Statistical Analysis Plan (SAP) for the KANON-Study

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STATISTICAL ANALYSIS PLAN (SAP) FOR THE KANON-STUDY

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1. STUDY SYNOPSIS

Anterior cruciate ligament (ACL) injuries are common, severe and disabling knee injuries occurring in young active athletes. Treatment could be either surgical or non-surgical, both involving extensive rehabilitation for at least 4-6 months. Two RCTs comparing surgical and non-surgical treatment of ACL injured knees was performed in the 80's and both failed to present any difference between the two treatment groups [1, 2]. Approximately 150 000 surgical reconstructions are performed annually in the US alone with an estimated cost of more than 2 billion dollars including the postoperative rehabilitation [3, 4]. This study was designed to investigate in a randomized, controlled trial whether the outcome of treatment according to a rehabilitation program after acute ACL disruption improved by adding ACL reconstruction.

2. STUDY OBJECTIVES

Primary Objective

The primary objective is to compare between the two treatment groups the change at 2 years in patient reported pain, other symptoms, function in sport and recreation and knee-related quality of life aggregated into one average score.

Secondary Objectives

The secondary objectives are to compare between the two treatment groups the change at 2 years in:

1. KOOS subscale scores:
    a) Pain
    b) Symptoms
    c) Activities of daily living (ADL)
    d) Sports & recreation function (Sport/Rec)
    e) Knee related quality of life (QOL)
2. patient reported health status (SF-36) separated into two components:
    a) mental health status (MCS)
    b) physical health status (PCS)
3. activity level with specific emphasis of the knee (Tegner Activity Score)
4. Adverse events

after acute ACL disruption treated according to a rehabilitation program alone or combined with an ACL reconstruction.

Exploratory objectives

To explore the longitudinal change (over a two year period from injury) of patients' own opinion of their knee and associated problems with regard to:

1. Pain
2. Symptoms
3. Activities of daily living (ADL)
4. Sports & recreation
5. Knee related quality of life

after acute ACL disruption treated according to a rehabilitation program alone or combined with an ACL reconstruction.

In addition, we aim to investigate the individual outcome (per patient) during the 2 year period using definitions of success / failure or similar dichotomisation of outcome.

Assessment of Objectives

Primary outcome

The Knee injury and Osteoarthritis Outcome Score (KOOS) [5, 6] is a 42-item self-administered questionnaire with five separate sub-scales: pain, symptoms, activities of daily living (ADL), sport and recreation function (Sport/Rec), and knee-related quality of life (QOL). Standardized answer options are given in Likert boxes and each answer is scored from 0 to 4. Sub-scale scores are given separately (a guide for sub-scale calculation is available at www.koos.nu), ranging from 0 to 100 where 100 is the best possible result. The KOOS is validated for different orthopedic procedures such as ACL reconstruction, meniscectomy and knee OA [5-7]. KOOS was registered at all visits (baseline and follow-up) during this trial (Figure 1)

Primary outcome of this study was an aggregated average score, compiled by 4 subscales of the KOOS: Pain; Symptoms; Sport and recreation function; and Knee related QOL. This aggregated score, referred to as $KOOS_4$, is ranging from 0 to 100 were 100 is the best possible result. Each subscale will be calculated according to the instructions in the user's manual. Thereafter an average of the four subscale scores will be calculated. Consequently each subscale will have an equally large impact on the final $KOOS_4$ score.

$$KOOS_4 = (KOOS_{pain} + KOOS_{symptoms} + KOOS_{sport\&rec} + KOOS_{QOL}) / 4$$

Younger active individuals, like most patients having ACL injury, report little difficulty with the items included in the KOOS subscale ADL (assessing issues like standing, raising from sitting to standing, putting on socks etc.) [5, 6]. Thus, to avoid an increase in noise, we will not include the subscale ADL in the aggregated score used as primary outcome in this study ($KOOS_4$).

Secondary outcomes

Change in all five KOOS subscales, including the ADL subscale, will be analyzed separately at two years.

Medical Outcomes Study 36-Item Short form Health Survey (SF-36) [8] was used to evaluate health status. The SF-36 is a multi-purpose, short-form health survey with 36 questions summarized in two major components of mental health status (Mental Component Score, MCS) and physical health status (Physical Component Score, PCS). SF-36 was registered at all visits during this trial (Figure 1).

Activity level with specific emphasis of the knee was registered using the Tegner Activity Score [9] which is a numeric score ranging from 1 to 10 where 1 is the least strenuous activity for the knee and 10 is the hardest. This score was validated as an assessor reported outcome in 1985 for evaluation of activity level in subjects suffering from ACL injury and has been widely used in evaluation of knee injuries. Consistent with previous publications we used a self-reported Tegner activity score [10-13], administered at baseline and all follow-ups except at 3 months (Figure 1). At baseline, subjects were asked to report their pre-injury activity score and at each follow-up subjects were asked to report the current activity score.

Safety variable

Events and features with a possible relation to patient safety were collected from all subjects throughout the trial using five main strategies in combination:

1. Instability in activity as reported by the subject was registered at each follow-up based on a direct question regarding a history of 'give-way' episodes.
2. Spontaneous report from the subject over the phone (collected by the study nurse) or at a clinical visit (entered in the medical chart by the assessor)
3. Subjects were specifically asked to report any adverse event (both knee related and not knee related) and doctors' visit during the first to years of the study at the two year follow-up.
4. A thorough review of each subjects' medical history after inclusion in the trial (including medical charts from other specialities and health care registrations) was performed by a research nurse at the time of two year follow-up.
5. Physiotherapists involved in the rehabilitation of the subjects registered any AE that interfered with the rehabilitation protocol.

Descriptive outcomes

Descriptive outcomes at baseline will be presented in a table (Table 1).

Patient characteristics at baseline were registered using items from a Swedish health survey [14] at the time of inclusion (Table 1).

Knee instability at rest was manually assessed by the pivot-shift test (i.e. rotational instability) and *antero-posterior laxity* was assessed by the Lachmann test at all visits during the study. In addition, antero-posterior laxity was assessed by the KT-1000 arthrometer [15, 16] at the two year follow-up. *Restrictions in range of motion of the knee* were assessed at baseline and all follow-ups. Baseline values as well as findings at two years will be presented for manual tests and two year findings will be presented for the KT-1000 assessment (Table 1 & 3).

In addition, associated injuries of the knee at baseline (as visualized on MRI) will be presented in a table (Table 1).

The following treatment related variables will be presented descriptively for the two year period: number of subjects who participated in the rehabilitation program; the number of physical therapy visits; the number of meniscal resections / fixations; the number of additional surgical procedures; the type of graft used at ACL reconstruction (Table 2).

Specification of endpoints

Primary endpoint

The primary outcome will be analyzed according to intent-to-treat (ITT) and per-protocol (PP) principles. The PP population will be defined as those who participated in the rehabilitation program and stayed in the treatment arm allocated by randomization during the 2 year period (i.e. those who did not participate in the rehabilitation program and those who were randomized to treatment according to a rehabilitation protocol alone but had an ACL reconstruction during the 2 year period will be excluded from PP analysis).

The trial was initially designed as a superiority trial, i.e. to investigate if patient reported outcome and ability to return to pre-injury activity level after an acute ACL disruption is better when treated according to a rehabilitation program and an ACL reconstruction (A) than according to a rehabilitation program alone (B). In terms of a 95% confidence interval for the estimated difference in treatment effect between A and B, superiority would have been shown when the lower limit exceeded 0. During the trial, however, it was decided that the more important question is whether a treatment benefit of ACL reconstruction is sufficiently great to outweigh the additional risks and costs of surgery, i.e. if the upper limit of the confidence interval exceeds a value representing the lowest relevant effect. It was thus decided to switch the primary objective of the trial from studying superiority of A to non-inferiority of B. This decision was taken, and the value representing the lowest relevant effect was defined, prior to any statistical analysis and before un-blinding data.

Treatment effect will be determined as change in the primary outcome $KOOS_4$ from baseline to 2 years of follow up. The result will be adjusted for baseline $KOOS_4$ values.

Change within one treatment group

Clinically important difference (CID) of the KOOS has not been formally assessed. However, the KOOS questionnaire contains the full and original version of the Western Ontario McMaster's University (WOMAC) index and WOMAC scores can easily be calculated. A CID of approximately 10 points obtained for the WOMAC has previously been applied to KOOS in power analyses and when determining cut-offs for improvement and deterioration [17]. Further, KOOS data was compared to the clinical knowledge of the rehabilitation phase following ACL reconstruction. Three months postoperatively, patients experienced some pain, swelling and restriction in range of motion and had not pushed their knee during sporting activities. This was reflected by statistically non-significant changes of 1 to 7 KOOS score points in pain, symptoms, and sport and recreation function over this time interval, compared to preoperative scores. Six months postoperatively however, patients had returned to more vigorous activities including sport and had few symptoms, reflected by statistically significant changes of 8-23 score points in all subscale scores [6, 17]. Consequently, an 8 points or greater change in KOOS scores seems to represent a clinically significant change following ACL reconstruction. Based on the findings described above, we decided to use a 10 points change in $KOOS_4$ as CDI in this study.

Between groups differences

There are no publications to support a definition of relevant difference between treatment groups with regard to $KOOS_4$. The sample size calculations in this study were however based on 80% power of detecting a 10 point improvement in $KOOS_4$ after 2 years and we intend to use this limit to define the non-inferiority margin (Δ=10 points).

Non-inferiority will be tested using the two-sided 95% confidence interval (CI) of the mean change in $KOOS_4$ between the two treatment groups. Treatment according to a rehabilitation program alone will be considered to be non- inferior to treatment according to a rehabilitation protocol and an ACL reconstruction when it could be concluded that the upper side of this 95% CI excludes the non-inferiority margin (Δ).

Secondary endpoints

Secondary endpoints will be supportive to the primary endpoint, analyzed for between group differences according to ITT and PP principles.

Each separate subscale of the KOOS and both components of the SF-36 will be presented graphically for development over the 2 year period. Statistical analyses will be made between groups, separately for each subscale / component, at 2 years.

Tegner Activity Scores will be presented as median (range) for each treatment group and between groups differences will be statistically assessed at 2 years. The number of individuals returning to pre-injury activity level or higher (i.e. return to sports responders) and the number of individuals with a lower activity level after 2 years (i.e. return to sports non-responders) will be calculated and compared between groups.

The safety variable will be assessed to determine whether it represents an adverse event (AE) or not. Categorization into knee related / not knee related will be performed as well as a classification with regard to severity and possible relationship with treatment. AE will be presented in a table and analyzed using ITT and PP analysis principles.

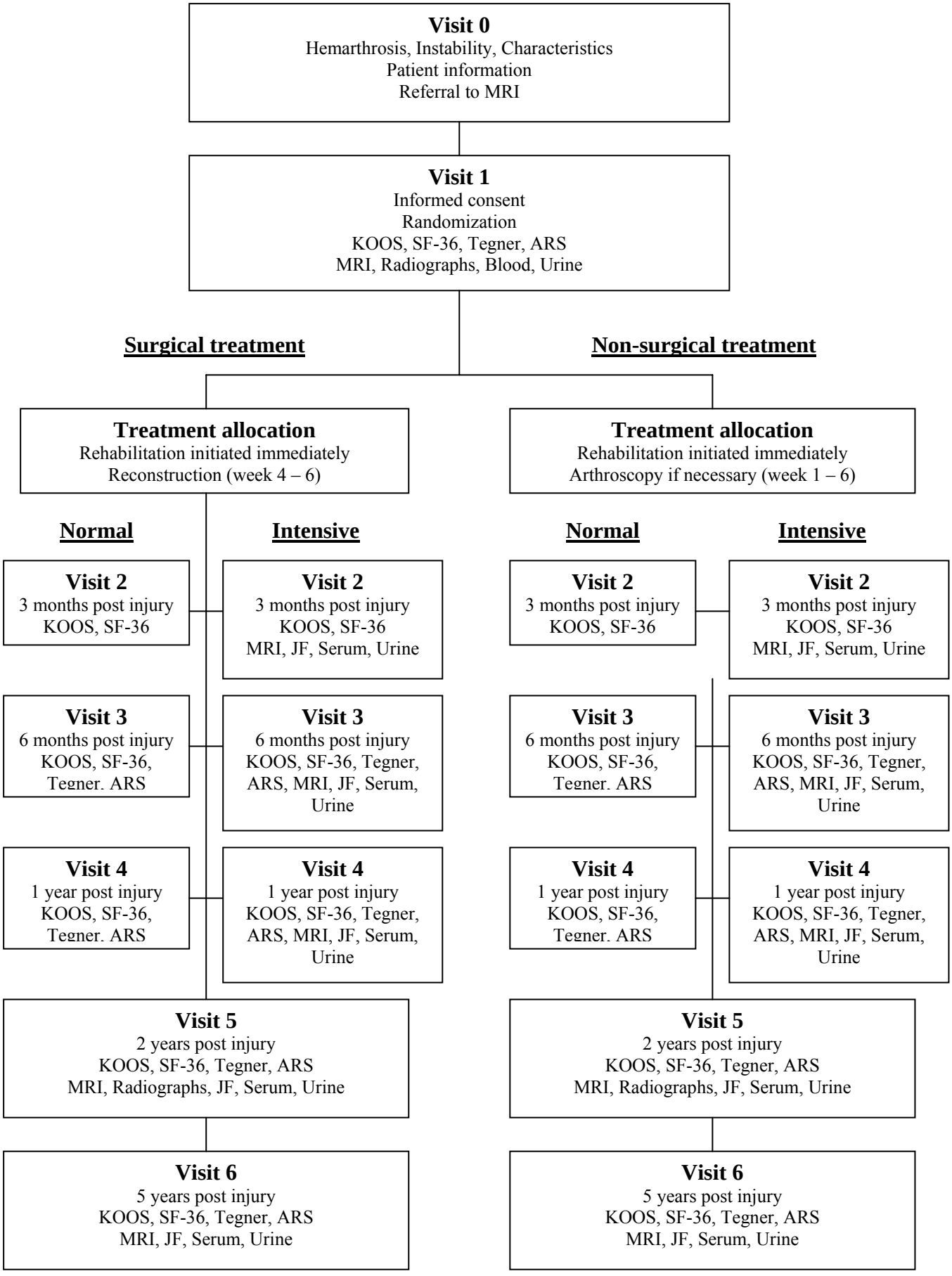

Figure 1.The course of follow-up and outcome registration in the KANON-study

3. STUDY DESIGN

Sample Size

A first sample size calculation was made prior to the start of the trial presenting an estimated sample size of 168 individuals (84 in each group). Here, we used the single $KOOS_{QOL}$ subscale and the standard deviations (SD) presented from two longitudinal trials. The power to detect a 10 point change (maximum of 100 points) was set to 80%, level of significance (alpha) was 0.05 and the calculated drop-out ratio was 20%.

A second sample size calculation was performed to justify the first at the time where approximately 25% of the sample was included in the trial. The sample size was adjusted to 100 individuals (50 in each group). The reduction in sample size was dependent of standard deviations (SD) from additional (newer) studies where it was found that SD of a total KOOS score (including all five subscales) was lower than SD for each individual subscale (≈ SD 11 for a total score versus SD 15-20 for individual scales). We also found that the drop-out ratio was low and thus decided to disregard drop-out ratio and calculated with an CID in the range of 6-11p between groups (α=0.05, SD 11-20, power to detect difference = 80%).

A last sample size calculation, based on the variables in the second sample size calculation described above, was made to test the clinical relevance and adequacy of switching from a superiority to a non-inferiority approach..

Randomization and Blinding

Stratification for activity level according to pre-injury Tegner Activity Score was an initial goal of this study. Thus, two boxes of sealed envelopes was prepared for each treatment arm and distributed to each recruiting center, one for each activity subgroup: High activity level (Tegner Activity Score 8-9); Low activity level (Tegner Activity Score 5-7). This randomization procedure was maintained during the trial although we did not meet the initial goal for stratification due to low recruitment in the low activity level group.

Annotations with unique six-figure study numbers as well as clear descriptions of treatment allocation was prepared and inserted in envelopes. Each annotation had an unique study number with a two letter- and four-digit combination where the first letter was ‘K’ for the KANON study, the second position indicated recruiting center (A for Helsingborg & C for Lund), the third position indicated activity level (1 for high activity level and 2 for low activity level), and the remaining three positions indicated the enrolment order (001--). A computer-generated randomization schedule was prepared in blocks of 20 where annotations for treatment according to a rehabilitation program alone (A) and combined with an ACL reconstruction (B) was used. Each envelope was carefully numbered according to randomization order and marked with allocated centre and stratification group. The envelopes were prepared with annotations and then sealed and ordered in blocks of 20 according to the randomization schedule. The same investigator, not involved in the randomization procedure, prepared all envelopes in the study.

At randomization an independent investigator picked the first envelope of the box for the corresponding center and activity level. For security reasons, the number of each envelope was double checked against the number of a control list attached to each box. Each

included subject opened and signed his/her unique envelope and all envelopes and annotations were saved for the monitoring of the treatment allocation procedure.

4. STUDY POPULATIONS

Subject Disposition

Recruitment strategies as well as inclusion- and exclusion criteria was published previously [18]. Those included in the trial were randomized to: A) treatment according to a rehabilitation program and an ACL reconstruction; B) treatment according to a rehabilitation protocol alone. Exclusion from the trial occurred both pre- and post randomization although the majority of exclusions will occur pre randomization. No subject could be excluded after receiving the allocated treatment [18].

For future exploratory analyses, a possibility of crossing over from the 'rehabilitation program alone' treatment arm was foreseen. Thus, a definition of 'treatment failure' in this group was developed prior to the start of this trial, in detail described in the study protocol. General criteria were: A score below 44/100p of the $KOOS_{QOL}$; a history of knee instability in activity (i.e. give-way episodes); rotational instability at rest (as assessed by the 'pivot-shift test'). A definition of 'treatment failure' in those randomized to treatment according to a rehabilitation program and an ACL reconstruction remains to be developed.

Assessment of safety variable (AE)

AE could be dependent on if the subjects underwent ACL reconstructive surgery or not and thus a separated analysis is called upon.
First, AE will be analyzed using ITT and PP as described above. Secondly, AE will be analyzed by treatment separating those undergoing ACL reconstruction during the two years and those who did not. The two groups are defined using the following criteria:

<u>AE associated with ACL reconstruction</u>

1. Those receiving ACL reconstruction by randomization
2. All treatment dependent AE reported <u>after</u> an ACL reconstruction was performed in those who had ACL reconstructive surgery in the 'Rehabilitation program alone' group throughout the follow up period

<u>AE associated with treatment according to a rehabilitation program alone</u>

1. Those remaining in the 'Rehabilitation alone' group throughout the follow up period
2. All treatment dependent AE reported <u>prior</u> to the ACL reconstruction in those who had ACL reconstructive surgery in the 'Rehabilitation program alone' group throughout the follow up period

Major Protocol Deviations

Stratification for activity level was defined in the protocol and randomization of subjects was performed according to this strategy throughout the study. We did however not reach a sufficient sample to maintain stratification due to low recruitment in the low activity group and consequently no separate analysis comparing those with a high and low activity level will be made with regard to the primary objective.

This trial was initially set up as a superiority trial and the initial sample size calculation was based on this design. Prior to data analysis we switched to a non-inferiority design, supported by a sample size calculation performed on data from previous publications.

5. STATISTICAL ANALYSIS

Treatment effect

The effect of each treatment (i.e. measured by change in $KOOS_4$ from baseline to 2 year follow up) will be adjusted for baseline values and calculated as:

Absolute, $KOOS_4$ at 2 years - $KOOS_4$ at baseline

Primary endpoint

Between groups comparisons of treatment effect as measured by change in $KOOS_4$ from baseline to 2 year follow up will be dependent on data distribution. We expect normal distribution of the change and analysis will med made using ANCOVA to adjust for baseline values. P-values and 95% CI will be presented to assess superiority and if no statistically significant difference is established, non inferiority will be assessed.

Secondary endpoints

Between groups comparisons of the 2 year outcome of all KOOS' subscales and the two components of SF-36 (mental & physical) will be handled similarly as the primary endpoint. Between groups comparisons of activity level will be made using Mann Whitney U test and return to sports responders using Chi^2 test.

6. EVALUATION OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and Baseline Characteristics

Baseline demographics (such as age, gender, BMI etc.) and characteristics (such as activity at injury, activity level, associated injuries at baseline etc.) will be presented in table (Table 1).

Medical History and Prior Medical Therapy

Subjects included in this trial had sustained an acute ACL tear in a previously un-injured knee and consequently no one had prior medical therapy for the investigated injury. All subjects were at least recreational athletes and general systemic diseases affecting physical function was an exclusion criterion.

7. EVALUATION OF TREATMENT COMPLIANCE AND EXPOSURE

Compliance to Treatment

All subjects were offered a similar rehabilitation program according to an identical rehabilitation protocol. Well-experienced PT's supervised the rehabilitation program and subjects were instructed to select a clinic from a pre-defined list of available PT's, similar for all subjects. Each PT registered all subjects who participated in the rehabilitation program as well as the number of visits for each subject. A battery of physical function tests was developed prior to the start of this trial. This battery was to be concluded prior to

the end of treatment and the rehabilitation program ended when the difference between injured / un-injured side was less than 10%.
For those randomized to an ACL reconstruction we expect to have full control of the compliance grade, registered in medical charts.

8. IMPLEMENTATION OF ANALYSIS PLAN

This SAP will be used as a work description for the statistician involved in this trial (Jan-Åke Nilsson). All analyses (including exploratory analyses not specifically described here) will be performed by the same statistician and consequently none of the investigators involved in this trial will perform any of the statistical analyses. The implementation of this SAP will be attended to as follows:

1. A 'data collection form' will be outlined in a collaboration between the database manager (Björn Slaug), statistician (Jan-Åke Nilsson) and principal investigator (Richard Frobell)
2. The database manager will code each treatment arm into 'treatment A' and 'treatment B' and thus leaving all others blinded from treatment during the analyses.
3. Blinded data will be delivered to statistician according to the 'data collection form'.
4. Primary- and Secondary endpoint analyses will be made blinded from treatment
5. Results will be presented to the steering committee of the trial (Stefan Lohmander, Richard Frobell, Harald Roos, Ewa Roos) where any uncertainties will be clarified and discussed prior to the un-blinding of data. Results will be presented and attended to in the following order:
   a. Primary outcome
   b. Secondary outcomes
   c. Exploratory outcomes
6. Exploratory analyses will be performed by the same statistician according to similar procedures as described above but after primary- and secondary analyses.

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Table 1. Baseline characteristics

	ITT		PP	
	Rehabilitation and ACL reconstruction	**Rehabilitation alone**	**Rehabilitation and ACL reconstruction**	**Rehabilitation alone**
Demographics				
Age (years), mean (SD)				
Women, n (%)				
Education				
Social status				
Work status, n (%)				
Full-time employment				
Part-time employment				
Un-employed				
Student				
Other				
Activity at injury, n (%)				
Sports				
Soccer				
Clinical				
Body mass index (kg/m^2), mean (SD)				
Stability				
Antero-posterior laxity, n (%)				
Lachmann +				
Lachmann ++ - +++				
Valgus instability > grade I, n (%)				
Range of motion				
Extension deficit > 10 degrees, n (%)				
Baseline MRI				
Total ACL rupture, n (%)				
Meniscal injury, n (%)				
Medial				
Lateral				
Cartilage defects, n (%)				

Depression fractures, n (%)				
Baseline KOOS, mean (SD)				
$KOOS_{4subscales}$				
Pain				
Symptoms				
Activities of daily living (ADL)				
Sports & Recreation				
Knee related quality of life (QOL)				
Baseline SF-36, mean (SD)				
Physical component				
Mental component				
Baseline activity level				
Tegner Activity Score, median (range)				

Table 2. Use of Physical and Surgical therapy in the study sample

	ITT		PP	
	Rehabilitation and ACL reconstruction	**Rehabilitation alone**	**Rehabilitation and ACL reconstruction**	**Rehabilitation alone**
Rehabilitation, mean (SD)				
Patients participating, n (%)				
No. of visits by participating patients, n (SD)				
Returned to sports, n (%)				
Underwent final testbattery				
Surgical therapy				
ACL reconstruction according to randomization				
Hamstringsgraft (HT)				
Bone-Patellatendon-Bone graft (BTB)				
Days from injury to ACL reconstruction				
ACL reconstruction during follow up				
Hamstringsgraft (HT)				
Bone-Patellatendon-Bone graft (BTB)				
Days from injury to ACL reconstruction				
Mensical surgery due to baseline findings				
Fixation				
Partial resection				
Complementary surgery during 2 yr follow up				
Arthroscopy				
Partial meniscal resection				
Diagnostic				
Other				
Other type of surgery				

Table 3. Outcome at 2 years

	ITT			**PP**		
	Rehabilitation and ACL reconstruction	**Rehabilitation alone**	**p-value**	**Rehabilitation and ACL reconstruction**	**Rehabilitation alone**	**p-value**
KOOS, mean (SD)						
$KOOS_{4subscales}$						
Pain						
Symptoms						
Activities of daily living						
Sports & recreation						
Knee related quality of life						
SF-36, mean (SD)						
Physical component						
Mental component						
Activity level						
Tegner Activity Score, median (range)						
Responders, n (%)						
Clinical outcomes						
Antero-posterior laxity						
KT1000 (mm), mean (SD)						
89N						
134N						
Manual max						
Lachmann, n (%)						
Negative						
+						
++ - +++						
Pivot shift, n (%)						
Negative						
Positive, grade 1						
Poistive, grade 2-3						
Valgus instability, n (%)						
Normal or grade 1						

Grade 2						
Varus instability, n (%)						
Normal or grade 1						
Grade 2						
Extension deficit, n (%)						
Normal or < 10 degrees						
> 10 degrees						