Research protocol

KneeMo Feedback Study

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Gait retraining by real-time feedback in patients with knee osteoarthritis

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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)**
ACR	**American College of Rheumatology**
ADL	**Activities of Daily Living**
AE	**Adverse Event**
AMS OA	**Amsterdam Osteoarthritis cohort**
AR	**Adverse Reaction**
BMI	**Body Mass Index**
BW	**Body Weight**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
COOA	**COmorbidity in knee OsteoArthritis**
CoP	**Centre of Pressure**
CRF	**Case Record Form**
CV	**Curriculum Vitae**
CVA	**Cerebral Vascular Accident**
DSMB	**Data Safety Monitoring Board**
EMG	**Electromyography**
ESP	**Early stage peak**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GRAIL	**Gait real-time analysis interactive lab**
GRF	**Ground reaction force**
GCP	**Good Clinical Practice**
GUG	**Get Up and Go test**
H	**Height**
HBM	**Human Body Model**
IB	**Investigator's Brochure**
IC	**Informed Consent**
ICC	**Intra class correlation**
IMP	**Investigational Medicinal Product**

IMPD	**Investigational Medicinal Product Dossier**
ITN	**Initial Training Network**
KAM	**Knee Adduction Moment**
KFM	**Knee Flexion Moment**
KJC	**Knee Joint Centre**
KL	**Kellgren Lawrence scale**
KOA	**Knee Osteoarthritis**
KOS ADLS	**Knee Outcome Survey Activities of Daily living Scale**
LSP	**Late stance peak**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
MS	**Mid-stance**
NRS	**Numeric Rating Scale (for pain)**
(S)AE	**(Serious) Adverse Event**
SENIAM	**Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie 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.**
SPSS	**Statistical Package for the Social Sciences (SPSS)**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
VR lab	**Virtual Reality lab**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Real-time visual and audio feedback of the gait pattern is assumed to be effective for gait retraining in patients with osteoarthritis of the knee (KOA). Modification of the gait pattern results in a change in knee joint loading. The external knee adduction moment (KAM) is considered to be a good surrogate measure of internal loading on the medial side of the tibiofemoral condyles. KOA patients with medial compartment OA often show a higher KAM compared to healthy subjects. In healthy subjects it has been shown that direct real-time visual feedback of the KAM was effective in reducing the knee joint loading. A gait training protocol with direct KAM feedback in which patients can develop preferred individual kinematic strategies needs to be developed.

Objective: (A) To evaluate the use of real-time visual and audio feedback on the knee adduction moment and on kinematic patterns during gait in patients with knee osteoarthritis to decrease the biomechanical load on the knee via implicit learning and explicit instructions; (B) To provide proof-of-concept for the use of real-time feedback as a clinical intervention on gait retraining to decrease the biomechanical load on the knee in patients with (medial compartment) knee osteoarthritis during a 6 weeks training and 3 and 6 months follow-up.

Study design: Cross-sectional observational study (A) and uncontrolled experimental study (B). In the first study (A) a biofeedback algorithm using computer modelling will be tested on its feasibility in a cross-sectional observational study to establish measurement capability and quality in patient with OA of the knee (n=41). In a second study (B) an n uncontrolled trial will be carried out during 6 weeks to provide evidence for real-time feedback as an intervention in modifying gait in a subsample of the previous study (n=30[1]). Follow-up measurements will be carried out 3 and 6 months after the end of the training. Modification of knee load and gait characteristics will be assessed by 3D motion analysis on the GRAIL (Gait real-time analysis interactive lab including an instrumented treadmill, a motion capture system and a semi cylindrical screen with virtual reality environment and real-time gait feedback).

Study population: 41 patients with medial knee osteoarthritis aged between 50 and 70.

Intervention (if applicable): Training protocol for gait modification once per week for 6 weeks, including feedback on the external knee adduction moment (KAM) and advice on home training.

Main study parameters/endpoints: Primary outcome measures are change in external knee adduction moment (KAM) between different conditions. KAM will be measured during

[1] Note that 24 patients are required for this part of the study (according to the power calculations). However, we will aim to recruit 30 to account for patient drop out between the start and the 6 month follow up.

the various gait modification conditions (study A: 1. baseline; 2. KAM feedback without kinematic instructions, audio and visual feedback; 3. Kinematic feedback without further instructions (toe-out or -in, step width and medial thrust); 4. KAM feedback with additional verbal kinematic instructions about an effective gait pattern that can be sustained in daily life: 5. maintaining the pattern from 4. without any feedback) and during and after the training sessions (study B: 1. baseline; 2. try to replicate the pattern learned in study A without feedback; 3. KAM feedback with kinematic instructions from study A; 4. maintaining the pattern from 3. without feedback; follow-up after 3 and 6 months). Linear mixed models will be used to calculate statistical differences. Secondary parameters will include external knee flexion moment (KFM), and kinematic pattern (joint angles and temporal-spatial parameters) as measured by the GRAIL; pain as measured by the numeric rating scale and will be assessed during the different gait modification patterns (as for the KAM).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Potential participants of the study are registered as members of the AMS-OA cohort (Reade) and will be invited to participate the study. If they pass the inclusion criteria and are willing to participate, they will be invited to come to the VUmc for a visit with the researcher. A final decision on eligibility will be made, based on the inclusion criteria. Participants will be assessed during a part of the day (maximum of three hours in study A, one hour in study B). In that time they will complete questionnaires and perform physical-performance tests, and walk on the treadmill with different gait modification conditions. To protect participants from falling, subjects will wear a safety harness during the walking trials. During the measurements, participants will be asked to modify the gait pattern. The risk of gait modification on side effects is negligible. Total risk of adverse events during the assessments and during walking on the treadmill is negligible. Also during the training, the risk on adverse events is negligible. Periods of rest will be allowed during/ between the measurements to prevent fatigue. Patients will also be asked about their pain levels and the training or measurements can be shortened if necessary in response to increasing pain (although from previous literature in the field we do not anticipate this problem). Patients will also be made aware that they are free to withdraw from the study at any time without giving a reason.

1. INTRODUCTION AND RATIONALE

Real-time bio-feedback has been used in several different pathological conditions to encourage patients to adopt a modified gait pattern. A systematic review of papers up to 2007 found that real-time feedback appears to result in moderate to large treatment effects, at least in the short-term[1]. Current literature also suggests that real time feedback might be effective for gait retraining in patients with osteoarthritis of the knee (KOA) [2-7]. Modification of the gait pattern has been shown to result in a change in knee joint loading [6;8-13]. KOA patients with medial compartment OA often show higher external knee adduction moments (KAM) compared to healthy subjects [14-19]. This high KAM is believed to be a measure of high internal loading on the medial side of the tibio-femoral condyles. It may be influenced by body posture during gait (gait pattern), body mass index, mal-alignment of the knee, muscle strength and co-contraction of the muscles around the knee [13;20-27;27-30]. The high loading affects the cartilage structure and may result in further progression of cartilage degeneration [29;31-37]. To delay further degeneration, to relieve symptoms such as pain and to postpone knee replacement, a change in loading pattern of the knee might be helpful [6].

Many studies have investigated the effect of modification of gait to lower the KAM [3;5;6;10;12;13;38;39]. The effect of modification on the knee flexion moment has also been studied [13;40]. Effective gait modifications include a toe-in or toe-out pattern (foot progression angle), ipsilateral trunk sway, change in walking speed, medial thrust gait (knees pointing medially), hip endorotation, change in step width, or weight transfer to the medial side of the foot. Table 1 summarises the current evidence and biomechanical reasoning for changes in knee adduction moment with four of the most commonly used gait modifications. The exact method of achieving the modification is not necessarily specified; for example an increased step width (distance between the ipsi and contralateral heels in the frontal plane) may be achieved through increased hip adduction, increased active valgus movement at the knee (although this may be difficult to achieve in practice) or increased toe-in position of the feet. In addition to those mentioned in Table 1, the use of increased lateral trunk sway to move the centre of mass closer to the stance foot has often been reported to be a successful method in reducing KAM [8;9;13;41]. Despite the success however there are some disadvantages to this method; namely a) an increase in energy cost of walking [42], which may reduce the potential to use the modified gait pattern in everyday life and b) can be uncomfortable for the person to adopt [8;9;13;41]. Private communications with clinicians working with patients with medial knee osteoarthritis have also suggested that increasing trunk sway may result in further complications, especially in the case of patients with osteoarthritis in other joints.

Table 1: Modifications to gait resulting in reduction of KAM in healthy and/or OA patients.

Gait Parameter	**A priori Knowledge and Biomechanical Rationale**
1) Step Width	In a study conducted in 17 healthy individuals at the VUmc, van den Noort and colleagues [43] found that when subjects were given real time feedback on KAM and asked to reduce the KAM (without further instruction on how to achieve this), there was a significant increase in step width, by 6-7cm. Similarly Fregly et al. [44] found that there was a corresponding decrease in KAM with an increase in step width. Increasing the step width causes a lateral shift of the centre of pressure (CoP) which in turn increases the moment arm from the knee joint centre to the line of action of the ground reaction force in the frontal plane This in turn has the effect of reducing the moment.
2) Foot Progression Angle – Toe in	In a study of 14 young healthy subjects, toe in strategy was successfully used to reduce the KAM, during early stance[13]. Shull et al. (2012) tested the effectiveness of toe-in gait in a group of 12 subjects with medial KOA and found a significant reduction in the first peak of the KAM [10]. Similarly in a six week gait re-training program, Shull et al. (2013) used feedback to encourage increased toe-in position [41]. After six weeks gait re-training the first peak KAM was reduced by 20%. Wheeler et al. (2011) healthy subjects with feedback on KAM and gave suggestions based on previous studies of how to reduce the KAM. They found that most subjects, 14/16, opted for a toe-in gait modification [7]. Increasing the internal rotation of the foot (toe in) has the effect of shifting the knee joint centre (KJC) medially and hence closer to the CoP. This in turn has the effect of reducing the moment arm from the KJC to the line of action of the force, as with an increase in step width, which reduces the KAM. It has also been suggested that the biomechanical reasoning for the reduction in the moment arm is a shift in the centre of pressure laterally due to an externally rotated heel [10].. This is in agreement with the finding that the KAM is typically only reduced in the first peak and not throughout stance.

3) Foot Progression Angle – Toe out	Hunt and Takacs (2014) trained 15 subjects with medial knee OA to walk with a toe-out gait [3] over a ten week gait modification program. At the end of the of the program, second stance KAM was significantly reduced. Patients also benefited from a reduction in pain and an improvement in function as indicated by changes in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score. Van den Noort et al. (2013) also reported a decrease in second peak KAM with an increased toe out position, in their study of 14 young healthy subjects [13]. However, in this investigation, the peak KAM in early stance was increased beyond the normal range. Although first peak KAM was not significantly decreased in the study by Hunt and Takacs there was a trend towards a reduction in KAM. The difference in the results may be a consequence of higher baseline KAM in the OA patients compared to the healthy subjects. Gerbrands et al. (2014) reported a reduction in the KAM impulse with increased toe-out position in a group of 37 healthy participants [8]. They concluded that individual selection of strategy was important for optimally reducing the knee joint loading. Guo et al. reported a significant reduction in second peak KAM during walking with a toe-out gait and during stair ascent in ten subjects with mild to moderate medial KOA [45]. Increasing the external rotation of the foot (toe out) has the effect of shifting the centre of pressure laterally in the second part of the stance phase. However, in the early part of the stance phase, the CoP is more medial than normal. This has the effect of increasing the moment arm to the ground reaction force, in the early part of the stance phase. This explains the increased in first peak KAM, reported by Van den Noort et al. (2013) [13]. As the centre of pressure progresses forward under the foot, the increased toe out position serves to reduce the moment arm and hence the KAM during the second peak of the GRF.
4) Medial Knee Thrust	Medial knee thrust was found to significantly reduce the KAM in healthy subjects, when instructed to ‘Move the right knee inwards/medial during right legged stance’ [8]. Schache et al. (2008)

	reported a decrease in knee adduction moment with medial thrust in a single individual subject [46]. The reduction was maintained throughout the stance phase, unlike some modifications which are effective only in early of late stance. However, since this applies only to a single subject, it has limited power. In another single case study, Fregly et al. (2009) reported a decrease in joint loading of 16% [47]. However, varus or lateral thrust is biomechanically difficult to correct when the knee is extended (or locked out) due to the tension in the ligaments and the interlocking of the condyles with the tibia. Therefore, this modification of the gait pattern will only be successful if combined with stance phase knee flexion. Patients with medial knee osteoarthritis often walk with a lateral (or varus) thrust of the knee, which serves to increase the adduction of the knee and hence the adduction moment [48]. Reversing this strategy, by encouraging a medial (or valgus) thrust of the knee has the effect of reducing the moment arm in the frontal plane and therefore reducing the KAM.

A few recently published studies investigated the use of real-time feedback to control and train the gait modification, either using haptic feedback [7;41;49] or visual feedback [2;3;7;13;50]. Both applied feedback methods have the potential to be used in clinical practice. Traditional physiotherapy interventions are generally focused on reducing pain at the joint, increasing the range of movements and strengthening the muscles around the joint. In addition gait retraining strategies have been developed to try to reduce the knee adduction moment, by reducing the perpendicular distance between the line of action of the ground reaction force and the knee joint centre. Such strategies include walking with a toe out gait or shifting the centre of pressure using a lateral trunk lean. A recent systematic literature review of gait modification strategies aimed at medial compartment osteoarthritis reported that both have the ability to reduce the KAM and therefore potentially reduce the medial compartment loading [12]. It is also important to recognise that patient adherence to exercise therapy is considered to be one of the key factors that influences the outcome and improvement of the patient's symptoms [51].

In clinical re-training, there is a focus on a dynamic walking pattern with a spring-like movement in the knee and ankle during loading response for shock absorption. Typically patients tend to adopt a stiff-knee gait pattern with reduced flexion of the knee during stance.

Stance phase flexion requires eccentric control of the quadriceps. Since the quadriceps strength is often reduced in patients with knee osteoarthritis, their gait is adapted to reduce the work required of this muscle group. Clinical therapy focuses on two main areas; firstly improving the co-ordination and timing of the loading and hence re-gaining the stance phase flexion to provide shock absorption and secondly on increasing muscle strength in the quadriceps by walking with bent knees. In clinical practice there is a focus on whole body coordination, including the arm and trunk movements.

In healthy subjects it has been shown that real-time visual feedback on the KAM was most effective in reducing the KAM, in contrast to feedback of a kinematic parameter assumed to influence the KAM [6]. In this study, kinematic feedback was provided on hip internal/ external rotation. By directly controlling the KAM itself, subjects did not show ineffective kinematic compensation strategies that oppose the effect on the KAM. Whether this also applies to KOA patients needs to be investigated and whether patients learn better through implicit learning (i.e. KAM feedback without explicit instructions of gait parameters to change) or explicit instructions on gait parameters remains to be determined. Furthermore, little is known about the effect of feedback training in KOA patients or about the optimal way of using the feedback in clinical practice. Only a few studies have been looked into gait retraining via feedback, using foot progression angles [3;10]. It is unlikely that there will be a “one size fits all” solution to the gait retraining due to the heterogeneous nature of patient cohort. Therefore individual re-training strategies may need to be developed, varying the type and amount of feedback that is presented.

A study comparing the effect of four different gait modification patterns on the KAM concluded that individual selection of strategy is vital for optimal reduction of medial knee joint loading [8]. However, a gait training protocol with direct KAM feedback [43] in which patients can develop preferred individual strategies [7;8;41;43] as well as the long term effects of such a protocol have not been studied yet. For the gait modification strategy to be adopted long term and used outside of the lab it is important to ensure patient preferences are taken into consideration to encourage long term adherence.

Implicit motor learning has been defined as the learning of information without the ability to verbally describe the knowledge of what is learnt [52]. This is particularly advantageous in rehabilitation strategies in certain neurological conditions, such as cerebral vascular accident (CVA or stroke) or Parkinson’s disease where explicit instructions (or an attempt to consciously control motor actions) may disrupt the optimal learning process. Explicit learning, by contrast, involves the learner exerting conscious control over the learning process [53], in the presence of factual knowledge of the task (i.e. specific instructions). Explicit learning is therefore synonymous with knowledge of rules while implicit learning takes place without

knowledge of the rules [54]. In skill learning (or in this case modifying of an existing skill), there are considered to be three phases or stages of learning; cognitive, associative and autonomous [55]. In the first phase, the cognitive phase, the movement is largely consciously controlled and there is considerable cognitive demand. During the associative phase, movements become more fluid and the cognitive demand is reduced. Finally, the autonomous phase is considered to occur once the little or no cognitive activity is required and the movement is undertaken without conscious control.

The focus of attention during the training sessions is an important consideration. An internal focus of attention, whereby the attention is on the movement pattern, may be required during the early stages of the feedback program. However, an external focus of attention, whereby the focus is on the effects of the movements rather than the movements themselves, may be more appropriate as the patient tends towards the associative phase of learning. In healthy persons learning a new motor skill, there is significant evidence that an external focus (that is, focussing not on specific movements but instead on achieving a specific task) is beneficial [56-58]. Furthermore, in certain neurological populations, it has been shown that provision of explicit instructions may actually reduce motor learning [59]. Whilst this may not appear to be as relevant to orthopaedic pathologies, the body of evidence for the benefit of an external focus in the healthy population suggests that it merits further investigation.

In order for the modified gait pattern to be adopted during activities of daily life, it may be necessary for it to become autonomous, such that it is adopted without (excessive) cognitive demand. Achieving such a stage of learning may require a change in the type and frequency of the feedback given to the patients between the first (initial) training session and last training session. In addition, regular home-based training using the modified gait pattern may help to internalise the new gait pattern and reduce the tendency to revert back to the original pattern. In this way the benefits of the training program may have increased applicability and may lead to a longer term reduction in medial knee pain. To examine the effects of training or skill acquisition on motor learning, dual tasking scenarios can be used. This allows an estimation of the cognitive demand of the primary task to be estimated by measuring the effect on the task of adding in an additional task [60].The secondary task may be a cognitive task, such as a memory test, or an additional motor task. Previous research in this area has tended to focus on neurological pathologies, in particular CVA, Parkinson's and Alzheimer's. However, in the orthopaedic population, Hiyama et al. [61] showed that a four week walking program improved patient's dual tasking performance compared to a control group. This suggests that the cognitive demand for performing the motor task (walking) was reduced,

allowing improved performance in the secondary task. This may have important consequences in activities of daily living (ADL).

Studies investigating the effects of gait modifications on KAM (including the proposed study) are usually conducted under idealised conditions, for example within a laboratory setting with an even, level flooring or on a treadmill at fixed pace with the belts level or at a fixed gradient. To increase the similarity to the real world environments, and hence improve applicability in the real-world environment, the addition of obstacles or such like to the laboratory environment may be necessary. Obstacle avoidance has been shown to be reduced in patients with knee osteoarthritis, therefore increasing the likelihood of trips [62].

Postural balance in patients with knee osteoarthritis is often reduced as a consequence of reduced proprioception at the knee joint [63] [64]. Increased co-contraction of the muscles around the knee may increase the stability of the joint. However increased co-contraction has also been associated with increased joint loading [21]. In early stage osteoarthritis it has been shown that changes in balance may precede changes in gait parameters (including KAM), therefore suggesting that neuro-muscular changes may occur prior to changes in gait [65]. Reduced confidence in the knee and reduced stability may contribute to the higher rate of falls and increased fear of falls in patients with medial knee osteoarthritis [63] [66]. Although the objective of the gait re-training program proposed in this study is not to target balance or stability, quantification of postural balance at the beginning and end of the training phase of this study, alongside self-reported measures of stability may be important in showing neuro-muscular changes.

Activity levels in patients with knee osteoarthritis are often reduced, probably as a consequence of pain and reduced function. In the United States of America, almost two thirds of people with knee osteoarthritis reported walking for less than 90 minutes per week [67]. A systematic review and meta-analysis reported that only a small proportion of people with knee osteoarthritis met physical activity guidelines and recommended daily steps [68]. A second substantial proportion of men and women (40.1% and 56.5%) being classified as inactive. However maintaining physical function is a critical factor for people with osteoarthritis in order to maintain an independent community lifestyle. A study of a large sample of patients (1788 participants) with or at high risk of knee osteoarthritis found that increasing the number of steps taken per day has the effect of increasing protection against functional limitation, as measured by performance and self-report [69]. In addition to protecting against a decline in function other benefits have previously been reported, such as lower prevalence of cardiovascular disease [70]. Benefits of increased activity are well established for the general population and there is also evidence that regular exercise has

beneficial effects for people with knee osteoarthritis [71]. A novel and individual intervention, such as gait retraining to reduce knee joint loading, may have the effect of increasing the activity levels, either as a consequence of reduced pain levels in the joint, or by increasing motivation. A web-based physical activity intervention showed an increased in physical activity levels in the intervention group compared to the control group 12 months after starting the program [72], providing evidence for the long term benefit of a novel intervention. Objective measurement of physical activity, in the form of number of steps taken per day, is easily captured using a smartphone with built in accelerometer and a freely available application. Therefore, although the main objective of the gait training program is not to increase activity levels, this may be an important side effect of the program and one which can be easily measured using widely available technology.

In summary, there is a large body of evidence to suggest that reduction in the knee adduction moment is beneficial for patients with medial knee osteoarthritis. Furthermore there is evidence to suggest that gait re-training using bio-feedback is beneficial in reducing the KAM. However further research is required in this area to determine the most effective feedback for motor learning in this population. While current research shows that bio-feedback has the immediate effect of reducing the KAM, the longer term effects, including the effect on physical activity level, and the extent of motor learning have not yet been evaluated. Similarly the effect of gait retraining on knee instability and postural balance has not yet been evaluated.

Therefore, the aims of the current study are: (A) To evaluate the use of real-time visual feedback on the knee adduction moment and on kinematic patterns during gait in patients with knee osteoarthritis to decrease the biomechanical load on the knee via implicit learning and explicit instructions; (B) To provide proof-of-concept for the use of real-time feedback as a clinical intervention on gait retraining to decrease the biomechanical load on the knee in patients with knee osteoarthritis during a 6 weeks training and 3 and 6 months follow-up. A biofeedback algorithm using computer modelling will be tested on its feasibility in a cross-sectional observational study to establish measurement capability and quality in patients with KOA. Secondly, a small-scale exploratory intervention will be carried out to provide preliminary evidence for real-time feedback as an intervention in modifying gait in a subsample of the previous study.

2. OBJECTIVES

The primary objective of study A is:

- To evaluate the use of real-time visual and audio feedback on the knee adduction moment during gait in patients with knee osteoarthritis to decrease the biomechanical load on the knee via implicit learning and explicit instructions.

The secondary objective of study A is:

- To evaluate changes in the kinematic patterns and electromyographic patterns between baseline (without feedback) and modified (with feedback) gait patterns.
- To identify factors based on the demographic, radiographic and baseline kinematics which increase the likelihood in reducing the KAM using the biofeedback training method.

The primary objectives of study B are:

- To provide proof-of-concept for the use of real-time feedback as a clinical intervention on gait retraining to decrease the biomechanical load on the knee in patients with knee osteoarthritis during a 6 weeks training and 3 and 6 months follow-up.
- To assess changes in pain and function as a result of the biofeedback gait training programme; this will be measured using the WOMAC questionnaire and NRS pain scale. Pain and function are important outcome measures for the patient and are therefore included as additional primary outcome measures.

The secondary objectiveof study B is:

i) To estimate the reduction in cognitive demand (and hence the extent of motor learning) of the gait modifications over the six week retraining period.

3. STUDY DESIGN

Cross-sectional observational study (A) and an uncontrolled experimental study (B).

Study A: A biofeedback algorithm using computer modeling will be tested on its feasibility in a cross-sectional observational study to establish measurement capability and quality in patients with KOA (n=41).

Study B: Secondly, an uncontrolled experimental study will be carried out to provide preliminary evidence for real-time feedback as an intervention in modifying gait in a subsample of the previous study (n=30). Participants will begin with weekly training sessions for a period of six weeks. Follow up measurements will be conducted during the final training

week and at 3 and 6 months after completion of the training to assess long term effects in both groups; hence for each group there will be a total of 4 full assessments (week 1 and 6 of the training sessions and 3 and 6 month follow ups) for study B in addition to the initial measurement for study A. Note, a full assessment will include measurement of kinematics and kinetics (specifically KAM) plus questionnaire based data; WOMAC pain and function. and knee confidence. At the interim training weeks, pain will be assessed using the Numeric Rating Scale (NRS) pain scale. Further details of the timing of assessments at each stage of Study B is presented in Appendix A2

		Week number												
30 patients from Study A		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**18**	**30**
		start of intervention **M1** T1	T2	T3	T4	T5	**M2** T6	Home practice of modified gait pattern						**M3**	**M4**

T1 to T6 indicate training sessions 1 to 6. M1 to M4 indicate measurement sessions 1 to 4. Further details relating to the measurements at each stage of the protocol can be found in Appendix A2.

Study A. N=41

Type of visual feedback: preference of patient
(bar, colour, polar, graph, number, etc.)

Conditions:

0. Familiarisation to treadmill and choice of visual feedback for individual patient
1. Baseline own shoes
2. Baseline standard shoes
3. Implicit learning phase (standard shoes):
   i). Visual feedback on KAM (subjects need to decrease the KAM by changing the gait pattern in the way they prefer)
   ii). Audio feedback on KAM (as above)
   (i and ii will be randomised such that some patients will start with visual feedback and some with audio feedback).
4. Observation phase:
   Observation by physical therapist and researcher from data of 1-3 and clinical observation what kinematic gait parameters need to be further retrained in order to decrease the KAM; determine max. 3 parameters *(toe-in/out, step width, medial thrust; parameters determined using decision tree- see Appendix A1)*
5. Training phase with explicit instructions:
   i. Feedback on KAM with verbal instructions about 3 kinematic gait parameters
   ii. Feedback on up to 3 kinematic parameters separately (after each other, most important first; instruction from researcher for gait modification) *(parameters determined using decision tree- see Appendix A1)*
6. Measurement without feedback while new pattern is applied

Study B. N=30 (subsample of study A)

Type of feedback:
(choice of visual and audio feedback, depending on the results of study A)

Conditions:

1. Baseline own shoes (ensure flat shoes and same/ similar shoes worn over the six week period)
2. Training phase:
   based on the results of study A,
3. Measurement without feedback while new pattern is applied
4. Measurement without feedback while new pattern is applied and secondary task is applied *
5. Advice for home training (e.g. gait pattern, stair climbing, getting-up from chair, cycling)

Repeating steps 1-5 once a week during 6 weeks

* *Steps only applied in week 44 to 6*

6. Follow-up experiment after 3 and 6 months:
   Baseline and replication of the learned pattern

Figure 1: Study Design

4. STUDY POPULATION

4.1 Population (base)

In the present study, patients from the Amsterdam Osteoarthritis (AMS-OA) cohort with a unilateral or bilateral diagnosis of knee OA according to the American College of Rheumatology (ACR) will be included [73-75]. The AMS-OA cohort contains patients with OA of the knee and/or hip who have been referred to a secondary care outpatient rehabilitation center (Reade, Center for Rehabilitation and Rheumatology, Amsterdam, the Netherlands). The examination protocol involves assessments by rheumatologists, radiologists and rehabilitation physicians. Further patients will be recruited directly through the VUmc and will be assessed by a VUmc rheumatologist. These patients will therefore not form part of the AMS-OA cohort but will require a radiograph of the knees to determine if they meet the inclusion criteria. All patients will provide informed consent according to the Declaration of Helsinki. The study will be submitted for approval to the Institutional Review Board of the VUmc. 30 patients from study A will also be enrolled in study B. Where there are > 30 patients meeting the criteria for study B (as specified in section 4.2), patients will be selected at random from the total number of potential study subjects.

4.2 Inclusion criteria

Inclusion criteria for the present study (A and B) are knee osteoarthritis on the medial compartment based on the ACR criteria (ACR criteria are age over 50 years, morning stiffness less than 30 minutes, crepitus on active motion, bony tenderness, or absence of palpable warmth of synovium), age between the 50 and 75 years old, Body Mass Index (BMI) between 20 and 30 kg/m2, maximal a score of 7 on the numeric rate scale (NRS) for pain intensity during the past two weeks.

The database of the AMS-OA cohort (Reade) will be screened to identify suitable patients based on the Kellgren-Lawrence (KL) score. This will allow patients with predominantly medial sided osteoarthritis to be identified.

There are several additional inclusion criteria for study B. These include patient satisfaction with the applied gait modification (assessed using the questionnaires in Sections F and G in F1 KneeMo Feedback Questionnaires). In addition, patients should be willing further learn the modifications in training sessions. Finally we require patients to show a clear reduction in the KAM value. Where possible the reduction in KAM (relative to baseline) should be 10%, but this will be at the discretion of the clinicians involved in the decision making process. The

10% KAM reduction is proposed based on previous literature that suggests that this value is attainable through gait retraining and is also clinically relevant in unloading the medial knee joint compartment Shull et al. (2013) and Hunt and Takacs (2014),. Importantly the reduction in knee adduction moment must occur without negative side effects such as a large increase in knee flexion moment or in pain. Furthermore, patients will be included only when there is no clear asymmetry in the change in KAM.

Finally, it is important that patients included in the study are able to walk for 30 minutes independently of a walking frame, crutches or other assistive device (excluding soft braces and orthotics).

4.3 Exclusion criteria

Total knee replacement, rheumatoid arthritis or any other form of inflammatory arthritis (i.e., crystal arthropathy or septic arthritis) are exclusion criteria. Similarly patients with hip osteoarthritis will be excluded. Patients who are already included in any other experimental research study (including but not limited to the Vitamin D study and the COOA study) will also be excluded. Subjects with poor eye sight, which would restrict their ability to understand and use the real time feedback will also be excluded,

4.4 Sample size calculation

The study is powered on the outcome variable external knee adduction moment (KAM).

Study A: Based on a significance level alpha = 0.05, power (1-β) = 0.80 and an effect size of >0.9 based on the reported changes in Van den Noort et al. [13] (see below for calculation of the effect size), the minimum number of subjects required for a statistically significant difference is 5. However, based on the work of Shull et al. (2013) and Hunt and Takacs (2014), we anticipate a smaller effect size when the intervention is used in patients with knee osteoarthritis than was shown in the initial pilot study with healthy controls. Moderate effect sizes (based on the KAM) were calculated from the data in the afore mentioned studies. Based on an anticipated small effect size of 0.45, significance level of 0.05 and power (1-β)=0.80, the minimum number of subjects required is 41. This is calculated using a two tailed t-test, assessing the difference between two dependent means (i.e. the differences in the KAM with and without feedback) [76;77].

Effect size calculations

calculated using $d = \frac{u_1 - u_2}{\sigma}$ where σ is the pooled standard deviation.

Van den Noort et al. (2015) [13]

	Mean (Standard deviation)[a]	Where found
KAM during early stance without feedback (baseline):	2.17 (1.03)	Table 2, page 280
KAM during early stance with feedback[b]	1.08 (1.07)	Table 2, page 280

[a]Standard deviation calculated from the standard error reported in the table (i.e standard error multiplied by square root of the number of subjects).

[b]Effect of different types of feedback not statistically significant; therefore the data presented here is the mean of the five different feedback types used in the study.

Shull et al. (2013) [41]

	Mean (Standard deviation)[a]	Where found
KAM (first peak) at baseline:	3.11 (1.40)	Table 2, page 1023
KAM (first peak) post training	2.61 (1.47)	Table 2, page 1023

Hunt and Takacs 2014 [3]

	Mean (Standard deviation)[a]	Where found
KAM (second peak) at baseline:	2.87 (0.92)	Table 2, page 909
KAM (second peak) at follow up	2.57 (0.84)	Table 2, page 909

Study B: Based on a significance level alpha = 0.05, power (1-β) = 0.80, and an anticipated effect size of 0.45 (as above) we require a minimum of 79 participants per group for a between group comparison (i.e. comparison of control and intervention group). This is calculated using a two tailed t-test, assessing the difference between two independent means. Since this is an initial feasibility study, it may not be feasible to recruit such a large number of subjects per group. Therefore we propose that a within group comparison of the baseline to post training may be more suitable. We also anticipate a higher effect size, due to the multiple training sessions. For a within group analysis, using the parameters as specified above and effect size of 0.6, a total of 24 patients are required. This is calculated using a two tailed t-test, assessing the difference between two dependent means (i.e. the differences in the KAM pre and post training) [76;77]. **To account for subject withdrawal we will aim to recruit 30 patients in total.**

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study parameter/endpoint

The main study parameter will be the **external knee adduction moment (KAM).** The KAM is determined by the ground reaction force (GRF) and its lever arm in the frontal plane and considered a surrogate for medial compartment loading.
The two KAM peaks (in early and late stance) have been linked to the presence, severity, and progression of knee OA [10;15]. Gait modification (e.g. toe-out/in, trunk sway, step width, medial thrust, hip rotation etc.) have been shown to influence the KAM (peaks in early and late stance, KAM during mid-stance and KAM impulse (area under curve) [12;13;43].

For study B, the change in KAM over the 6 weeks training period and at 3 and 6 month follow-ups will be evaluated.

5.1.2 Secondary study parameters/endpoints (if applicable)

The first secondary parameter is the external knee flexion moment (KFM, determined by the GRF and its lever arm in the sagittal plane). The KFM has been shown to play an important role in medial compartment loading and has an interaction with the KAM and internal knee load [13;18;40;78;79]. Pain can cause patients to stiffen the knee during gait, which has a direct influence on the KFM since this alters the lever arm.

Pain is also a secondary study parameter (as measured with the NRS scale), particularly in study B, where it will be assessed on a weekly basis (i.e. at each training session). Patient reported outcome measures are becoming increasingly important in experimental studies such as the proposed study. Therefore, the WOMAC questionnaire will be used to assess changes in pain, function and stiffness of the knee. Patients will be asked to complete this questionnaire five times 1) during Study A and then where applicable to the individual patient 2 and 3) at the start and end of the training phase in Study B 4) at the three month follow up and 5) at the six month follow up.

The amount of muscle co-contraction is also a secondary study parameter, measured with electromyography (EMG) (medial muscles: vastus medialis, medial hamstrings, medial

gastrocnemius; lateral muscles: vastus lateralis, lateral hamstrings, lateral gastrocnemius; and the rectus femoris). Co-contraction will influence the load on the knee [21;27;80-82].

Finally, the kinematic strategies (i.e. joint angles and temporal-spatial parameters like gait velocity, step width and step length) that patients use to decrease the KAM are secondary study parameters.

5.1.3 Other study parameters (if applicable)

Other study parameters are muscle strength, activity limitations, self-reported knee joint stability, performance-based activity limitations (GUG, 10-m walk test), co-morbidity, duration of (gait) complaints and radiographic Kellgren/Lawrence score.
A series of demographic variables will be obtained including age, gender, height, weight.

Other study parameters specific to study B are satisfaction and adherence of the gait modification. The change in cognitive demand of the gait modifications between the initial and final training weeks will also be considered in study B.

5.2 Study procedures

The below text describes the individual measurements that will be undertaken during Study A and Study B. For an overview of what will be measured in Study A and at each interval of Study B, see APPENDIX A2.

Gait Real-time Analysis Interactive Lab (GRAIL)

Experiments and training will be conducted on the GRAIL, Gait Real-time Analysis Interactive Lab (MOTEKForceLink), situated in the VR-laboratory of the VU medical centre, rehabilitation department. This high-tech gait lab consists of a virtual reality system for gait biofeedback.
The GRAIL uses a dual-belt instrumented treadmill, an immersive virtual reality environment, an optoelectronic movement recording system with wireless, light-reflecting markers for accurate (<0.5 mm) and easily analysable 3D motion capture (Vicon), electromyography (EMG, ZeroWire), software for system integration and control (D-Flow [83]), and software for real-time musculoskeletal modelling (Human Body Model HBM [43;84]).
The instrumented treadmill has two full 6D force plates underneath each belt. This configuration enables measurement of ground reactions forces under each foot separately

during walking. This is needed as an input to calculate real-time joint kinetics (net joint moments and joint load), kinematics and muscle forces.

The length of the treadmill is 2.20m to accommodate almost unrestricted walking, and to allow for some positional changes of the subject during walking at self-paced walking speed (i.e. the speed of the belt is automatically adjusted to the subject's comfortable walking speed [85]). The GRAIL offers the possibility to obtain many consecutive strides, which can each be measured accurately. Subjects will wear a safety harness during the trials, to protect them in the event of a fall.

Figure 1. Gait Real-time Analysis Interactive Lab, VUmc

Marker placement

Prior to measurement, 42 markers for the reconstruction of the position and orientation the lower limb bones in space (kinematics) will be placed on the subjects. During the measurements, the Human Body Model [84] will be used to calculate real-time kinematics and kinetics that can be used for the real-time feedback.

In the data-analysis post-measurement, anatomical frames according to Cappozzo will be used to calculate the joint kinematics [86;87]. The kinematic data (joint angles) and kinetic data (GRF and knee joint moments) will be time normalized to 100% of the stance phase. The external knee moments will be expressed with respect to the femur anatomical frame and will be normalized to body weight (BW in N) and height (H in meters)(%BW * H). The early stance peak (ESP), midstance (MS) and late stance peak (LSP) will be determined on the basis of the characteristic shape of the vertical component of the GRF vector.

Segment	Anatomical landmark
Thorax (5)	Navel

	Processus Xyphoideus
	Incisura jugularis
	Processus Spinosus Thoracalis 10
	Processus Spinosus Cervical 7
Pelvis (5)	Right Spina Iliaca Anterior Superior
	Left Spina Iliaca Anterior Superior
	Right Spina Iliaca Posterior Superior
	Left Spina Iliaca Posterior Superior
	Os Sacrum
Thigh (6 on right and left)	Trochanter Major
	Lateral side upper leg (at different heights to distinguish left and right leg)
	Anterior side upper leg (same height as lateral)
	Anterior side upper leg (inferior position)
	Epicondylus Lateralis
	Epicondylus Medialis
Shank (7 on right and left)	Lateral side lower leg (at different heights to distinguish left and right leg)
	Anterior side lower leg (same height as lateral)
	Anterior side lower leg (inferior position)
	Malleolus Lateralis
	Malleolus Medialis
	Caput Fibulae
	Tuberositas Tibia
Foot (5 on right and left)	Calcaneus
	Phalanx distalis 1 (on top)
	Caput Metatarsale 1
	Caput Metatarsale 2
	Caput Metatarsale 5

Protocol real-time feedback

During the experiment, input from the marker data and the GRFs are used in the Human Body Model [84] to calculate in real-time the KAM, the foot progression angle (toe-in/out), medial thrust (from the marker positions on the thigh) and step width.

Prior to measurement, comfortable walking speed will be determined using small increases in the treadmill speed whilst the patient provides feedback on how comfortable they are at that speed. Fixed pace walking is considered to be preferable for the measurements (compared to self-paced mode) due to differences in the kinetic moments caused by changes in speed. .

The following protocol will be used in Study A:

Condition	Description	Time (minutes)	Purpose	Recording time (seconds)
0	Acclimatization to treadmill	3 (max)	To determine the average (mean) speed of walking of the	0

Condition	Description	Time (minutes)	Purpose	Recording time (seconds)
			patient for use in further trials.	
1	Baseline condition- own shoes	2	30 seconds familiarization plus 90 seconds recording time	90
2	Baseline condition- standard shoes	2	30 seconds familiarization plus 90 seconds recording time	90
3i	Implicit learning phase- standard shoes with real time visual feedback on KAM	2	30 seconds familiarization plus 90 seconds recording	90
3ii	Implicit learning phase- standard shoes with real time audio feedback on KAM	2	30 seconds familiarization plus 90 seconds recording	90
4	Training phase with explicit instructions	3 x 2 mins	Feedback on up to 3 kinematic parameters separately 30 seconds familiarisation plus 90 seconds recording	270
5	Measurement- new pattern with feedback	2	Measurement of pattern with direct KAM feedback (30 seconds familiarization and 90 seconds recording)	90
6	Measurement- new pattern	2	Measurement of pattern without any feedback (30 seconds familiarization and 90 seconds recording)	90
		Total walking time: **19.0 minutes maximum** (N.B. Regular breaks can be taken as necessary to prevent fatigue).		**Total recording time: 720 seconds =**12.0 minutes in 8 individual recordings.

In stage 3 of the assessment, the subject will be instructed to decrease the KAM. The subjects will therefore apply an individual kinematic strategy to reach this goal [8;43]. Feedback will provide the subject with knowledge of result but not knowledge of performance

so it will up to the individual to devise their own strategy. At this stage no further instructions will be given about kinematic strategies or compensations. This will allow measurement of the implicit motor learning using an external focus of attention [58].

In step 4, explicit verbal instructions will be given on the gait pattern in addition to the real-time visual KAM feedback to further develop a pattern that can be sustained in daily life (e.g. toe-in/out <15deg). Hunt and Takacs (2014) mentioned that a toe-out position of ±>15 (difference from baseline) is difficult to obtain [3]. Reference values of step width and medial thrust/ frontal plane position of the knee, will be obtained from the baseline trial and the initial trials with feedback on the KAM. This will enable threshold limits to be set such that the step width (for example) is not increased to an excessive degree. The values of all of the kinematic and kinetics will be available for the researcher in real time. In this way, the instructions to the patient can be adapted to suit the individual patient, based on objective information. In step 6, the optimal gait pattern will maintained by the subject without any feedback.

The following protocol will be used in Study B for each of the two sub-groups.:

Condition	**Description**	**Time**	**Purpose**	**Recording time (seconds)**
0	Acclimatization to treadmill	Up to 4 minutes	To determine the average (mean) speed of walking for use in training period	0
1	Baseline condition- own shoes	60 seconds minutes	15 seconds familiarization plus 45 seconds recording time	45
2	Training phase	Up to 21 minutes depending on the week	This will be based on the results of study A. Explicit guidance will be given as required. Frequency of the feedback will be adjusted if necessary to avoid dependence on it and encourage motor learning.	0
3	Measurement without feedback while new pattern is applied	60 seconds	15 seconds familiarization plus 45 seconds recording time	45
4i*	Measurement without feedback, -with dual tasking (Stroop test/ memory test)	75 seconds	30 seconds familiarization plus 45 seconds recording	45
	•			

5	Advice for home training	~8 minutes	Clinician/ physio to offer advice for home training	0

Steps 0,1,2,3 and 5 repeated at weekly intervals.

* Steps 4i, 4ii and 5 will only be applied during week 4 to 6, thus the time taken for training sessions 1 to 3 will be shorter.

Note, the patient can take a break at any time during the training/ assessment The total walking time will depend on the week number; see also Figure 2, which presents the faded feedback approach that will be used. The total duration of the training sessions will be increased during the course of the intervention, with a decrease in the feedback time. This approach (termed faded feedback) has been shown to improve motor learning {Winstein, 1990 265 /id} and has been implemented successfully in several studies related to biofeedback for gait retraining including Barrios et al. (2010), Hunt and Takacs (2014) and Shull et al. (2013).

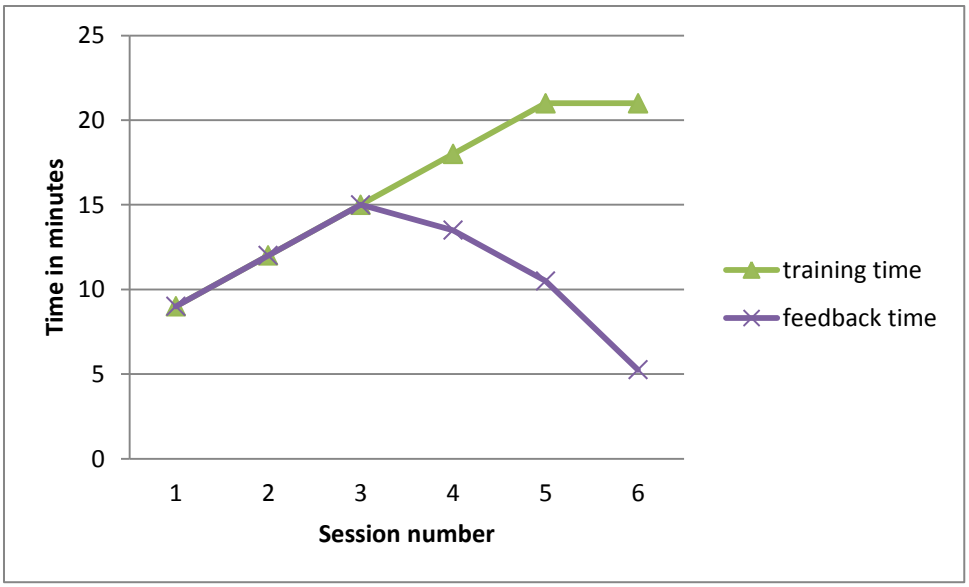

Figure 2: Progression of training and feedback time during the study

In step five, the researcher will provide the patient with home training advice based on the gait retraining methods used in the preceding stages. This may include advice on how to stand up from a chair or how to ascend/ descend stairs. It is important the home training advice complements the advice provided during the gait re-training session.

In addition to the weekly sessions described above, further measurements will be obtained 3 and 6 months after the last training session. This final measurement will consist of both a baseline measurement and replication of the learned pattern, with and without the cognitive dual tasking.

Real-time visual feedback will be provided on the semi-cylindrical screen of the GRAIL. Various types of feedback are available: e.g. bar plot, polar plot, colour change, graph [43] or a number of the actual peak value. Figure 3 shows some examples of feedback that have been used previously in gait modification protocols on the GRAIL. However, other types of visual feedback, such as footsteps indicating desired foot progression angle and/ or step width have been proposed for this study, and have been given a favourable opinion by clinicians. Audio feedback will also be evaluated in Study A.

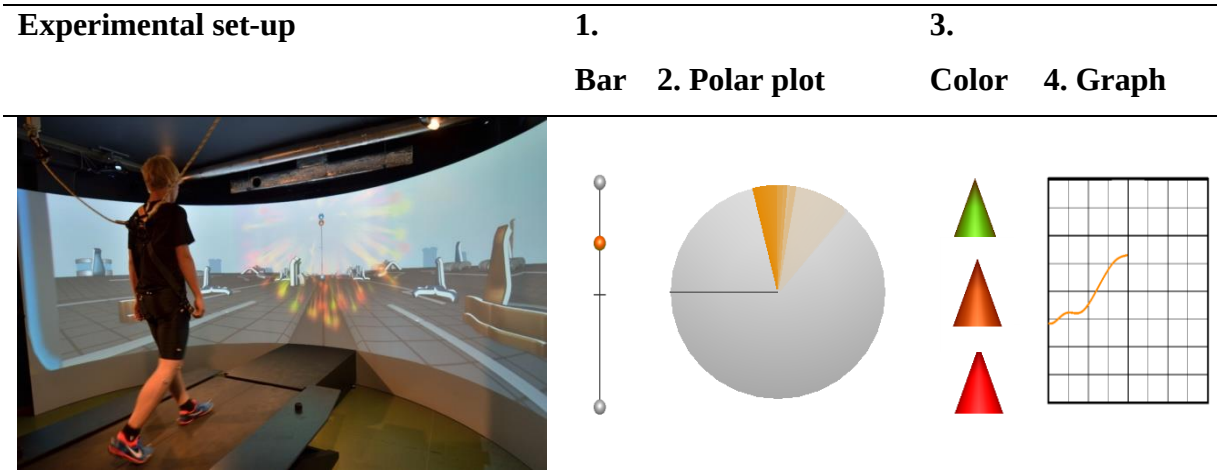

Figure 3: Examples of different types of real-time visual feedback that can be used on the GRAIL [43].

Knee pain

Knee pain (study A and B) over the past week will be assessed by an 11 point numeric rating scale (NRS; 0 -10), with higher scores representing more pain. Patients will be asked: “What was your pain rating on average over the past week?”

Knee pain will also be assessed during walking at the different gait modification conditions by an NRS scale. Prior to walking, patients will be asked “What is your pain rating at the moment?”. Patients will also be asked about pain during walking: “What was your pain rating on average during walking?” to determine if there is immediate pain relief. To account for the effect of analgesics, patients will be asked if they have taken any pain-killers in the two hours prior to the gait training session.

Muscle activity (EMG)

EMG data will be collected from the following muscles (study A and B, weeks 1, 6 and 3 and 6 months follow up): medial and lateral vastus muscle, medial and lateral hamstrings, medial

and lateral gastrocnemius and rectus femoris. EMG electrodes will be placed conform the EMG guideline protocol (Seniam) in use at our movement labs.

Satisfaction

Satisfaction with the learned gait pattern in study A ("how satisfied are you with the modified gait pattern?" and "how likely are you to continue using this technique after leaving here?") and study B ("how satisfied have you been during the last week with your modified gait pattern since leaving the VUmc where you were assessed?") will be measured. Responses will be required on a 6-point Likert scale, ranging from "completely dissatisfied" to "completely satisfied".

Adherence

Adherence of applying the modified gait pattern during the last week in the training period (study B) will be evaluated through use of a questionnaire, aiming to score the duration, as well as the duration as percentage of total walking time. Patients will be provided with a weekly diary to mark down the duration of time spent using the new walking pattern and their total walking time on a daily basis. It is hoped that in this way, the tendency to over-estimate the duration when asked by a clinician will be avoided. The diary will also include spaces for any side effects, like fatigue, back or knee pain etc. to be reported.

Muscle strength

Muscle strength will be assessed in study A and at the beginning and end of the training period and at 3 and 6 months follow up in study B, specifically for the knee flexors and extensors using an isokinetic dynamometer (Humac Norm, CSMi, Boston, USA). Quadriceps and hamstrings strength are measured isokinetically at 60^0/second. All patients will be assessed according to a previously described device and protocol [88]. The mean in Nm per kg body weight (Nm/kg) for quadriceps and hamstrings strength of the right and left maximum voluntary contraction obtained from three measurements will be used for analysis.

Self-reported stability

Knee instability will be measured in study A by questioning the perception of knee stability [89] and by questioning the perception of knee confidence during walking [90]. Self-reported knee instability has been defined as the sensation of an episode of buckling, shifting or giving way of the knee in the previous three months [89]. Persons reporting knee instability will be additionally asked for the number of episodes of instability, whether these episodes concerned the left, right or both knees, if any episodes had resulted in a fall, and the

particular activity that induced an episode of instability [26]. Also the amount of falls related to the perception of knee instability will be assessed.

Activity limitations

A self-report questionnaire will be used to assess limitations in daily activities (study A and at the beginning and end of the training phase in study B and at the 3 and 6 months follow us): the Western Ontario and MacMasters Universities Osteoarthritis Index (WOMAC) [91;92]. The Dutch version of the WOMAC will be used [93].The WOMAC is a disease specific measure of pain, stiffness, and physical function for individuals with OA of the knee. The WOMAC, with a possible range of 0-96, includes 5 items related to pain, 2 items related to stiffness, and 17 items related to physical function (PF). Each item is scored on a 5-point Likert scale. Reliability and validity of the WOMAC have been established [93]. Higher scores on the WOMAC represent greater reduction in functional ability. The ICC for Dutch WOMAC physical-functioning is 0.92 [93].

Performance-based activity limitations

Performance based activity limitations will be assessed in study A and at the 3 and 6 months follow up in study B with both two standardized physical performance tests (GUG, and 10-meter walk test, respectively). As a performance-based measure of function a get up and go (GUG) test [94;95], and a 10m-walk test [96], all timed with a stopwatch, will be used. The GUG test is conducted over a distance of 15 m, comparable to Hurley et al. [94]. The intra class correlation coefficient (ICC) for the intra-tester reliability of the GUG test is 0.98 and the ICC for the inter-tester reliability is 0.98 [95]. The 10m-walk test is a test assessing the time to walk a distance of 10 m along a level and unobstructed corridor. Patients will be instructed to walk as fast as possible and timed with a stopwatch.

Radiography

Radiographs of the knee are scored in a blinded fashion by an experienced radiologist using the grading scales proposed by Kellgren & Lawrence (KL) [73-75]. Weight-bearing, anteroposterior radiographs of the knee joints are obtained following the Buckland-Wright protocol [97].

Patients recruited directly through the VUmc and not through the AMS-OA cohort will be requested to have a radiograph of their knee(s) at the VUmc to confirm or refute the presence of osteoarthritis primarily in the medial compartment.

Demographics

A series of demographic variables will be obtained including age, gender, height, weight, and duration of (gait) complaints.

5.3 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 investigator can decide to withdraw a subject from the study for urgent medical reasons.

5.4 Replacement of individual subjects after withdrawal

Individual subjects will be replaced after withdrawal.

6. SAFETY REPORTING

6.1 Section 10 WMO event

In accordance to 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.

6.2 AEs, SAEs and SUSARs

6.2.1 Adverse events (AEs)

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 intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

6.2.2 Serious adverse events (SAEs)

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;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

The sponsor will report the SAEs 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 events.

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 event. This is for a preliminary report with another 8 days for completion of the report.

6.3 Follow-up of adverse events

All AEs 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.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

7. STATISTICAL ANALYSIS

7.1 Primary study parameter(s)

To assess the effect of feedback on external knee adduction moment (KAM) a linear mixed model and repeated measure analysis of variance will be used. Four outcomes parameters will be extracted from the gait cycle, i.e. the KAM peaks at early and late stance with the corresponding KFM values, the KAM during mid-stance, and the impulse (area under curve in %BW*H*sec) [13;43]. In Study A comparison will be made between baseline and gait modification conditions; in Study B the change over time will be calculated for both baseline and replication of learned pattern. The associations between the changes in KAM, KFM, kinematic pattern and pain will be determined.

To identify the factors which predict whether an individual is likely to achieve a good result using the bio-feedback training method, a linear mixed model will again be used.
Statistical significance will be accepted at p-values of less than 0.05. All analyses will be performed using SPSS software, version 21.0 (SPSS, Chicago, IL).

Changes in pain and function over time in study B, as reported using the WOMAC questionnaire and NRS pain scale will also be assessed using a linear mixed model. Patient reported pain and function will be compared during a no-treatment period (immediately following assessment for Study A) and also over time during the intervention period.

7.2 Secondary study parameter(s)

The secondary outcome measures, external knee flexion moment (KFM), kinematic strategies (i.e. angles of foot, ankle, knee, hip, pelvis and trunk and temporal-spatial parameters) that patients use to decrease the KAM and pain (NRS scale) will also be assessed using a linear mixed model and repeated measure analysis of variance. Linear mixed model will also be used to determine the change of muscle co-contraction, measured with electromyography (EMG) between the different conditions, the adherence, and satisfaction with the program.

7.3 Other study parameters

Changes in postural balance and gait during dual tasking will be also be assessed using a linear mixed model. Changes in physical activity levels between the initial time point and end point of the study, and between the control and intervention group, will be assessed using analysis of variance. As for the primary study parameters, all analyses will be performed using SPSS.

Descriptive statistics will be performed for demographic variables (age, gender, height, weight and duration of (gait) complaints), muscle strength, activity limitations, instability and radiographic Kellgren/Lawrence score.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (Fortaleza, Brazilian amendment, October 20013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

8.2 Recruitment and consent

An information letter will be sent to the participants of AMS-OA cohort by the study investigator with the request to participate the study. Participants will be given two weeks to respond to the letter if they are interested in participating using the reply form to state their intentions. If no response is received after this time, a follow up letter will be sent to offer patients the opportunity to take part in the study. An investigator from the research team will inform subjects about the study and seek consent from the subject. Informed consent will be obtained from each subject, after the information letter has been provided. The study investigator will make sure that the volunteers are given complete, adequate, written and oral information regarding the nature, aims, possible risks and benefits of the study. It will be explained to the volunteers that they are free to interrupt their participation in the study at any moment without any consequence. The volunteers must keep a copy of the information sheet and informed consent form.

8.3 Benefits and risks assessment, group relatedness

The application of gait modifications and walking on a treadmill has no known side effects. Subjects will wear a safety harness while walking on the treadmill. Periods of rest will be allowed during the measurements to prevent fatigue. (see also risk analysis, appendix B2).

Although there may not be a direct benefit to the subjects in Study A, specifically those who do not go on to Study B, it is anticipated that these patients may benefit through obtaining more knowledge on their own gait pattern. For subjects in Study B, it is anticipated that they will benefit through modification to their gait pattern, resulting in a reduction of pain.

8.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the Clinical Research in Humans (Staatsblad 2003, 266), subsection 9 of the WMO (Onderlinge

Waarborgmaatschappij Centramed B.A., Postbus 191, 2270 AD, Voorburg, The Netherlands; policy number 624529201; Appendix G1).

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, 266). This insurance provides cover for damage to research subjects through injury or death caused by the study.
1. € 650.000,-- (i.e. six hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 5.000.000,-- (i.e. five million Euro) for death or injury for all subjects who participate in the Research;
3. € 7.500.000,-- (i.e. seven million five hundred thousand 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. Participants in the study will be informed in writing about the insurance.

8.5 Incentives (if applicable)

There are no special incentives, compensation or treatment for the participants. Participants will receive reimbursement for their travel expenses..

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

The data of each subject will be stored in a case record form (CRF, patient data file) and in a computer file for analysis. Subjects will be anonymous as each participant will be identified in the database by a specific study number. The code is filed separately and will be available to the participating investigators for the duration of the study only. The CRF is available to the investigators and the subject involved and will not be disclosed to a third party. The subjects will be informed in writing about these data storing and handling procedures, with a clear statement that discretion will be guaranteed. The administration of the study will be performed by the study investigators.

9.2 Monitoring and Quality Assurance

An independent monitor (quality officer) will monitor the study data according to Good Clinical Practice (GCP). A selection of the test subjects Informed Consents forms will be checked. Additionally, during the onsite monitoring Source Data verification will be performed to ensure that data in the Case Report Forms (research forms / questionnaires) match the source data (patient records, lab results, etc.). The intensity of this verification is related to the risk of the study. data will be monitored in any event, the inclusion and exclusion criteria and the primary outcomes of the study. The monitor will also look at whether all (S) AEs and SUSARs are adequately reported within the timelines as required by law - and regulations.

Data storage and methodological procedures will be monitored annually by the Clinical Research Bureau. All files will be made available for audits as required by the Clinical Research Bureau.

9.3 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.

9.4 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.

9.5 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 within 15 days, 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.

9.6 Public disclosure and publication policy

There are no conflicts of interest. There are no specific arrangements made between the sponsor and the investigator concerning the public disclosure. All members of the project team will be involved as co-authors in publications.

10. PLANNING

The total project will take 3 years (36 months) from September 2015 to February 2018.

Month 1-3:	Start of project, training assessments
Month 4-20:	Patient inclusion period
Month 21-25:	Data analysis
Month 26-35:	Report on effectiveness
Month 36:	End of project

11. PROJECT TEAM

Executive members

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Clinical members

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International members

Prof. D, Rosenbaum, University of Münster, Institute of Musculoskeletal Medicine, Germany.

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KNEEMO is led from Glasgow Caledonian University, and includes VU University Medical Centre Amsterdam, University of Münster, Aalborg University, University of Southern Denmark, Paracelsus University Salzburg, XSens and Peacocks as full partners.

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13. APPENDIX A1

The below decision tree is proposed to help the researcher and clinician determine the appropriate feedback instructions for the individual patient based on a) their baseline measures b) their measures during the implicit learning phase (where no instruction will be provided) and c) a priori knowledge (see Table 1). In this way we hope that the subjectivity is removed. Clear instruction will be provided to the patient to ensure that they are aware of how their movements are represented in the on-screen feedback.

If the patient reports pain or discomfort during any of the modifications, then the specific modification thought to be associated with the increased pain level, will be contraindicated for the specific patient. Indications of pain will be recorded on the case record form.

Abbreviations used in the table are explained below.
FPA – foot progression angle, for the purposes of the below table a foot progression angle of greater than 0 (FPA>0) refers to an internally rotated FPA and a foot progression angle of less than 0 (FPA<0) refers to an externally rotated FPA.
KAM- knee adduction moment
KF- knee flexion (referring specifically to the stance phase knee flexion; i.e. during weight bearing.)
SW- step width
TS- trunk sway (note this is included as a variable to monitor, but it will not be used as a variable that is fed back to the patients in order to reduce KAM).
MKT – medial knee thrust. Since we cannot measure knee adduction angle in real time, feedback of this should be the position of the lateral knee marker with respect to the centre of mass in the frontal plane.
Subscript baseline and implicit refer to the data collected in the baseline phase or implicit learning phase.
Subscript patient refers to the average step width in both the baseline and implicit learning phase.
Subscript references refers to normal step width (note this is from healthy individuals walking on the treadmill, but may not be aged matched to the population in this study).

Gait modification	**IF**	**AND**	**AND**	**THEN**	**INSTRUCTION TO PATIENT (internal focus of attention)**	**INSTRUCTION TO PATIENT (external focus of attention)**	**FEEDBACK EXAMPLE (S)**
Foot Progression Angle	$FPA_{baseline} < FPA_{implicit}$	$KAM_{implicit} < KAM_{baseline}$	$FPA_{baseline} - FPA_{implicit} \lesssim \pm 15$	Modification of FPA considered appropriate for this patient.	Rotate your foot more towards the centre of the treadmill.	Keep the marker on your big toe pointing further towards the centre of the treadmill	1) Target FPA shown by footprints projected onto treadmill and screen with sound effect/ visual reward when target angle is matched- Knowledge of results 2) Foot progression angle, depicted by a graph with target area shaded- Knowledge of performance
	$FPA_{baseline} > FPA_{implicit}$	$KAM_{implicit} < KAM_{baseline}$	$FPA_{baseline} - FPA_{implicit} \lesssim \pm 15$		Rotate your foot more towards the centre of the treadmill.	Keep the marker on your big toe pointing further towards the centre of the treadmill	
Step width	$SW_{baseline} < SW_{implicit}$	$KAM_{implicit} < KAM_{baseline}$		Modification of step width considered appropriate for this patient	Increase your step width	Increase the distance between the centre of the treadmill and the marker on your big toe	1) Target step width shown by footprints projected onto treadmill and screen with sound effect/ visual reward when target angle is matched- Knowledge of results 2) Step width depicted by a graph with target area shaded – knowledge of performance
	$SW_{baseline} \approx SW_{implicit}$	$SW_{patient} < SW_{reference}$	$KAM_{reference} < KAM_{patient}$				
Medial knee thrust	$MKT_{baseline} < MKT_{implicit}$	$KF_{baseline} \leq KF_{implicit} \geq 0$	Patient not reporting discomfort in	Modification of the medial knee thrust considered	When you take the weight onto your ‘left/ right’ leg, try to	When you take the weight onto your ‘left/ right’ leg, try to bend	1) Graph showing movement of marker on knee in frontal plane during stance phase

Gait modification	**IF**	**AND**	**AND**	**THEN**	**INSTRUCTION TO PATIENT (internal focus of attention)**	**INSTRUCTION TO PATIENT (external focus of attention)**	**FEEDBACK EXAMPLE (S)**
			the knee	appropriate for this patient	bend your knee and move your knee towards the centre of your body.	your knee and move the marker on your knee towards the centre of your body	with target region – knowledge of performance 2) Target value for medial knee thrust based on $MTK_{implicit}$ shown, with reward when target is reached- knowledge of results
Trunk lean/ sway	$TS_{implicit} \gg TS_{baseline}$			Trunk sway being used excessively to control KAM	Reduce trunk sway		No feedback given

14. APPENDIX A2: Patient measurements at each stage of the patient journey

		Study A		Study B			
		M1		M1	M2	M3	M4
	Consent	✓					
	Basic demographics	✓					
Questionnaires	WOMAC	✓		✓	✓	✓	✓
	NRS pain over last week	✓		✓	✓	✓	✓
	Knee instability	✓				✓	✓
	Knee confidence	✓				✓	✓
	NRS pain during walking on treadmill	✓		✓	✓	✓	✓
	Feedback on feedback	✓					
	Satisfaction with the program						
	Compliance with the modified gait pattern				✓	✓	✓
Activity/ performance tests	Timed GUG	✓		✓		✓	✓
	10m walk test (fast)	✓		✓		✓	✓
	10m walk test (comfortable)	✓		✓		✓	✓
	Muscle strength	✓		✓		✓	✓
Gait and balance	Baseline own shoes	✓		✓	✓	✓	✓
	Implicit learning	✓					
	Explicit learning 1	✓					
	Explicit learning 2	✓					
	Explicit learning 3	✓					
	Training			✓	✓		
	Retention	✓		✓	✓		
	Dual tasking- cognitive			✓	✓	✓	✓
	Dual tasking- physical			✓	✓	✓	✓

	Study B					
	T1/	T2	T3	T4	T5	T6/

	M1					M2
NRS pain during last week	✓	✓	✓	✓	✓	✓
NRS pain during walking on treadmill	✓	✓	✓	✓	✓	✓
Activity levels over last week- step counter	✓	✓	✓	✓	✓	✓
Difficulty and "normalness" of learned walking pattern	✓	✓	✓	✓	✓	✓
Compliance with modifications over the last week	✓	✓	✓	✓	✓	✓