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The challenge of recruiting patients with anterior cruciate ligament injury of the knee into a randomized clinical trial comparing surgical and non-surgical treatment

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Abstract

Aims -- To determine the number of patients needed to be screened (NNS) and allocated (NNA) to include one participant into a randomized clinical trial (RCT), and to compare the characteristics of patients accepting or declining participation in the RCT.

Methods -- The recruitment process of an ongoing multicenter RCT, comparing surgical and non-surgical interventions after acute anterior cruciate ligament (ACL) injury of the knee is described. We use the known concept Number Needed to Screen (NNS) and introduce the new concept Number Needed to Allocate (NNA) as variables to support a priori sample size calculations of future investigations.

Results -- 560 patients were screened to identify 162 patients (29%) eligible for inclusion in the RCT. 41 of those declined participation for various reasons, the most common being unwillingness to undergo surgery (n=23) or unwillingness to risk conservative treatment (n=8). 19 patients were excluded after MRI assessment or arthroscopy. Thus, 102 (18%) patients were allocated to one of the two treatments in the RCT. The NNS was 5.5 individuals with an acute knee injury, and the NNA was 1.6 individuals eligible for inclusion, to include 1 patient in the RCT. Patients declining to participate in the RCT were more frequently self-employed and less frequently injured in sports activities than those accepting RCT participation.

Conclusions -- We suggest that the a priori sample size calculation needs to be multiplied by at least 5.5 to provide an estimate of the number needed to screen, or 1.6 to provide an estimate of the number needed to allocate in order to include the desired number of patients in a trial comparing surgical and non-surgical treatment of the ACL injured patient.

Keywords

Randomized controlled trials, Patient selection, Sample size, Knee injuries, Anterior cruciate ligament injuries, surgical ligament reconstruction, rehabilitation

Introduction

Designed properly, the randomized clinical trial (RCT) is a powerful tool to evaluate medical treatments [1, 2]. However, RCTs evaluating surgical treatments are challenging to design and conduct. In particular, the recruitment of patients has been described as difficult and time-consuming [2-4]. Possibly, the greatest threat to the success of a randomized clinical trial is the inability to recruit an adequate number of subjects. Yet, there are few reports on the RCT recruitment process in general and RCTs involving surgical treatment in particular.

An a priori sample size calculation is indispensable in the planning of an RCT but nevertheless rarely reported in the literature [5, 6]. The sample size calculation, when performed, provides an estimate of the number of patients needed to include in the trial in order to reject the null hypothesis with a reasonable power. However, the sample size does not approximate the number of patients needed to screen and allocate for the trial. In clinical practice, where the recruitment for the trial takes place, a well supported estimate of the number of patients needed to screen and/or allocate would aid in attaining a properly powered RCT.

Different barriers to participation in RCTs have been suggested [3], and patients' willingness to participate in RCTs is a known limiting factor for recruitment. Factors characterizing patients declining to participate in RCTs have been identified, generally in hypothetical trials [3, 7, 8], but also using a qualitative approach based on patient interviews [9, 10]. However, the majority of available studies were performed in cancer or cardiovascular diseases [3]. To our knowledge there are no reports describing the recruitment process of an RCT comparing surgical and non surgical interventions in the orthopedic field.

Anterior Cruciate Ligament (ACL) tear is a serious injury to the knee joint with an annual incidence of about 8 per 10 000 inhabitants aged between 10 and 64 years [11]. There is no scientific evidence to support the hypothesis that surgical treatment is superior to non-surgical treatment of ACL injury with regards to return to ordinary daily activities, sports activities, pain or satisfaction with treatment [12]. Nevertheless, over 90 000 surgical reconstructions are performed annually in the USA alone and some 3500 reconstructions are performed annually in Sweden.

This report describes the patient recruitment process of an ongoing RCT comparing surgical and non-surgical treatment of ACL injuries. We describe the number of patients needed to be screened (NNS), and the number of patients needed to be allocated (NNA), in order to include the required number of participants into the RCT. We further compare the demographics and characteristics of those patients accepting and declining participation in the RCT.

Methods

We recruited and screened, at two different centers, patients aged 18-35 years, having a high to moderate physical activity level and a not more than four weeks old ACL rupture (Figure 1). Eligible patients were randomized to surgical reconstruction or non-surgical treatment after having agreed to participate in the RCT and signed informed consent. Patients randomized to surgical reconstruction were operated on within 6 weeks of randomization. All patients were assigned to an identical rehabilitation protocol.

Screening strategies

Helsingborg Hospital: All patients with a rotational knee trauma combined with a rapid effusion were referred to a sub-acute MRI at the time of their initial visit to the orthopedic emergency unit [11]. The

MRI referral was electronically forwarded to the department of radiology where a secretary was asked to announce all patients aged between 18-35 years to the study nurse. However, 8% (n=43) of all patients announced from the radiology department did not fulfill the inclusion criteria for age. All patients reported this way entered the screening group, and their medical records were reviewed. If general criteria for eligibility were met (Figure 2), based on medical records, the patient was scheduled for a baseline/screening visit (visit 0).

University Hospital Lund: All patients with a rotational knee trauma combined with a rapid effusion seen at the orthopedic emergency room were scheduled for a clinical visit at the orthopedic department within 1-2 weeks. At the clinical visit, an experienced clinician also involved in the RCT (RF), examined the patient. If general criteria for eligibility (Figure 2) were met the visit was extended into a baseline visit for the RCT.

Baseline visit (visit 0)

At the baseline visit, all patients were assessed clinically for eligibility by the same experienced clinician (RF). Prior to clinical examination, a history of knee injury and/or knee surgery, medication, and presence of any general systemic disease relevant to the trial was collected. Age, gender, social status, education, working status, activity at injury and activity level was collected by a self administered questionnaire. Patients eligible for inclusion received information about the RCT.

Randomization and intervention allocation procedure

Randomization was done prior to the MRI scan for clinical logistics reasons and patients could thus be excluded post randomization but prior to treatment allocation (Figure 3). Any surgical intervention was

made 4-6 weeks post randomization and in a few cases patients were excluded at the time of surgery (Figure 1). Some patients had already established a rehabilitation contact prior to randomization and in the remaining cases the patients were asked to start their rehabilitation procedure directly after randomization.

Activity level

Activity level was assessed using the Tegner scale [13], a self administered questionnaire. The Tegner scale for activity is a 1-10 scale commonly used for knee related activities. Level 1-4 on this scale represent low activity levels, 5-7 moderate, 8-9 high activity and 10 professional level [13]. Patients on a moderate to high activity level, corresponding to 5-9 on the Tegner scale, fulfilled physical activity criteria for eligibility (Figure 2). Examples of activities at level 5 are working as a fireman or snowboard skiing on a recreational level. Level 9 corresponds to activities such as competitive, but not professional, level soccer or ice hockey.

Patient information

Patients fulfilling inclusion criteria all received the same written information, including the telephone number to the investigator (RF) for questions related to the RCT. A video tape with patient information (described below) was used throughout the study and distributed to all patients fulfilling the inclusion criteria. To ensure sufficient time for consideration, none of the patients were allowed to agree on participation at visit 0. Two patients, both males, declined to receive the patient information and thus refused to take part in the RCT already at the baseline visit. Neither one of them wanted to take the risk of undergoing any kind of surgery. Answers about willing/not willing to take part in the RCT were obtained by telephone by the RCT study nurse. None of the patients included in this RCT agreed on

participation on the same day as information about the study was presented to them; the average time between receiving information and calling the study nurse was 3 days (1-13).

Video recorded patient information

Prior to study start a videotape, approximately 10 minutes long, was recorded. Firstly, a randomly selected patient, not recruited into the RCT, with a fresh ACL tear was interviewed and video recorded throughout a clinical visit. The function and localization of the ACL was described to the patient using a knee model. Secondly, a sequence was recorded at the physical therapist's office where the rehabilitation procedure was summarized. Finally, the videotape ended with a panel of three experienced orthopedic surgeons discussing surgical and non-surgical treatment of ACL injuries. Throughout this panel discussion scientific evidence and clinical opinions for and against the two treatment options were presented. These surgeons subsequently operated on patients participating in the RCT.

Number Needed to Screen (NNS) and Number Needed to Allocate (NNA)

Number Needed to Screen is a concept previously used and described in the literature. This concept has been statistically described [14] and used in studies with radiographic assessment of different diseases, presented according to Number Needed to Treat (NNT) analysis terminology [15]. With the clear similarities between radiological and clinical screening, we suggest that the use of NNS is appropriate in the present clinical trial. The NNS was calculated by dividing the number of patients screened for eligibility with the number of patients included in the trial. The NNS provides an estimate of how many patients were needed to be screened to include one patient into the trial. Multiplied with the a priori determined sample size this is an estimate of how many patients need to be screened.

In addition, we used the concept Number Needed to Allocate (NNA). The concept is similar to NNS and has, to our knowledge, not been described previously. All patients eligible for inclusion were regarded as allocated. The NNA was calculated by dividing the number of allocated patients with the number of included patients. This would present an estimate of how many patients eligible for inclusion that would need to be allocated in order to include one patient in the trial. In a similar manner as NNS, the NNA multiplied with an a priori sample size would present an approximation of the total number of patients fulfilling inclusion criteria necessary to allocate.

Statistical analysis

Means and standard deviation (SD) were calculated for all continuous variables except for the Tegner score where median and range were reported. Group comparisons of age were made using one-way ANOVA and group comparisons of activity level were made by Kruskal-Wallis test. All other comparisons on group level were made using the Chi square test.

Results

Since study start, 560 patients with acute knee trauma entered the screening group, with 162 patients eligible for inclusion prior to randomization. However, 41 patients declined to participate due to various reasons. In addition, 19 were excluded after MRI and/or arthroscopy which resulted in 102 patients included in the RCT (Figure 1).

The NNS was 5.5 individuals with an acute knee injury, and the NNA was 1.6 individuals eligible for inclusion, to include 1 patient in the RCT.

Demographic within group differences

Patient characteristics were available for 88% (n=36) of the patients declining participation, and 90% (n=37) reported their pre-injury activity level (Table 1). Characteristics and activity level were available for all patients accepting to participate in the RCT. The two most common reasons for declining participation were: not willing to risk surgical treatment (n=23); not willing to risk non-surgical treatment (n=8). Considering the reason for declining participation, we found no differences in characteristics within this group of patients who declined to participate.

However, patients declining participation were more frequently self employed (p=0.009) and less frequently injured during sports activities (p=0.045) compared to patients accepting participation in the RCT. No differences in age, gender, activity level, working status or level of education were found between the two groups (Table 1).

Discussion

Low recruitment leads to poor statistical power and compromises the ability of the RCT to detect meaningful differences. A report on the unethical conduct of underpowered trials was recently published, suggesting that investigators still fail to calculate appropriate statistical power prior to study start, or at least fail to provide such information in the published study report [6]. The statistical power calculation is a method to determine the final sample size needed. However, it does not take into account loss to follow-up, eligible patients declining RCT participation, or the larger number of patients needed to screen to identify those eligible for the trial. A translation of theory (sample size calculation) into clinical practice (individual differences) could help approximate the efforts needed to successfully complete a clinical trial with sufficient power. We present NNS and NNA as determined from the clinical reality of a trial comparing surgical and non-surgical treatment. The use of these ratios could help an investigator find a reliable estimate of the number of patients needed to be screened and/or allocated in order to include a sufficient number of patients in the trial.

NNS in this RCT was 5.5 patients with acute knee injury to include one patient into the RCT. An acute rotational trauma to the knee combined with a rapid effusion and/or verified hemarthrosis is strongly associated with an ACL injury [11], and we screened all patients demonstrating these features in the acute phase. The NNS value found was liable to be influenced by the fact that acute ACL injuries are difficult to detect and assess by clinical examination in the acute phase. Any NNS is affected by screening filter design or the identification of the screened population and hence could vary considerably between different trial designs.

NNA, as calculated in this study, was 1.6 patients fulfilling criteria for eligibility to include one patient into the RCT. We have not found any study presenting results from the recruitment process of an RCT on surgical treatment and/or using this concept. However, hypothetical trials were reported from which the NNA could be extrapolated. A hypothetical RCT on arthroscopic surgery in OA knees [7] found that 39 out of 88 patients were “definitely not willing” to participate in this RCT, which would yield an NNA of 1.8. Yet, an additional 30 patients in this study were “unsure or probably willing” to participate, bringing the NNA up to 4.6. In another hypothetical RCT on hormone therapy [8] including only women, 28 of 50 patients were “not willing” to participate in RCT providing a calculated NNA of 2.3. Halpern and co-workers conducted a hypothetical RCT on antihypertensive drug therapy vs. placebo on 126 patients where approximately 47% (n= 59) where willing to participate in the trial [16]. The calculated NNA for this study would be 2.1.

Our NNS and NNA values, drawn from reality in an RCT on surgical vs. non-surgical treatment, are lower than those calculated from hypothetical trials. Possibly, patients facing a serious injury do not react as anticipated from a hypothetical scenario. Moreover, we invested significant efforts into the

development of patient information material and all patients eligible for inclusion were given sufficient time to consider this information. Reports from the recruitment process in clinical trials could thus provide valuable information, not detectable in hypothetical scenarios. A limitation in the estimation of NNS and NNA in this study could be that some patients eligible for inclusion were incorrectly classified as not eligible. Based on our findings and extrapolated data from previous studies, the introduction of NNA and its use in the a priori sample size calculation is of value in RCT planning.

Demographic factors, such as age, race, gender and level of education have been shown to relate to patient's willingness to participate in clinical trials [3, 4, 17-19]. We found no differences between patients accepting or declining participation in our study with regard to any of these factors. However, we assessed acute symptomatic ACL injuries in the age range 18-35 years and it is possible that this age range was too narrow to be able to detect influence of age. On the other hand, we found that those self employed were more likely to decline participation in the RCT. The self-employed declining participation stated either "not willing to undergo surgery" (n=3), "not willing to undergo conservative treatment" (n=1) or "not willing to participate in scientific trial" (n=1) as reasons for declining participation. Possibly, the self-employed do not prioritize the time needed to undergo the prolonged intense rehabilitation following surgical treatment. Self employed are known to have a substantially lower benefit from social insurance and are also often irreplaceable in their small businesses. Thus, they are likely to suffer economically from a post-surgical prolonged sick-leave. Considering the limited number of patients in this study, we suggest that further studies need to address the issue of employment.

We also found a significant difference with regard to activity at injury, where patients injured in sports activities were more positive towards RCT participation. We have found no other studies addressing this issue. However, sportsmen/women with ACL injuries are more likely to have a stronger preference for

surgical treatment since the attitude in sports medicine is likely to recommend surgical reconstruction of the injured ACL. In the south of Sweden, the waiting list för ACL reconstruction is 6 months to one year. In the present study, patients randomized to surgical treatment were operated on within 6 weeks of randomization. This could be one explanation why patients injured in sports activities were more willing to participate in this particular RCT. On the other hand, patients dissatisfied with their treatment allocation are likely to seek surgical treatment elsewhere resulting in an increased drop-out ratio. However, only one patient dropped-out during the 4 year RCT.

In conclusion, we suggest that the use of Number Needed to Screen (NNS) and Number Needed to Allocate (NNA) in planning for an RCT is valuable, especially in surgical specialties. An a priori sample size calculation needed to be multiplied with a NNS of at least 5.5 to provide an estimate of the number of patients needed to screen in a trial comparing surgical and non-surgical treatment in ACL injured subjects. Further, 1.6 patients fulfilling inclusion criteria needed to be allocated to include one patient into the RCT.

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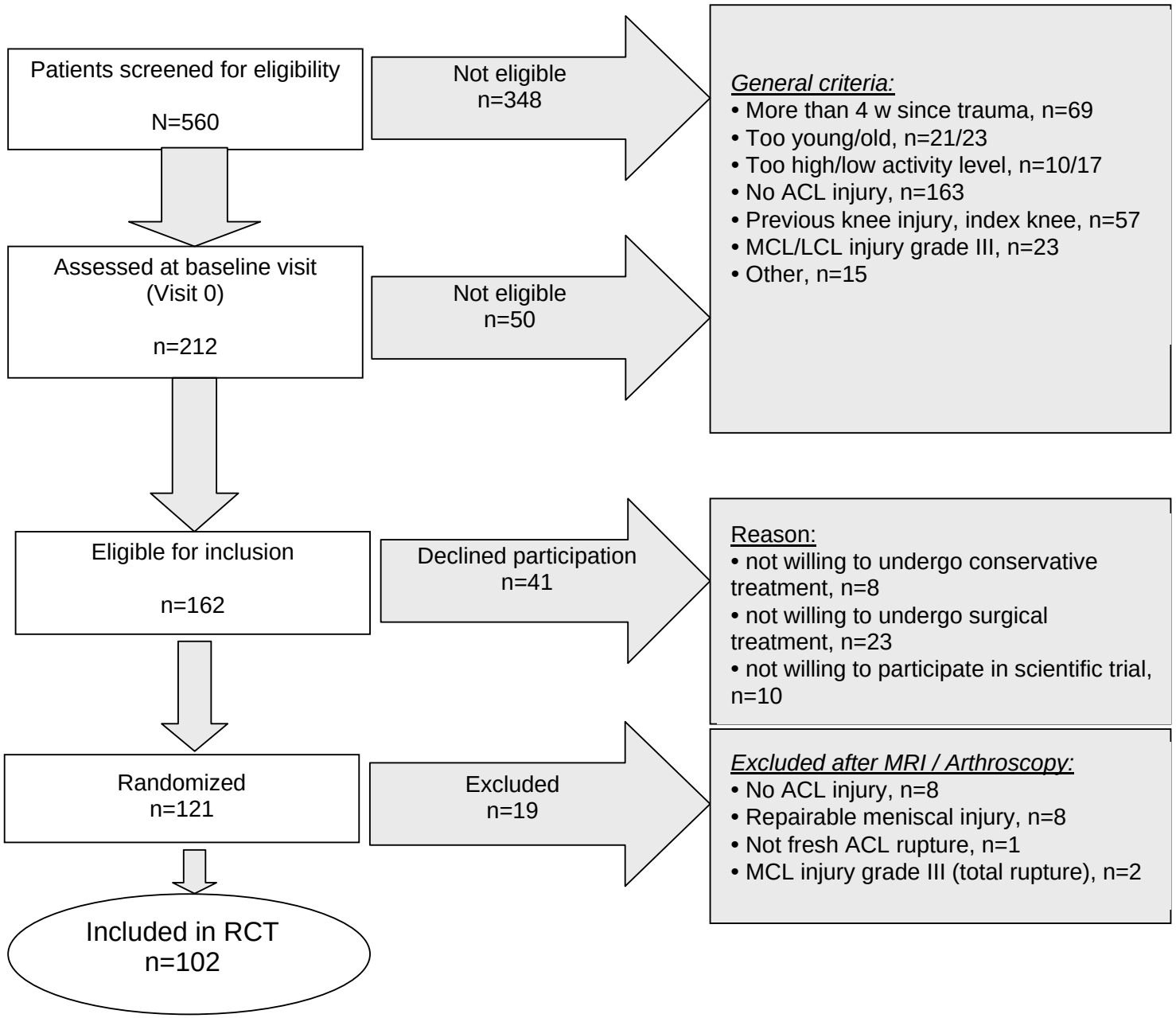
Figure legends

Figure 1. Flow chart over the recruitment process in this RCT

Figure 2. Criteria for eligibility in the randomized controlled trial of surgical versus non-surgical treatment of ACL injury.

Figure 3. Inclusion- and exclusion criteria for eligible patients in the randomized controlled trial of surgical versus non-surgical treatment of ACL injury.


Patients screened for eligibility
N=560
Not eligible
n=348
General criteria:
• More than 4 w since trauma, n=69
• Too young/old, n=21/23
• Too high/low activity level, n=10/17
• No ACL injury, n=163
• Previous knee injury, index knee, n=57
• MCL/LCL injury grade III, n=23
• Other, n=15
Assessed at baseline visit
(Visit 0)
n=212
Not eligible
n=50
Eligible for inclusion
n=162
Declined participation
n=41
Reason:
• not willing to undergo conservative treatment, n=8
• not willing to undergo surgical treatment, n=23
• not willing to participate in scientific trial, n=10
Randomized
n=121
Excluded
n=19
Excluded after MRI / Arthroscopy:
• No ACL injury, n=8
• Repairable meniscal injury, n=8
• Not fresh ACL rupture, n=1
• MCL injury grade III (total rupture), n=2
Included in RCT
n=102

General criteria for eligibility

1. Age 18-35 at entry
2. An activity level of 5-9 on the Tegner activity rating scale prior to injury (Tegner et al. 1985)
3. A not more than 4 weeks old trauma to the knee
4. An ACL insufficiency as determined by clinical examination (positive pivot shift and/or positive Lachmann test). The ACL injury can be either "isolated" or combined with a clinically assessed MCL injury grade I-II
5. None of the following features isolated and/or in combination:
    a. Earlier major knee injury to the index knee (ACL or PCL injury, patella dislocation or fracture)
    b. Previous knee surgery (other than diagnostic arthroscopy) to index knee
    c. Associated PCL injury or MCL injury grade III in index knee
    d. Concomitant severe injury to contra-lateral knee at the time of assessment (i.e. ACL or PCL injury, patella dislocation or fracture)
    e. Injury to the lateral/posterolateral ligament complex with significantly increased laxity
    f. Pregnancy
    g. A history of deep vein thrombosis (DVT) or a disorder of the coagulative system
    h. Claustrophobia
    i. General systemic disease affecting physical function, any other condition or treatment interfering with the completion of the trial, including patients with metal devices or motion disorders
    j. Systemic medication/abuse of steroids

Inclusion criteria for eligible patients

1. An ACL insufficiency as determined by clinical examination (positive pivot shift and/or positive Lachmann test) AND a complete ACL tear as visualized on MRI. The ACL injury can be either "isolated" or combined with one or several of the following injuries visualized on MRI and/or arthroscopy:
    a. A meniscus tear that is either left untreated or treated with a partial resection
    b. A small, stable meniscus tear treated with fixation, but fixation not interfering with the rehabilitation protocol
    c. Cartilage changes verified on MRI with arthroscopically determined intact surface
2. A radiographic examination with normal joint status or combined with either one of the following findings:
    a. A small-avulsed fragment located laterally, usually described as a Segond fracture
    b. JSN grade 1 *or* osteophytes grade 1 as determined by the OARSI atlas (Altman et al. 1995)
3. Agreement to participate in the study and signed informed consent prior to inclusion.

Exclusion criteria for eligible patients

1. One of the following associated injuries to the index knee as visualized on MRI and/or arthroscopy:
    a. An unstable longitudinal meniscus tear that requires repair and where the following postoperative treatment (i.e. bracing and limited ROM) interferes with the rehabilitation protocol
    b. Bi-compartmental extensive meniscus resections
    c. A cartilage injury representing a full thickness loss down to bone
    d. A total rupture of MCL/LCL as visualized on MRI

Factor	Accepted participation in RCT n=121	Declined participation in RCT n=41	p- value
Age, mean (range)	*26 (18-35)*	*25 (18-35)*	*0.423*
Gender			*0.669*
Male	92 (81%)	33 (76%)	
Education		*(n=36)*	*0.736*
High school or lower	7 (6%)	1 (3%)	
Some college	75 (62%)	24 (67%)	
University	39 (32%)	11 (30%)	
Social status		*(n=36)*	*0.342*
Married / living with someone	53 (44%)	13 (36%)	
Living alone	33 (27%)	9 (25%)	
Living with parents	31 (26%)	14 (39%)	
Other	4 (3%)	0	
Immigrant (1st or 2nd degree)	*15 (12%)*	(n=35) *8 (23%)*	*0.124*
Working status		*(n=35)*	***0.009***
Employed	74 (61%)	13 (37%)	
Unemployed	10 (8%)	5 (14.5%)	
Student	34 (28%)	12 (34%	
Self employed	3 (3%)	5 (14.5%)	
Activity at injury		*(n=36)*	***0.045***
sports	119 (98%)	33 (92%)	
Pre injury activity level		*(n=37)*	0.419
Tegner, median (range)	9 (5-9)	8 (4-9)	

Table 1. Characteristics and demographics of patients that accepted (n=121) and declined (n=41) to participate in RCT.