Efficacy of MRI in primary care for patients with knee complaints due to trauma: protocol of a randomised controlled non-inferiority trial (TACKLE Trial)

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ABSTRACT

Background: Patients with traumatic knee complaints regularly consult their General practitioners (GP's). Magnetic resonance imaging (MRI) might be a valuable diagnostic tool for GP's in making appropriate treatment decisions and reducing costs. The objective of this study is to assess the cost-effectiveness of referral to MRI by the GP compared to usual care in patients with persistent traumatic knee complaints.

Methods: The design of the study is a multi-centre, open labelled randomised controlled non-inferiority trial in combination with a concurrent observational cohort study. Patients (aged 18-45 years) with knee complaints due to a trauma or sudden onset occurred in the preceding 6 months consulting their GP are eligible and randomised into two groups; 1) MRI group; referral for MRI of the knee by the GP, or 2) usual care group (no MRI). Primary outcomes are knee related daily function, direct and indirect medical costs and quality of life. Secondary outcomes are disability due to knee complaints, severity of knee pain, patients' perceived recovery and satisfaction. Outcomes will be measured at baseline and at 1.5, 3, 6, 9, and 12 months follow-up. Furthermore we will collect demographic data, GPs' initial working diagnosis and GP's preferred management at baseline, and MRI findings.

Discussion: The additional diagnostic value and cost-effectiveness of direct access to knee MRI for patients presenting with traumatic knee complaints in general practice is unknown. The last years, GP's in the Netherlands increasingly refer patients to MRI, however the Dutch clinical guideline 'traumatic knee complaints' for GP's does not recommend referral to MRI mainly because the cost-effectiveness is not known.

INTRODUCTION

General practitioners (GP's) are often consulted by patients with traumatic knee complaints. For musculoskeletal disorders, knee complaints are the second most frequent reason (after low back pain), for consulting the GP.[1] Traumatic knee complaints are knee complaints due to a trauma of the knee or are at least of a sudden onset, and therefore likely to be traumatic. Traumatic knee complaints could be caused by bone bruise, fracture, and/or soft tissue injuries such as lesions of menisci, cruciate ligaments, collateral ligaments and muscles.[2-4] The incidence and prevalence of knee complaints in the Netherlands in general practice are estimated at 20 and 30 per 1000 persons per year respectively.[1] The incidence and prevalence of traumatic knee complaints in the Netherlands in general practice are estimated at 5.3 and 6.8 per 1000 persons per year respectively.[1]

For GP's diagnosing other knee injuries than fracture or locked knee is very difficult.[5-8] Magnetic resonance imaging (MRI) of the knee might be helpful in establishing the right diagnosis or help with excluding other diagnosis. This knowledge is used for deciding on subsequent treatment and referral for patients with traumatic knee complaints. MRI is a powerful diagnostic tool for detecting lesions of ligaments, tendons, bone, cartilage and menisci.[4,9,10] MRI showed a sensitivity of 86%, 91%, 76%, a specificity of 95%, 81%, 93% and an accuracy of 93%, 86%, 89% for anterior cruciate ligament, medial and lateral meniscus lesions respectively.[9]

Recommendations for diagnosis and management of patients with traumatic knee complaints presenting in primary care in the Netherlands are described in the clinical guideline 'traumatic knee complaints' issued by the Dutch College of General Practitioners in 2010.[2] At GPs' initial consult an urgent referral to a medical specialist is needed when there are signs of a fracture, an acute locked knee or severe complaints after patella dislocation.[2] If not, patients are managed conservatively which comprises information and advice about the knee complaints, medication for pain reduction and if indicated referral to physical therapy. When the complaints have not decreased at follow-up the GP can refer to an orthopaedic surgeon who will either request an MRI or perform an arthroscopy or surgery.[11] The study of Wagemakers et al. reported that at one year follow-up 57% of the patients with traumatic knee complaints in the Netherlands consulted their GP more than once, about one third was referred to physical therapy and 21% were referred to an orthopaedic surgeon.[12]

Direct referral to MRI might be a valuable tool for GP's in making appropriate and informed decisions.[13] Negative MRI findings may enable GP's to reassure patients, treat them conservatively and avoid unnecessary orthopaedic referrals. Positive MRI findings could confirm the GPs' diagnoses and the decision either to advice conservative treatment or to refer to an orthopaedic surgeon in a more early stage.[14]

The DAMASK trial showed that an MRI referral by the GP prior to a provisional orthopaedic appointment yielded statistically significant benefits in patients' knee related quality of life when compared with direct referral to an orthopaedic surgeon.[15] The study of Patel et al. showed that

an early MRI of the knee in patients in secondary care with suspected internal derangement facilitates faster diagnosis at a cost comparable level when compared to physical therapy.[16] At three months follow-up patients who were randomised for an early MRI reported significantly less pain, less activity limitations and better patient satisfaction.

Aim

Whether MRI of the knee should enter the diagnostic pathway in primary care, through direct access by GP's, depends on whether it improves patient outcomes, reduces costs and affects subsequent diagnosis and management. The objectives of this study over a period of 12 months follow-up are:

1. To assess the cost-effectiveness of MRI referral by the general practitioner compared to usual care in patients with persistent traumatic knee complaints
2. To assess if MRI referral by the general practitioner is noninferior compared to usual care in patients with persistent traumatic knee complaints regarding self-reported knee related daily function.

METHODS

This study has received ethical approval from the Medical Ethics Review Committee of the Erasmus Medical Centre and is registered by the Dutch Trial Registration: NTR3689.[17]

Design

The design of the study is a multi-centre, parallel group, open labelled, randomised non-inferiority trial. See figure 1 for the flow chart of the study. The follow-up will last 12 months. For assessing generalizability of the findings, patients who are eligible but decline randomisation are invited to participate in the concurrent observational cohort study, with identical inclusion criteria and measurements as for the randomised patients. By including these patients in an observational cohort we will be able to get insight in potential selection of patients entering the randomised cohort. Furthermore, we will be able to assess the course (e.g. medical consumption and outcomes) in daily practice of these non-randomised patients presenting with knee complaints after a trauma within the participating general practices, including the frequency of MRI referral and referral to orthopaedic surgeons.

Study population

GP's in the South West of the Netherlands will recruit eligible patients. The GP informs the patient and sends contact data to the researchers. The researcher will contact the patient by phone and check the criteria for eligibility.

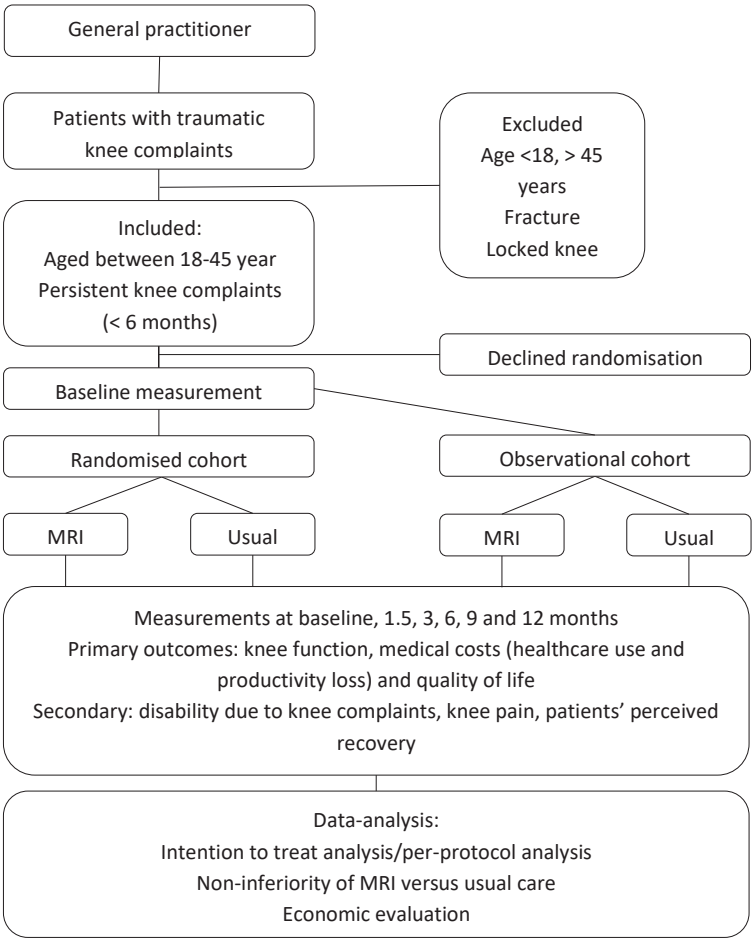

Figure 1 Flowchart of the study

Patients will be eligible for inclusion if they (re)consulted their GP with knee complaints (knee pain and/or disability) due to trauma or sudden onset in the preceding six months and are aged 18 to 45 years. Patients will be excluded if there is an indication for direct referral to an orthopaedic surgeon (fracture or locked knee). Patients will also be excluded if the knee complaints are already managed in secondary care, if the patient is known with osteoarthritis in the affected knee (diagnosis confirmed by a medical specialist), if there is other non-traumatic arthropathy (for example infection, Reiter's syndrome, gout, inflammatory bowel disease or neuropathic pain) or isolated patellofemoral joint pain, if there is a previous MRI of the knee within the same episode of knee complaints, if there is a previous surgical intervention of the affected knee or if there are contra-indications for MRI (i.e. claustrophobia, metal implants or pregnancy).

Randomisation and interventions

When patients are eligible for inclusion and completed the informed consent procedure, the baseline measurement takes place. Hereafter, the patients will be randomly allocated to the MRI or the usual care group. An independent person produces a randomisation list by computer using random blocks of 4 and 6. Allocation by one of the researchers (KvO or NS) will be concealed and cannot be influenced or predicted because the randomisation list will not be accessible for the members of the research team.

The MRI group:

Patients will be referred for an MRI scan of the affected knee at one of the participating MRI centres (in Rotterdam, Amsterdam, Alkmaar, Goes, or Leiden) within two weeks after referral. The MRI will be performed on a 1.5 T system using the 'acute knee scanning protocol' which is present in all participating centres and is adjusted for the specific magnetic resonance machine. These protocols all include imaging in 3 planes: coronal, sagittal and transversal and all include a T1 and a PD-weighted sequential, with or without fat-suppression. All participating musculoskeletal radiologists (n= 12) are used working with these predefined protocols.

In the Netherlands, there is no standardized way for a radiologist to score and report MRI findings for patients with traumatic knee problems. For this reason, a standardized and digitalized report was developed for the TACKLE Trial. The report was composed as an online questionnaire, using an open source survey application called Limesurvey.[18] All radiologists are trained in this standardized scoring of the MRI features.

The following items are scored in the MRI report: the quantity of synovial fluid and soft tissues, menisci, anterior and posterior cruciate ligaments, medial and lateral collateral tendons and the bone and cartilage. The report will produce a treatment/referral advice for the GP, based on the latest consensus in the literature, expert opinion and daily practice.[11,19] An overview of the most significant findings and the treatment/referral advice for the GP is listed in table 1.

The radiologist will report the details on possible pathology to the GP, together with a treatment/referral advice, based on table 1. In case of positive MRI findings the advice of the radiologist will be to refer to an orthopaedic surgeon. The orthopaedic surgeon will decide whether arthroscopy or surgery is required, based on clinical findings and the Dutch orthopaedic guidelines.[11,19] In case of negative MRI findings the advice of the radiologist will be to continue treatment in primary care according to the Dutch clinical guideline 'traumatic knee complaints' (see usual care group). In case of equivocal findings the radiologist will decide, based on the severity of the injury, if the advice will be to continue treatment in primary care or to refer to an orthopaedic surgeon. Finally, the GP will decide whether to refer the patient or not, based on the radiologists' report and the patients' current complaints.

The inter-rater reliability of the radiologists' advice was determined for eight participating radiologists using ten MRI's of patients with traumatic knee complaints. The intra-class correlation coefficient was 0.65, reflecting reasonable agreement.

Table 1 Types of findings on MRI and related advice

Positive findings (advice for referral to orthopaedic surgeon)	Equivocal findings (advice based on radiologist's judgement)	Negative findings (advice for treatment in primary care)
Pigmented villonodular synovitis	Synovitis, bursitis, hoffitis, any other cyst	Effusion, Baker's cyst, ganglion, plica, subcutaneous oedema
	Lesions of the m. quadriceps tendon, the patellar tendon or the patellar retinacula	
Osteochondrosis dissecans fracture	Lesions of the trochlea or patellar alignment	Bone bruise or bone marrow oedema
Meniscal tears*		Parameniscal cyst, meniscal extrusion, discoid meniscus, isolated lesions of meniscal ligaments or meniscal capsular lesions
Partial or complete anterior or posterior cruciate ligament tears		Mucoid degeneration of the cruciate ligaments
Grade III injury (complete rupture) of the medial collateral ligament or the posterolateral corner		Grade I and II injury of the medial collateral ligament or the posterolateral corner
Grade IV chondromalacia		Grade I to III chondromalacia

*A meniscal tear is defined as an abnormal shape of the meniscus OR as a high signal intensity unequivocally contacting the surface of the meniscus. The latter must be seen on at least 2 adjacent slices in one plane.

The usual care group:

These patients will be treated according to the Dutch clinical guideline 'traumatic knee complaints', which is without MRI.[2] When there are signs of contusion, distortion, medial or lateral collateral ligament lesion, patients will be advised to continue their daily activities and load the knee as much as possible. When there are indications of meniscal lesions and/or cruciate ligament lesions, patients will be advised to take rest for a few days and to use elbow-crutches if necessary. When pain and effusion decreases patients are advised to flex and extend the knee without load bearing, to do isometric muscle training of the quadriceps muscle, and gradually increase their daily activities. For additional support regarding exercises the GP can refer to a physical therapist. Follow-up consultations are planned with an interval of at most two weeks.

Outcomes

Patients will fill in questionnaires at baseline and at 1.5, 3, 6, 9 and 12 months follow-up (see table 2). The questionnaires will be sent by e-mail. This e-mail contains a secured hyperlink to the questionnaire. For this purpose the survey application Limesurvey will be used.[18]

The primary outcomes are:

Patients' knee related daily function measured with the Lysholm Scale.[20] The Lysholm Scale is well documented according to validity, reliability and responsiveness in patients with traumatic knee

Table 2 Measurement of primary and secondary outcomes

	Baseline	1.5 months	3 months	6 months	9 months	12 months
Primary						
Lysholm	X	X	X	X	X	X
iMCQ/iPCQ	X	-	X	X	X	X
EQ-5D-3 L	X	X	X	X	X	X
Secondary						
KOOS	X	X	X	X	X	X
NRS	X	X	X	X	X	X
GPE	X	X	X	X	X	X
Satisfaction	X	X	X	X	X	X

injuries.[21,22] The Lysholm Scale summarizes activity limitations and symptoms related to activity. The score consists of 8 different items on a 100-point scale with 25 points each attributed to instability and pain.[20] A higher score means better knee function.

Health care use measured with the Medical Consumption Questionnaire from the institute for Medical Technology Assessment (iMCQ), adjusted to fit our population.[23] The iMCQ includes questions related to frequently occurring contacts with health care providers. Health care costs will be calculated by multiplying health care use with Dutch standard prices.[24]

Productivity loss measured with the Productivity Cost Questionnaire from the institute for Medical Technology Assessment (iPCQ).[24] The iPCQ consist of 12 items in three modules: lost productivity at paid work due to absenteeism, lost productivity at paid work due to presenteeism and lost productivity at unpaid work. Productivity costs will be calculated by multiplying productivity losses by standard Dutch, age and sex specific, prices per hour.[25]

Patients' quality of life measured with the EuroQol 5-Dimensions (EQ-5D-3L). The EQ-5D-3L consists of 6 items. Item 1 to 5 measure the health state on five dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: level 1, indicating no problems, level 2, indicating some problems, level 3, indicating extreme problems. Item 6 measures the self-rated health on a vertical visual analogue scale where the endpoints are labelled: best imaginable health state (100) and worst imaginable health state (0).[26] Previous research shows evidence of construct validity and reliability for patients with knee injuries.[27]

The secondary outcomes are:

Disability due to knee complaints assessed with the Knee Injury and Osteoarthritis Outcome Score (KOOS).[28] This questionnaire consist of 42 questions for five dimensions; pain, symptoms, function in daily living, function in sport and recreation, and knee-related quality of life. The answer options are standardised and rated on a scale from 0 to 4. The total score will be calculated for each subscale on a scale from 0 to 100, a higher score indicating more symptoms. The KOOS has good validity, reliability, responsiveness, internal consistency and no floor or ceiling effect.[28]

Severity of knee pain assessed with the Numeric Rating Scale (NRS). The NRS is an 11-point Likert scale, where 0 indicates no pain and 10 indicates unbearable pain. The NRS is a valid, reliable and appropriate rating scale for capturing severity of pain in clinical practice.[29]

Patients' perceived recovery assessed with the Global Perceived Effect (GPE). The GPE is a 7-point Likert scale ranging from completely recovered to worse than ever.[30] The reliability of the GPE is excellent.[31]

Patients' satisfaction with the treatment measured on a 7-point Likert scale ranging from absolutely satisfied to absolutely dissatisfied.

At baseline we will collect the following demographical data: age, gender, height, weight, education level, co-morbidity, duration of complaints and previous knee complaints. Furthermore we will collect data on GPs' initial working diagnosis and GP's preferred management at baseline and MRI findings.

Sample size calculation

The sample size is based on the Lysholm Scale. At 12 months follow-up, the effect (Lysholm Scale) of the usual care in general practice in our pilot-study was estimated at a mean difference of -23 with a standard deviation of 17 (95% confidence interval -27.8; -18.2).[12] To obtain 80% statistical power with a 2-sided alpha of 0.05, 225 patients per treatment group are necessary to establish the non-inferiority of MRI referral by the GP compared with usual care within 4.8 points on the Lysholm Scale. Hence, using a 2-sided alpha of 0.05 and 225 patients per group, the trial has a 91% power to detect superiority of MRI referral over usual care assuming a clinical relevant difference of 15% in knee function. Based on previous studies we expect a loss to follow up of 15%, therefore we require 520 patients with traumatic knee complaints in our trial.[12,14]

Statistical analysis

Success of the randomisation and distribution of outcome measures will be checked before actual analyses are done. The baseline characteristics of the non-randomised patients in the cohort will be analysed and compared with the baseline characteristics of the randomised patients to get insight in potential selection bias.

The economic evaluation will be a cost-utility analysis from the societal perspective (costs per a Quality Adjusted Life Year (QALY)), based on patients' reports. A one-year time horizon will be used, without discounting. Costs related to outcome will be statistically analysed using net-benefit acceptability curves, multiple imputation, and bootstrapping, including only the uncertainty due to trial sampling error. Cost price analyses will be performed for MRI and orthopaedic consultations. Other costs will be valued using standard prices (including time and travel costs).[25] QALYs will be estimated as the area under the observed 1-year utility curves. Utilities will be estimated using the EQ-5D-3L (primary analysis, Dutch tariff) and the patients' health Visual Analogue Scale (VAS), transformed to a utility scale using the power transformation $U = 1-(1-VAS/100)^{1.61}$.

We will evaluate whether MRI referral by GP's is non-inferior compared to usual care conform clinical guideline beyond a specified non-inferiority margin (delta) with a defined confidence interval. Non-inferiority of MRI over usual care will be accepted if the upper bound of the 95% CI around the estimated difference in primary outcome (Lysholm Scale) lies below delta. A delta of 4.8 was adopted, based on the expected effect in the usual care group as found in our pilot-study (see sample size calculation), and a judgement about the difference between treatments that would be clinically meaningful.

The outcome of both groups will be analysed on the basis of the 'intention to treat' principle. We will use linear mixed models with repeated measurements to calculate the group differences over time. We will adjust for variables with a clinical meaningful difference between the two groups at baseline. In non-inferiority trials, intention to treat analysis could increase type I error; the risk of falsely claiming non-inferiority.[32] Therefore we will additionally perform a per-protocol analysis.

Additionally, we will perform exploratory analysis to identify clinical indicators for better (cost) effectiveness over a period of 12 months using univariable and multivariate logistic regression analysis. Different usual thresholds (16, 20 and 40 thousand euros per QALY) for the maximum willingness to pay for an extra QALY will be explored.

DISCUSSION

GP's in the Netherlands increasingly refer patients with knee complaints to MRI. At present there is a lack of evidence whether this is cost-effective care. We reported the design of a non-inferior RCT that will investigate the cost-effectiveness of an MRI on referral of the GP compared to usual care in patients with traumatic knee complaints.

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