advisory board and the chairman of the Dutch National Osteoporosis Patient Society were asked for advice concerning the feasibility of the current protocol. The protocol was adjusted to minimise the burden for patients per their advice. The patient advisory board also checked and agreed to the patient information form and questionnaires that will be provided to the study participants to ensure clear formulation and optimal understanding for patients.

ETHICS AND DISSEMINATION

The study will be conducted according to the principles of the Declaration of Helsinki in the current version of Brazil, 2013[56] and in accordance with the Medical Research Involving Human Subjects Act. All data will be handled in accordance with the Dutch General Data Protection Regulation.

The current study has been approved by the local Medical Ethics Committee, the METC University Hospital Maastricht and Maastricht University (METC azM/UM) (NL74552.068.20) and the board of directors from all participating centres. Modifications to the protocol which may impact the conduct of the study, potential benefit to the patient or potentially affect patient safety will require a formal amendment to the protocol. Such amendments will need to be approved by the METC azM/UM prior to implementation and health authorities will be notified in accordance with local regulations. Before study participation, oral and written patient information will be provided to all potential study candidates. Patients interested in participating will be included only after verification of their eligibility and after the treating physician has obtained written informed consent (online supplemental appendix 1). All data will be collected in the participating hospitals. Source documentation will be handled confidentially and stored securely at study site. All reports, forms and data will be identified using coded identification numbers to maintain participant confidentiality. Both source documentation and clinical research forms (CRFs) will be stored for 15 years after the study is concluded. Patients' data may be used for future analyses in line with this research if patients provide written informed consent specifically for this purpose and after permission of the ethical committee. The trial is registered on http://trial-register.nl under NL8746. Findings will be disseminated through publications in peer-reviewed journals and attendance at conferences and events. Documentation of the research process, audiovisual material, processed data and raw data will be available for further research and validation. Metadata as well as research data will be made publicly available for subsequent research after conclusion of the trial via DataHub, the central infrastructure available within MUMC+.

Author affiliations

[1]Department of Orthopedics and Research School CAPHRI, Maastricht University Medical Center+, Maastricht, The Netherlands
[2]Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht Universitair Medisch Centrum+, Maastricht, The Netherlands
[3]Department of Health Services Research, Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, The Netherlands
[4]Trimbos Institute, Utrecht, The Netherlands
[5]Department of Nutrition and Movement Sciences, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center+, Maastricht, The Netherlands

[6]Department of Health Services Research, Faculty of Health, Medicine and Life Sciences (FHML), Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, The Netherlands
[7]Faculty of Health, Medicine and Life Sciences (FHML), School of Health Professions Education (SHE), Maastricht University, Maastricht, The Netherlands
[8]Department of Internal Medicine, Research School NUTRIM, Maastricht University Medical Center+, Maastricht, The Netherlands
[9]Department of Internal Medicine, VieCuri Medical Centre, Venlo, The Netherlands
[10]Department of Epidemiology, Maastricht University Medical Center+, Maastricht, The Netherlands
[11]Department of Finance, Maastricht University, Maastricht, The Netherlands
[12]Department of Internal Medicine, Subdivision Rheumatology, CAPHRI Care and Public Health Research Institute, Maastricht University Medical Center+, Maastricht, The Netherlands
[13]Department of Orthopedic Surgery, VieCuri Medical Centre, Venlo, The Netherlands
[14]Department of Orthopaedic Surgery and Traumatology, Zuyderland Medical Centre, Heerlen, The Netherlands
[15]Department of Orthopaedic Surgery and Trauma, Catharina Hospital, Eindhoven, The Netherlands
[16]Department of Orthopaedic Surgery and Trauma, Maxima Medical Centre, Eindhoven, The Netherlands
[17]Department of Orthopedics, Radboudumc, Nijmegen, The Netherlands

Twitter Paul C P H Willems @Paul C Willems

Contributors PCPHW, SMAAE, EJ, SMJvK, EMCJ and AW participated integrally in the study design. AW, SMDH, SMJvK, SMAAE, EMCJ, RS, ATGP, JPWvdB, RAdB, JMRM, SPGB, MH, ERCJ, IC, WLWvH, MGMS, PdB, NCS, WAdB, JGEH, W-YL, MdK, MHP, MLvH, EJ and PCPHW contributed significantly to the study set-up and study data interpretation. AW, EJ and SMDH drafted the initial manuscript and all the authors performed at least one review of the manuscript, provided feedback and approved the final version. Furthermore, AW, MH, ERCJ, IC, WLWvH, MGMS, PdB, NCS, WAdB, JGEH, W-YL, MdK, MHP, MLvH, EJ and PCPHW will be responsible for including patients and collecting patient data as described in this manuscript. RS and SMDH will be responsible for collecting patient data for the gait and balance assessment in the MUMC+ subpopulation. SMJvK greatly contributed to the Methods and analysis section and will also use his expertise to help with data analysis. SMAAE and ATGP greatly contributed to all sections concerning the cost-effectiveness and process evaluation, respectively.

ORCID iDs
Annemarijn Weber http://orcid.org/0000-0003-3634-0069
Sander M J van Kuijk http://orcid.org/0000-0003-2796-729X

REFERENCES

1 Hernlund E, Svedbom A, Ivergård M, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International osteoporosis Foundation (IOF) and the European Federation of pharmaceutical industry associations (EFPIA). *Arch Osteoporos* 2013;8:136.
2 Sözen T, Özışık L, Başaran Nursel Çalık. An overview and management of osteoporosis. *Eur J Rheumatol* 2017;4:46–56.
3 Reginster J-Y, Burlet N. Osteoporosis: a still increasing prevalence. *Bone* 2006;38:4–9.
4 Rosen CJ. Pathogenesis of osteoporosis. *Baillieres Best Pract Res Clin Endocrinol Metab* 2000;14:181–93.
5 Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006;17:1726–33.
6 Luthman S, Widén J, Borgström F. Appropriateness criteria for treatment of osteoporotic vertebral compression fractures. *Osteoporos Int* 2018;29:793–804.
7 Broy SB. The vertebral fracture cascade: etiology and clinical implications. *J Clin Densitom* 2016;19:29–34.
8 Luo J, Pollintine P, Gomm E, et al. Vertebral deformity arising from an accelerated "creep" mechanism. *Eur Spine J* 2012;21:1684–91.
9 Katzman WB, Wanek L, Shepherd JA, et al. Age-related hyperkyphosis: its causes, consequences, and management. *J Orthop Sports Phys Ther* 2010;40:352–60.
10 Wei Y, Tian W, Zhang GL, et al. Thoracolumbar kyphosis is associated with compressive vertebral fracture in postmenopausal women. *Osteoporos Int* 2017;28:1925–9.
11 Lin T, Lu J, Zhang Y, et al. Does spinal sagittal imbalance lead to future vertebral compression fractures in osteoporosis patients? *Spine J* 2021;21:1362–75.
12 Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. *JAMA* 2001;285:320–3.
13 Ailon T, Shaffrey CI, Lenke LG, et al. Progressive spinal kyphosis in the aging population. *Neurosurgery* 2015;77 Suppl 4:S164–72.
14 Richtlijn Osteoporose en Fractuurpreventie. *Derde herziening (2011)*. Nederlandse Vereniging voor Reumatologie, 2011.
15 Kanis JA, Cooper C, Rizzoli R, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2019;30:3–44.
16 Parreira PCS, Maher CG, Megale RZ, et al. An overview of clinical guidelines for the management of vertebral compression fracture: a systematic review. *Spine J* 2017;17:1932–8.
17 Ameis A, Randhawa K, Yu H, et al. The global spine care initiative: a review of reviews and recommendations for the non-invasive management of acute osteoporotic vertebral compression fracture pain in low- and middle-income communities. *Eur Spine J* 2018;27:861–9.
18 Jin YZ, Lee JH. Effect of brace to osteoporotic vertebral fracture: a meta-analysis. *J Korean Med Sci* 2016;31:1641–9.
19 Goodwin VA, Hall AJ, Rogers E, et al. Orthotics and taping in the management of vertebral fractures in people with osteoporosis: a systematic review. *BMJ Open* 2016;6:e010657.
20 Newman M, Minns Lowe C, Barker K. Spinal Orthoses for vertebral osteoporosis and osteoporotic vertebral fracture: a systematic review. *Arch Phys Med Rehabil* 2016;97:1013–25.
21 Rzewuska M, Ferreira ML, McLachlan AJ, et al. The efficacy of conservative treatment of osteoporotic compression fractures on acute pain relief: a systematic review with meta-analysis. *Eur Spine J* 2015;24:702–14.
22 Longo UG, Loppini M, Denaro L, et al. Conservative management of patients with an osteoporotic vertebral fracture: a review of the literature. *J Bone Joint Surg Br* 2012;94:152–7.
23 Longo UG, Loppini M, Denaro L, et al. Osteoporotic vertebral fractures: current concepts of conservative care. *Br Med Bull* 2012;102:171–89.
24 Zhu R-S, Kan S-L, Ning G-Z, et al. Which is the best treatment of osteoporotic vertebral compression fractures: balloon kyphoplasty, percutaneous vertebroplasty, or non-surgical treatment? A Bayesian network meta-analysis. *Osteoporos Int* 2019;30:287–98.
25 Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med* 2009;361:557–68.

26 Kallmes DF, Comstock BA, Heagerty PJ, *et al*. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med* 2009;361:569–79.

27 Firanescu CE, de Vries J, Lodder P, *et al*. Vertebroplasty versus sham procedure for painful acute osteoporotic vertebral compression fractures (VERTOS IV): randomised sham controlled clinical trial. *BMJ* 2018;361:k1551.

28 Wulff KC, Miller FG, Pearson SD. Can coverage be rescinded when negative trial results threaten a popular procedure? the ongoing SAGA of vertebroplasty. *Health Aff* 2011;30:2269–76.

29 Kushchayev SV, Wiener PC, Teytelboym OM, *et al*. Percutaneous vertebroplasty: a history of procedure, technology, culture, specialty, and economics. *Neuroimaging Clin N Am* 2019;29:481–94.

30 Jacobs E, Senden R, McCrum C, *et al*. Effect of a semirigid thoracolumbar orthosis on gait and sagittal alignment in patients with an osteoporotic vertebral compression fracture. *Clin Interv Aging* 2019;14:671–80.

31 Meccariello L, Muzii VF, Falzarano G, *et al*. Dynamic corset versus three-point brace in the treatment of osteoporotic compression fractures of the thoracic and lumbar spine: a prospective, comparative study. *Aging Clin Exp Res* 2017;29:443–9.

32 Li M, Law S-wai, Cheng J, *et al*. A comparison study on the efficacy of SpinoMed® and soft lumbar orthosis for osteoporotic vertebral fracture. *Prosthet Orthot Int* 2015;39:270–6.

33 Pfeifer M, Begerow B, Minne HW. Effects of a new spinal orthosis on posture, trunk strength, and quality of life in women with postmenopausal osteoporosis: a randomized trial. *Am J Phys Med Rehabil* 2004;83:177–86.

34 Pfeifer M, Kohlwey L, Begerow B, *et al*. Effects of two newly developed spinal orthoses on trunk muscle strength, posture, and quality-of-life in women with postmenopausal osteoporosis: a randomized trial. *Am J Phys Med Rehabil* 2011;90:805–15.

35 Valentin GH, Pedersen LN, Maribo T. Wearing an active spinal orthosis improves back extensor strength in women with osteoporotic vertebral fractures. *Prosthet Orthot Int* 2014;38:232–8.

36 Hou Y, Luo Z. A study on the structural properties of the lumbar endplate: histological structure, the effect of bone density, and spinal level. *Spine* 2009;34:E427–33.

37 Landham PR, Gilbert SJ, Baker-Rand HLA, *et al*. Pathogenesis of vertebral anterior wedge deformity: a 2-Stage process? *Spine* 2015;40:902–8.

38 Krul-Poel YHM, Vrijlandt P, Elders PJM. [Osteoporosis and increased risk of fractures]. *Ned Tijdschr Geneeskd* 2020:164.

39 Shein-Chung Chow JS, Wang H, Lokhnygina Y. *Sample size calculations in clinical research*. Chapman and Hall/CRC, 2018.

40 Barker KL, Newman M, Stallard N, *et al*. Exercise or manual physiotherapy compared with a single session of physiotherapy for osteoporotic vertebral fracture: three-arm prove RCT. *Health Technol Assess* 2019;23:1–318.

41 Lips P, Cooper C, Agnusdei D, *et al*. Quality of life in patients with vertebral fractures: validation of the quality of life questionnaire of the European foundation for osteoporosis (QUALEFFO). Working Party for quality of life of the European foundation for osteoporosis. *Osteoporos Int* 1999;10:150–60.

42 Stevenson M, Gomersall T, Lloyd Jones M, *et al*. Percutaneous vertebroplasty and percutaneous balloon kyphoplasty for the treatment of osteoporotic vertebral fractures: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2014;18:1–290.

43 Gallizzi M, Gagnon C, Harden RN, *et al*. Medication quantification scale version III: internal validation of detriment weights using a chronic pain population. *Pain Pract* 2008;8:1–4.

44 Fairbank JC, Couper J, Davies JB, *et al*. The Oswestry low back pain disability questionnaire. *Physiotherapy* 1980;66:271–3.

45 Craig CL, Marshall AL, Sjöström M, *et al*. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc* 2003;35:1381–95.

46 Pesenti S, Pomero V, Prost S, *et al*. Curve location influences spinal balance in coronal and sagittal planes but not transversal trunk motion in adolescents with idiopathic scoliosis: a prospective observational study. *Eur Spine J* 2020;29:1972–80.

47 Senden R, Savelberg HHCM, Grimm B, *et al*. Accelerometry-based gait analysis, an additional objective approach to screen subjects at risk for falling. *Gait Posture* 2012;36:296–300.

48 Fritz S, Lusardi M. White paper: "walking speed: the sixth vital sign". *J Geriatr Phys Ther* 2009;32:2–5.

49 IJzerman MJ. *Richtlijn voor Het uitvoeren van economische evaluaties in de gezondheidszorg*. Zorginstituut Nederland, 2016.

50 Lvd H-Rvan, Bouwmans K, Kostenhandleiding ST. *Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg*. Institute for Medical Technology Assessment Erasmus Universiteit Rotterdam, 2016.

51 Saunders RP, Evans MH, Joshi P. Developing a process-evaluation plan for assessing health promotion program implementation: a how-to guide. *Health Promot Pract* 2005;6:134–47.

52 Drost P, Ruwaard E. *Handleiding intersectorale kosten en baten van (preventieve) interventies*. Classificatie, identificatie en kostprijzen: Faculty of Health, Medicine and Life Sciences, 2016.

53 Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005;14:487–96.

54 Moerkamp A. Rapport kosteneffectiviteit in de praktijk. In: . Zorginstituur Nederland, 2015.

55 Sullivan SD, Mauskopf JA, Augustovski F, *et al*. Budget impact analysis-principles of good practice: report of the ISPOR 2012 budget impact analysis good practice II Task force. *Value Health* 2014;17:5–14.

56 World Medical A, World Medical Association. World Medical association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191–4.

57 Haefeli M, Elfering A. Pain assessment. *Eur Spine J* 2006;15 Suppl 1:S17–24.

58 M Versteegh M, M Vermeulen K, M A A Evers S, *et al*. Dutch tariff for the five-level version of EQ-5D. *Value Health* 2016;19:343–52.

59 Thorn JC, Coast J, Cohen D, *et al*. Resource-use measurement based on patient recall: issues and challenges for economic evaluation. *Appl Health Econ Health Policy* 2013;11:155–61.