Rationale and design of the STARR trial: should a traumatic meniscal tear be resected? - a randomized controlled trial

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ABSTRACT

Objective: Arthroscopic partial meniscectomy is the most performed orthopedic intervention. However, evidence is lacking regarding the efficacy of an arthroscopic intervention for traumatic meniscal tears. The primary objective of the presented study is to evaluate the (cost-) effectiveness of arthroscopic partial meniscectomy compared to a non-operative treatment strategy. The hypothesis is that an arthroscopic partial meniscectomy is a (cost-) effective intervention to treat patients with clinical complaints of the knee with a traumatic meniscal tear.

Methods: The STARR trial is an open-labelled randomized controlled trial. Patients aged 18-45 years with an MRI-verified meniscal tear and a recent history of trauma after which current knee symptoms developed, are eligible. Patients will be randomized to arthroscopic partial meniscectomy (control group) or a standardized exercise program under supervision of a physical therapist and pain medication if required (intervention group). The primary outcome measure is the change in clinical outcome measured with the International Knee Documentation Committee (IKDC) questionnaire over a two-year period. Secondary outcomes are the cost-effectiveness over the two-year period and early cartilage degeneration, measured by quantitative magnetic resonance imaging (T_2 mapping).

Discussion: The STARR trial will provide evidence concerning the (cost)-effectiveness of a partial arthroscopic meniscectomy compared to non-operative treatment for patients with clinical complaints of the knee with a traumatic meniscal tear. This study addressess an important evidence gap and the results will have great impact on clinical decision making in patients with a traumatic meniscal tear.

INTRODUCTION

Meniscal tears are among the most common knee injuries and are frequently found in younger and active persons [1]. The incidence of persons with meniscal tears presenting to an orthopedic trauma department is 23.8/100.000 per year [2]. Meniscal tears are traditionally classified into traumatic and degenerative tears. Patients with traumatic meniscal tears have a history of an acute onset (often during sport activities). Patients with degenerative meniscal tears tend to have a more gradually development of complaints.

Health care efficiency problem

Patients with complaints of a meniscal tear are limited in sport and daily activities, which influences the quality of life. So far, the natural course of these complaints is unknown. Eventually, the majority of the patients with a meniscal tear will develop osteoarthritis (OA) at relatively early age [3,4]. When a patient present to a physician with a symptomatic meniscal tear, decisions need to be made regarding the most optimal treatment. Treatments options for a meniscal tear are non-operative (i.e., exercise therapy, pain medication, relative rest) or operative (i.e., arthroscopic partial meniscectomy or meniscal repair). The treatment choice for patients with signs and symptoms of a meniscal tear should be based on benefits and disadvantages of potential interventions. First, the gain on symptom level should be considered. On society level, it is also worthwhile to take into account the medical and productivity costs of the chosen treatment. Furthermore, a meniscal tear is strongly related to the onset of osteoarthritis, therefore the potential influence of the chosen treatment on osteoarthritic changes should also be considered. Finally, in case of an operative intervention, the risk of potential peri-operative complications should be considered. Thus, the optimal treatment of the individual patient should be based on a weighted decision on the abovementioned effect levels. A recent systematic review based on several high-quality RCTs reported that an arthroscopic partial meniscectomy is not beneficial compared to exercise therapy or even placebo surgery for patients with a degenerative meniscal tear [5]. However, for patients with a traumatic meniscal tear there is a paucity of evidence whether an arthroscopic partial meniscectomy is the most optimal intervention.

Anticipated cost-effectiveness

In general, it can be said that young and active patients in the prime of their career will have considerable economic burden in time off work because of their meniscal tear. The potential clinical benefit of an effective arthroscopic procedure has to be weighed against the costs of a surgical procedure, rehabilitation costs, and costs due to potential surgical complications. An arthroscopic partial meniscectomy is financially fully covered by the health insurance in The Netherlands. Usual care in The Netherlands comprises that orthopedic surgeons perform an arthroscopic partial meniscectomy soon after the injury, and not later during the follow-

up after unsuccessful non-operative treatment. Additionally, nowadays an arthroscopic intervention has become more readily available because of an increasing number of private clinics.

Standard care

An arthroscopic partial meniscectomy remains the most frequently performed procedure by orthopaedic surgeons in The Netherlands, approximately 40.000 procedures yearly [6].

Trial objectives

In spite of the high frequency of performed arthroscopic partial meniscectomies, the (cost-) effectiveness of this procedure has been increasingly questioned. Especially, in case of a traumatic meniscal tear without a "fixed locked knee", the Dutch and other guidelines are not conclusive whether an arthroscopic intervention is the most optimal treatment. The aim of the present study proposal is to evaluate the (cost-) effectiveness of an arthroscopic partial meniscectomy in patients with a traumatic meniscal tear. An arthroscopic partial meniscectomy will be compared to non-operative treatment (i.e., exercise therapy and pain medication). Our hypothesis is that an arthroscopic partial meniscectomy is a (cost-) effective intervention to treat patients with clinical complaints of the knee because of a traumatic meniscal tear (superiority study).

Primary objectives:

1. To assess whether there is a clinically relevant effect of an arthroscopic partial meniscectomy compared to a non-operative treatment over a 2-year period in patients with a traumatic meniscal tear.
2. To assess whether an arthroscopic partial meniscectomy is a cost-effective intervention over a 2-year period in patients with a traumatic meniscal tear.

Secondary objectives:

1. To identify potential predictors for a clinically relevant better outcome of an arthroscopic partial meniscectomy over a 2-year period.
2. To assess whether there are differences in early cartilage degeneration on quantitative MRI over a 2-year period between an arthroscopic partial meniscectomy and non-operative treatment.

METHODS

Study design

The design of the present proposal is an open-labelled randomized controlled trial. Patients will be randomized into a group receiving arthroscopic partial meniscectomy (a); or in a group receiving non-operative treatment (b). Approval was obtained by the Erasmus MC Medical Ethics Committee (registration code NL46822.078.13). The study has been registered in the Dutch Trial Registry (registration number NTR4511.

Setting

The study will be conducted at the department of orthopedic surgery of Erasmus MC University Medical Center (Rotterdam), Máxima MC (Eindhoven/Veldhoven), Haaglanden MC (The Hague), Elisabeth Hospital (Tilburg), *St.* Antonius Hospital (Utrecht), Onze Lieve Vrouwe Gasthuis (Amsterdam), Catharina Hospital (Eindhoven) and Noordwest Hospital group (Alkmaar).

Study population

Inclusion criteria

In order to be eligible to participate in this study, a patient must meet the following criteria: age between 18 and 45 years; a history of a knee trauma (in the past six months) after which current knee complaints were initiated, and the presence of a meniscal tear (grade 3) on MRI.

Exclusion criteria

A potential subject who meets any of the following criteria are excluded from participation in the STARR trial: a fixed locked knee (i.e., when the patient is unable to extend or bend the index leg); a reparable meniscal tear (based on MRI, according to the patient's attending physician); rupture of the anterior or posterior cruciate ligament (in medical history or concurrent with meniscal tear); radiographic knee OA (based on radiograph and/or MRI); disabling co-morbidity; and insufficient command of Dutch or English language.

Recruitment

Patients, who visit the outpatient clinic of one of the participating hospitals and meet the inclusion criteria, are informed about the study by their orthopedic surgeon. The potential eligible patients receive written information and are invited to participate. If they are interested, the researcher contacts them and screen on in- and exclusion criteria. When the patient still conforms to the eligibility criteria and gives written informed consent, baseline measurements are carried out. Thereafter patients is randomized into one of the two treatment groups.

Randomization

Allocation to type of intervention takes place by receiving the consecutive randomization number from the coordinating investigator. A computer-generated randomization list is used (block randomization, with variable size of the blocks; stratified for orthopedic surgeon). After this the allocation of the type of intervention is open to the orthopaedic surgeon, and to the patient. Data analysis are obtained and analysed by the researcher who is blinded for group allocation and patient characteristics. After complete data analysis, unblinding will take place.

Interventions

Control arm: arthroscopic partial meniscectomy

Arthroscopic partial meniscectomy is performed within 6 weeks after randomization with the patient under general or spinal anesthesia and with the use of a tourniquet. During arthroscopy, the orthopedic surgeon evaluates all knee compartments on articular lesions according to the Outerbridge classification. Location and type of meniscal tears are registered, thereafter excision of the meniscal tear is performed. If during the arthroscopic procedure the orthopedic surgeon decides that suturing of the tear is indicated, this is allowed. According to Dutch guidelines of physical therapists and orthopedic surgeons, physical therapy is indicated solely in case of (expected) delayed recovery following meniscectomy and is performed accordingly.

Intervention arm: non-operative treatment strategy

A standard exercise program has been developed in collaboration with participating physical therapists and sport physicians, and patients are treated accordingly. The goal of the exercise program is to reduce pain, restore full range of motion and to restore knee function. It consists of exercises for improving muscle strength and endurance, muscle flexibility as well as balance and proprioception. The exercise therapy protocol takes about 12 weeks. There is no restriction regarding physical therapist in the STARR trial; patients are free to choose their therapist. The costs of exercise therapy are covered for patients who participate in the STARR trial; financial arrangements in this context are established with health insurance companies. The intensity of exercise therapy (i.e., frequency of therapy sessions and exercises per week) is determined by the attending physical therapist and the patient. At baseline, an information brochure comprising home exercises is provided to the patient by the researcher. A routine pain medication protocol is used [7].

Outcome measurement

Outcome measures used at the different time points can be found in Table 1.

Table 1. Summary of study timing and activities*

	STUDY PERIOD			
	Enrolment	**Allocation**	**Post-allocation**	**Close-out**
ENROLMENT	Baseline	Randomization	3, 6, 9, 12-months FU	24-months FU
Eligibility screening	X			
Informed consent	X			
Allocation		X		
INTERVENTIONS				
Intervention group: arthroscopic partial meniscectomy			X	
Control group: non-surgical treatment			X	
ASSESSMENTS				
Demographics: age, sex, side, BMI, education level, comorbidity	X			
IKDC questionnaire	X		X	X
KOOS questionnaire	X		X	X
WOMET questionnaire	X		X	X
Lysholm & Tegner questionnaire	X		X	X
NRS pain questionnaire	X		X	X
Satisfaction questionnaire				X
EQ-5D questionnaire	X		X	X
iMCQ and iPCQ questionnaire	X		X	X
MRI knee including T_2 mapping	X			X
Adverse events			X	X

* According to standard protocol items: recommendation for interventional trials (SPIRIT)
BMI = Body Mass Index, IKDC = International Knee Documentation Committee, KOOS = Knee injury and Osteoarthritis Outcome Score, WOMET = Western Ontario Meniscal Evaluation Tool, NRS pain = Numerical Rating Scale for pain, iMCQ = iMTA Medical Cost Questionnaire, iPCQ = iMTA Productivity Cost Questionnaire, FU = follow up
Standard protocol items: recommendation for interventional trials (SPIRIT)

Patient characteristics

At baseline, patient characteristics are obtained: age, sex, side affected (i.e., left or right), height, weight, education level, (musculoskeletal) comorbidity, duration of complaints, and previous surgery.

Primary outcome measure

The primary endpoint of the STARR trial is a clinically relevant difference in change in International Knee Documentation Committee (IKDC) questionnaire over a two-year period.

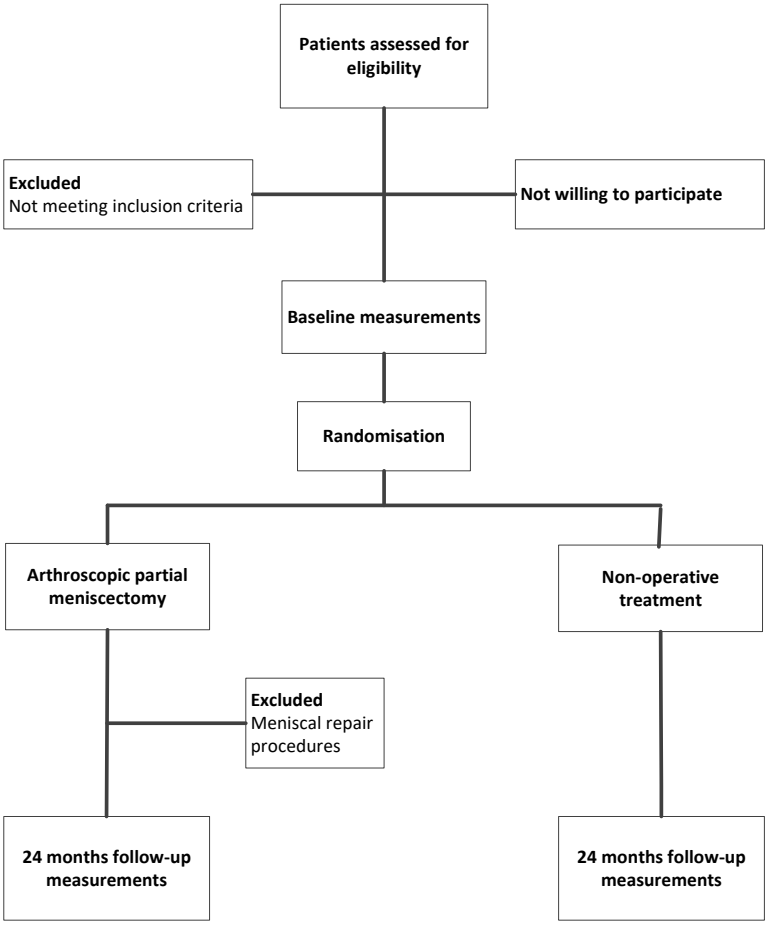

Figure 1. Flow diagram of the STARR trial, according to Consolidated Standards of Reporting Trials (CONSORT).

Main secondary outcome: cost utility

During the two-year follow-up, information regarding medical consumption (such as contact with general practitioner (GP), physical therapist, medical specialist, diagnostic imaging, arthroscopy and other knee procedures, hospital stay, medication, appliances, home modifications and home care), productivity loss due to the meniscal tear, and the amount of informal care provided are collected. Data on the amount of medical consumption within the hospital is collected by the researcher. We register all medical procedures, diagnostic imaging, and length of stay. Non-hospital medical consumption and patient travel costs is collected using the iMCQ patient questionnaire (iMTA Medical Cost Questionnaire) [8] at all timepoints as described above. The questions refer to GP contact, contact with physicians from other hospitals, physical therapists, manual therapists, other paramedics, home care, medication (especially pain medication), hours of informal care, etc. Productivity costs are measured

using the iPCQ (iMTA Productivity Cost Questionnaire) [9] at all measurement moments. The cost per unit of medical consumption, patient time, informal care and per hour of work lost are estimated, using updated information from the Dutch Manual for economic evaluation of health care [10].

The most important patient outcome for the cost utility is quality of life, which will be measured by means of the EQ-5D instrument. The EQ-5D comprises five dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Utility values of the general Dutch public for these health states will be applied in this study [11]. Two cost utility ratios are calculated: incremental medical costs per QALY gained of arthroscopic partial meniscectomy versus non-operative treatment; incremental societal costs per QALY gained of arthroscopic partial meniscectomy versus non operative treatment. The societal costs include: medical costs, productivity costs and patient costs.

Other outcome measures

Secondary clinical outcomes in the STARR trial are differences in scores of the Knee injury and Osteoarthritis Outcome Score (KOOS), Western Ontario Meniscal Evaluation Tool (WOMET), work- and sports load (Lysholm, Tegner), Number rating Scale for knee pain (NRS), and patient satisfaction. Measurements take place after 3, 6, 9, 12 and 24 months of follow-up. A standardized MRI examination of the knee is obtained at baseline and at two-year follow-up. Semi-quantitative MRI assessment of the whole knee, using the MRI OA Knee Score (MOAKS) as advised by the Osteoarthritis Research Society International (OARSI), is used as outcome measure [12]. To quantify early stages of cartilage degeneration, changes in composition and matrix integrity of cartilage are evaluated using quantitative MRI (T_2 mapping). Other secondary outcomes are use of pain medication and presence of adverse events.

Sample size and power calculations

Sample size calculation for the STARR trial was performed using the studies of Barber and Rodkey [13,14]. Barber et al. reported preoperative data of patients with eligibility criteria similar to the STARR trial with a mean Lysholm score of 47.3 (SD of 29.9). Rodkey reported mean change in Lysholm score after two-year follow-up of 28 (SD not provided). A surgical intervention should have a clinically relevant additional effect compared to a non-operative approach. Clinically relevant difference is defined as a difference between both groups of minimally 15 points (effect size 0.5). For a power of 80% with an alpha of 0.05, the required sample size is 63 patients per intervention group; thus, a total of 126 patients. To accommodate 15% potential dropout rate over the 2-year follow-up and to compensate for per-operative conversions from meniscectomy to meniscal repair (an estimated 5% of STARR participants in the arthroscopy group), our initial aim was to include 152 patients. However, based on lower actual dropout rate and the standard deviation of included study population, we recalculated the required sample size, in agreement with the trial sponsor. With 100

patients, a clinically relevant additional effect of an effect size of minimally 0.5 of a surgical intervention can be detected, with the same assumptions of a power of 80% and an alpha of 0.05 (two-sided testing).

Feasibility of recruitment

Phase 1 [15]: Each of participating hospitals perform approximately 100 (range 70-180 per Hospital) arthroscopic partial meniscectomies yearly. We checked records of patients with a meniscal tear who visited an orthopedic surgeon in Erasmus MC University Medical Center or Haaglanden MC during the past two years on eligibility criteria. Yearly around 60-110 patients fulfilled these criteria. Hence, we expected that recruiting 152 patients should be feasible in 15 months.

Phase 2: Two orthopedic surgeons from participating hospitals are project members of the STARR trial and were extensively involved with the development of this proposal. Our institution has built up extensive experience regarding including patients for clinical studies. The hospitals participating in the STARR trial have participated in previous studies of our group. Each hospital has concentrated the appointments of young patients with acute knee complaints at their outpatient clinic. Consequently, it will be feasible for the researcher to be present at each location when potential eligible patients will be seen at the outpatient clinic of participating hospitals. Prior to the start of the study, clear arrangements will be made with participating orthopedic surgeons regarding co-authorship in future scientific publications. The researcher will perform all measurements and will be responsible for all logistics.

Phase 3: Because of the absence of an adequate patients' association regarding meniscal tears, we composed a FOCUS group of patients with a recent knee trauma. The information form for patients has been evaluated by patients of this group.

Data management

All patient data are handled confidentially and anonymized in compliance with the Dutch Personal Data Protection Act ("Wet Bescherming Persoonsgegevens"). Questionnaires are collected digitally, and the patient study data are stored in a coded way using secured data management software (Gemstracker version 1.6.3, Erasmus MC, Rotterdam, the Netherlands). Each patient gets an anonymized study number that is used for all documentation, study reports and publications. The key to this study number is handled by an independent researcher. All data will be stored during the study period, after the study is finished the data will be stored for 15 years in the Erasmus MC University Medical Center secured research archive.

Statistical analysis

Analysis of STARR trial outcomes will primarily be performed by "intention to treat". That is, all participants randomized in the STARR trial will be included in the analysis according to

their treatment allocation, even if they did not receive the intervention they were allocated to receive. A secondary analysis will be performed, limited to the participants that were compliant to the treatment protocol of the groups to which they were randomized (i.e., per protocol analysis). Distribution analysis of all variables will be tested using Shapiro-Wilk tests. For normally distributed variables, parametric tests will be used. For non-normally distributed variables, nonparametric test will be used.

Primary study parameters

The difference between intervention groups in mean change in IKDC score after two years will be used as primary outcome. Primary analyses will be performed using repeated measurements for linear regression analysis. Fixed effects will be the variable "time", and the covariates we adjust for. For patients who are lost to follow-up, we will include all observed data in the analysis. Adjustment will be done for those baseline variables that change the effect estimate with more than 10%. If necessary, adjustments for unbalanced covariates will take place. The assumptions of constant variance and linear relationships will be assessed using scatterplots. Should any of these assumptions seriously fail then variable transformations of the dependent or independent variable(s) (where applicable) will be used. The choice of which transformation (e.g. square root, logarithm) will be used based on the specific distribution of the residuals.

Secondary study parameters

Predictors for a clinically relevant better efficacy over a two-year period of an arthroscopic partial meniscectomy will be identified by using logistic regression analyses (clinically relevant increased effect over a period of 2 years as dependent variable). Variables of which a priori is known that they are associated with patient satisfaction, based on previous studies or based on a strong clinical rationale, will be considered covariates in the primary analysis. Whether an arthroscopic partial meniscectomy can decrease the risk of early degenerative changes compared to a non-operative treatment, will be analyzed by using logistic regression analyses. The presence of early degenerative changes will be assessed by quantitative MRI (T_2 mapping) and semi-quantitative MRI OA Knee Score (MOAKS).

Cost-effectiveness analyses

By means of non-parametric bootstrapping (i.e., drawing 2500 observations at random from the available patient sample), the degree of uncertainty for costs and health effects and the cost utility ratio will be depicted on the so-called cost-effectiveness plane. In addition, an acceptability curve will be drawn, which indicates the probability that the health care program has lower incremental costs per QALY gained than various thresholds for the maximum willingness to pay for an extra QALY.

Budget impact analysis (BIA)

In the budget impact analysis, we will compare the budget impact for the government, health insurers and patients for the following scenarios: arthroscopic partial meniscectomy; a non-operative strategy (with an immediate reduction of maximally 40% of 40,000 surgical interventions) and a gradual decrease in surgical interventions.

Cost analysis

When the number of meniscectomies would reduce, patients will be more often treated with physiotherapy (at least 10 sessions per patient, which might (or not) be reimbursed by supplementary health insurance). We wil closely examine the reduction in surgery and the probability of substitution care. The annual budget impact for each scenario mentioned above will be calculated from the perspective of the government, both using the societal costs (direct and indirect costs, with prices from the manual cost calculation, and using the prices of the Dutch Healthcare Authority. For the perspective of the health insurer and the patients we will use the Dutch Healthcare Authority tariffs and co-payments when applicable.

DISCUSSION

The STARR trial is the first trial to analyses the (cost-) effectiveness of partial arthroscopic meniscectomy compared to non-operative treatment strategy, in patients aged 45 year or younger with a traumatic meniscal tear.

An arthroscopic partial meniscectomy is the most frequently performed procedure by orthopedic surgeons in The Netherlands; over 40.000 procedures yearly [6] . Because of an increasing number of private clinics, this procedure has become more readily available. Due to the fact that only around 5% of the meniscal tears are suitable for meniscal repair [16], a partial meniscectomy is still the most performed surgical procedure for a meniscal tear. The main evidence of the effectiveness of a meniscectomy is based on studies in patients with degenerative meniscal tears with already signs of OA [17]. For these so called degenerative meniscal tears the evidence is clear; the guidelines recommend therefore that a meniscectomy is not indicated as an initial treatment for degenerative tears. However, for young and active patients with a meniscal tear due to a trauma, the evidence is limited, and the effectiveness of this procedure is increasingly questioned. The current evidence of the effectiveness of a meniscectomy in young and active patients is based on retrospective studies [17] and one small RCT which compared the effectiveness of arthroscopic partial meniscectomy with a non-surgical therapy in patients with clinical symptoms of a traumatic meniscal tear [18]. These studies suggest that a partial meniscectomy is an effective intervention for those patients on the short term. However, after surgical removal of the damaged parts of meniscal tissue, knees are at high risk for the long-term development of OA [19,20] . On the other hand, also

without surgical intervention, meniscal damage is a potent risk factor for the development of OA [3,21]. Thus, there is a clear need for well-designed studies investigating the effectiveness of an arthroscopic partial meniscectomy for young and active patients with a meniscal tear.

Strengths of the study include the solid methodological framework, in which patient will be randomly assigned to partial arthroscopic meniscectomy or non-surgical treatment. Secondly, the study has a pragmatic design in which both interventions are frequently used in daily clinical practice. This aids to the generalizability of the study results, limits the burden for the study population and increases the likelihood for patients to be willing to participate.

A challenge of the proposed study is that some patients and also orthopedic surgeons might have problems with committing to the randomization process. This is a more often seen in surgical trials, in which a surgical intervention will be compared to a non-surgical intervention.

Trial status

The study inclusion has started in August 2014.

Declaration

Ethics approval and consent to participate

The study has been reviewed and approved by the Medical Ethics Committee (registration code NL46822.078.13) of the Erasmus MC. All participants signed a written informed consent form prior to start of the testing procedures.

Consent for publication

No individual person's data will be published, therefore consent for publication is not applicable.

Competing interests

The authors declare that they have no competing interests.

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Trial sponsor

The Netherlands Organization for Health Research and Development (call efficiency studies)

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