Summary

In **chapter 1**, we described the general introduction of this thesis. Patients with traumatic knee complaints regularly consult their General practitioner (GP). Magnetic resonance (MR) imaging might be a valuable diagnostic tool for GPs in making appropriate treatment decisions and reducing costs. However, MR imaging is not recommended in the Dutch clinical guideline 'traumatic knee complaints' for GPs, mainly because the diagnostic value and cost-effectiveness of direct access by the GP to knee MR imaging is unknown. Whether MR imaging of the knee should enter the diagnostic pathway in primary care, through direct access by GP, depends on whether it improves patient outcomes, reduces costs and affects subsequent diagnosis and management. Therefore, the primary aims of this thesis were to describe over a period of 1-year follow-up whether MR imaging referral by the GP was non-inferior compared to usual care in patients with persistent traumatic knee complaints regarding self-reported knee related daily function and whether MR imaging by the GP is cost-effective compared to usual care in patients with persistent traumatic knee complaints. To assess the additional value of an MR scan in patients with traumatic knee complaints in general practice we conducted a randomised controlled non-inferiority trial with several clinical outcomes alongside cost-effectiveness analyses from the societal and healthcare perspective (TACKLE trial). We compared a group of patients with traumatic knee complaints receiving the usual care, containing information on the course of knee complaints, and a referral to a physiotherapist or orthopaedic surgeon when indicated (but not based on MR imaging) to a group of patients receiving a GP initiated MR scan on top of the usual care. With that, we were able to assess if adding MR imaging by the GP was at least not worse concerning clinical outcomes and we also were able to assess the differences between the groups in costs. We assumed that introducing the MR scan in an more early stage in the diagnosis of traumatic knee complaint, would led to less referrals to an orthopaedic surgeon.

In **chapter 2**, we identified the proportion of MR scans requested by the GP in patients aged between 18 and 45 years presenting with traumatic knee complaints in general practice in 2011, 2012 and 2013, because it was unclear how often GPs request MR scans in patients with a traumatic knee complaint. We also assessed the medical consumption e.g. referral to physiotherapy or an orthopaedic surgeon.

We designed a cohort study with data originating from the Integrated Primary Care Information database, a longitudinal database of electronic medical records of GPs in The Netherlands. Included were patients aged 18 to 45 years, diagnosed with knee complaints due to a trauma. Excluded were patients with a chronic internal knee trauma in the past or with known osteoarthritis of the knee, patients who visited the emergency department for current knee complaints and patients in whom the knee trauma was more than six months ago. The main outcome was the referral to knee MR imaging by the GP. In total, 303, 300 and 187 patients with traumatic knee complaints were included in 2011, 2012 and 2013 respectively. In 2011 50 (17%) of these patients were referred to an MRI, in 2012 35 (12%) and in 2013 18 (10%). We concluded that from 2011 until 2013, yearly 10 to 17% of the patients with traumatic knee complaints were referred

to an MR scan by their GP. Secondary outcomes showed that of the patients with traumatic knee complaints about one fifth was referred to a physiotherapist and one third to an orthopaedic surgeon.

In **chapter 3**, we describe the research protocol of the TACKLE trial. To assess the cost-effectiveness of referral to MR imaging by the GP compared to usual care in patients with persistent traumatic knee complaints we conducted a multi-centre, open labelled randomised controlled non-inferiority trial. Patients (aged 18-45 years) with knee complaints due to a trauma or sudden onset occurred in the preceding 6 months consulting their GP were eligible and randomised into two groups; 1) MR imaging group; referral for MR imaging of the knee by the GP, or 2) usual care group (no MRI). Patients in the usual care group received care according to the clinical guideline 'Traumatic knee complaints' issued by the Dutch College of GPs, i.e. information on the course of knee complaints, and a referral to a physiotherapist or orthopaedic surgeon when indicated (but not based on MR imaging). The primary outcome measure was knee-related daily function measured with the Lysholm scale (0 to 100; 100=excellent function) over 1 year, direct and indirect medical costs and quality of life. Secondary outcome measures were generic quality of life measured with the EuroQol 5-Dimensions (EQ-5D), the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales for pain, symptoms, function in daily living, function in sport and recreation, and knee-related quality of life, severity of knee pain measured with a numeric pain rating scale (NPRS), and perceived recovery and patient satisfaction on a 7-point Likert scale, as well as the healthcare provided assessed using a medical consumption questionnaire. Outcomes were measured at baseline and at 1.5, 3, 6, 9, and 1-year follow-up. Furthermore, data on demographics, the GPs' initial working diagnosis, the GPs' preferred management at baseline, and MR findings were collected.

In **chapter 4** we determined the frequency of MR findings in patients (18-45 years) with posttraumatic knee complaints seen in general practice and determined the associations with patient and trauma characteristics, duration of complaints and clinical scores at baseline using the results of the MR imaging group of the TACKLE trial only. Prior to the start of this study, two orthopaedic surgeons (JV and RN), employed in two different participating centres of the TACKLE trial, defined 'positive' MR findings that may need further specialized assessment and treatment by an orthopaedic surgeon. These were a trabecular fracture, a complete rupture of a collateral ligament, a meniscus tear, a cruciate ligament rupture and a full thickness cartilage defect. We developed a standardized knee MR report and trained the involved radiologists. We showed that 76 out of 174 patients (39%) had a positive MR finding, predominantly anterior cruciate ligament (ACL) ruptures (22%) and/or traumatic meniscal tears (15%). Patients with a pre-existing musculoskeletal comorbidity had a two-fold lower prevalence of positive MR findings (21%), OR 3.0 (95% confidence interval [CI] 1.3 to 7.0). A 'sports related trauma' showed the highest OR of 4.6 (95% CI 2.2 to 9.3) for a positive MR finding. Clinical scores were statistically, significantly worse in

patients with positive MR findings, with mean differences ranging from 10 to 20%. Furthermore, increasing duration of complaints was correlated with decreasing prevalence rates of positive MR findings. Overall, a popping sound and direct swelling showed the highest positive predictive value of 65% for the presence of positive MR findings.

In **chapter 5** we determined the proportion of patients with a knee trauma that returned to sports at 6-weeks and 3-months follow-up. Also examined were associations between no return to sports and baseline patient and trauma characteristics, knee complaints and MR findings, as well as the additive value of MR findings in predicting no return to sport. Included were patients with traumatic knee complaints included in the TACKLE trial. Patients were classified as 'no return to sports' (not able to participate in sports because of the knee complaints) or return to sports' (sports at the same level as before the knee trauma, or at an adapted level). Potential baseline predictors for no return to sports were assessed using logistic regression analyses in which separate models were built for patient characteristics, trauma characteristics and baseline severity of knee complaints. The final model of patient characteristics, trauma characteristics and baseline severity of knee complaints was used in the subgroup of patients to assess the additive value of the MR scan. The area under the curves (AUC) were compared. Of the 356 patients included in the TACKLE trial, 282 (79%) participated in sports before the knee trauma and were included in the present study. We showed that at 6-weeks and 3-months follow-up, 147 (59%) and 175 (74%) patients, respectively, reported return to sports. Combining patient characteristics, trauma characteristics and knee complaints predicted no return to sports with an AUC of 0.86 (95% CI 0.81 to 0.90) at 6-weeks and of 0.82 (95% CI 0.76 to 0.88) at 3-months follow-up. After adding MR findings, the AUC was 0.79 (95% CI 0.71 to 0.87) at 6-weeks and 0.79 (95% CI 0.70 to 0.88) at 3-months follow-up. We concluded that 1 out of 4 patients reported no return to sport at 3-months follow-up. For patients who experienced a trauma during sport, for those who reported effusion during the previous week at baseline, and for patients who reported more pain in the previous 48 hours at baseline, the odds of reporting no return to sports increased. Adding MR findings to the patient characteristics, trauma characteristics and baseline severity of knee complaints did not improve the prediction of no return to sports.

In **chapter 6**, we described the impact of MR imaging after referral by the GP on knee pain, knee symptoms, function in daily living, sport and recreation, and quality of life. A total of 356 patients were included and randomised to MR imaging (n=179) or usual care (n=177) from November 2012 to December 2015. MR imaging was non-inferior to usual care concerning knee-related daily function during 1-year follow-up, for the intention-to-treat (overall adjusted estimate: 0.33; 95% CI -1.73 to 2.39), and per-protocol (overall adjusted estimate: 0.06; 95% CI -2.08 to 2.19) analysis. Regarding the secondary outcomes, no differences were found between the groups on the EQ-5D scores, the KOOS subscales, and the NPRS. Nevertheless, patients in the MR group more often perceived themselves to be (completely/much) recovered (overall adjusted OR: 1.49; 95% CI 1.10

to 2.02), and more often reported to be (absolutely/very) satisfied (overall adjusted OR: 1.84; 95% CI 1.31 to 2.57) during the 1-year follow-up. There were no differences between both groups in the amount of patients visiting other healthcare providers. We concluded that MR imaging in general practice in patients with traumatic knee complaints was non-inferior to usual care regarding knee-related daily function during 1-year follow-up. After adding MR imaging, although more patients perceived to be recovered and more were satisfied, the amount of referrals to other healthcare providers did not decrease.

In **chapter 7** we described the cost-effectiveness of referral by the GP for MR imaging compared with usual care in patients aged 18–45 years with traumatic knee symptoms, assessed with a cost-utility analysis. A total of 356 patients with traumatic knee symptoms were included (mean age, 33 years ±8 [standard deviation]; 222 men [62%]). Patients were randomly assigned to usual care (n = 177) or MR imaging (n = 179) within 2 weeks after injury. The main outcome measures were quality-adjusted life years (QALYs) and costs from a healthcare and societal perspective. Multiple imputation was used for missing data. The Student t test was used to assess differences in mean QALYs, costs, and net benefits. The mean QALYs were 0.888 in the MR imaging group and 0.899 in the usual care group (P = .255). Healthcare costs per patient were higher in the MR imaging group (€1109) than in the usual care group (€837) (P = .050), mainly due to higher costs for MR imaging, with no reduction in the number of referrals to an orthopaedic surgeon in the MR imaging group. We concluded that MR imaging referral by the GP was not cost-effective in patients with traumatic knee symptoms; in fact, MR imaging led to more healthcare costs, without an improvement in health outcomes.

In **chapter 8**, we evaluated the effectiveness of exercise therapy in patients with meniscal lesions in a systematic review and meta-analysis. Nine databases were searched up to July 2015, including EMBASE and Medline OvidSP. Randomized and controlled clinical trials in adults with traumatic or degenerative meniscal lesions were considered for inclusion. Interventions had to consist of exercise therapy in non-surgical patients or after meniscectomy, and had to be compared with meniscectomy, no exercise therapy, or to a different type of exercise therapy. Primary outcomes were pain and function on short term (≤3 months) and long term (>3 months). Two researchers independently selected the studies, assessed the risk of bias, and extracted data. We found that of the 1415 identified articles 14 articles describing 12 studies were included; all had some concerns about the risk of bias. There was no significant difference between exercise therapy and meniscectomy for pain (MD 0.27; 95% CI -4.30 to 4.83) and function (SMD -0.32; 95% CI -0.68 to 0.03). After meniscectomy, there was conflicting evidence for the effectiveness of exercise therapy when compared to no exercise therapy for pain and function. There was no significant difference between various types of exercise therapy for pain (MD 19.30; 95% CI -6.60 to 45.20) and function (SMD 0.01; 95% CI -0.27 to 0.28). We concluded that exercise therapy and meniscectomy yielded comparable results on pain and function. Exercise therapy compared

to no exercise therapy after meniscectomy showed conflicting evidence at short term, but was more effective on function at long term. The preferable type, frequency and intensity of exercise therapy remains unclear. The strength of the evidence was low to very low.

In **chapter 9**, we described the general discussion of this thesis. Our study provides high quality evidence confirming that routine MR imaging of the traumatic knee should not enter the diagnostic pathway in primary care through direct access by the GP, as it does not improve patient outcomes nor reduces costs nor prevent from referral to secondary care. There were some methodological issues that may have impacted on the results of the TACKLE trial. Firstly, the patients were not blinded to the allocated intervention. The lack of blinding may have affected the subjective clinical outcomes. Secondly, the Lysholm scale was used to measure knee related daily function. Detecting small improvement in patients with reasonable knee function using the Lysholm scale might be difficult. However, all secondary clinical outcomes show consistent results of no differences between usual care and MR imaging. Also, we were faced with some challenged during the conduct of the TACKLE trial, mainly caused by the fewer eligible patients that participated in our trial by the GP during the consultation than anticipated. In order to collect sufficient data we had to make some changes to the TACKLE protocol after the trial commenced. This might have diminished the effect we found between the groups, however, explorative subgroup analysis in the originally defined patients showed consistent results of non-inferiority and no cost-effectiveness of MR imaging compared to usual care during the 1-year follow-up. Concerning the generalizability of our results, we have to be aware that in the TACKLE trial, GPs were instructed to invite all patients with traumatic knee complaints to participate in the study, while in daily practice GPs tend to identify patients who they consider to be in need of additional diagnostics. No consensus exist among GPs about which patients are in need of additional diagnostics and there is no scientific ground on which these criteria can be based. The guideline panel of the Dutch clinical guideline 'traumatic knee complaints' for GPs stated that MR imaging might play a role in primary care in indications for surgery. However, the most common traumatic knee complaints that are referred to an orthopaedic surgeon by the GP are meniscal lesions and cruciate ligament injuries. Especially in patients with degenerative meniscal lesion, MR imaging will not affect subsequent management, since international clinical guidelines recommend conservative treatment in these patients. Future research should focus on indications for meniscal repair and a possible subgroup of patients with anterior cruciate ligament injuries who may benefit from surgery. In case these possible subgroups are identified, the efficacy of MR imaging in primary care in these patients needs to be re-established. Although, indications for surgery may also solely be based clinical findings rather than abnormalities seen on MR imaging.

Until that, the treatment by the GP may be refined by enhanced and targeted information and advice, by making the preferences, expectations and illness perceptions transparent during the first consultation.