North Cumbria Integrated Care NHS Foundation Trust

HIKE

Hyaluronate [Viscoseal] Injection after Knee surgery; an Evaluation

A multi-centre, randomised, single-blinded trial assessing patient and clinical outcomes of Viscoseal injection after meniscal repair surgery

Version 1.3, dd 21 May 2021

Chief Investigator's Statement of Ownership and Content.

I, Mr Cristian Nita, confirm that this protocol is my work and is owned by me. The protocol conforms with standards outlined in the Declaration of Helsinki 1964.

Name (PRINT):_____

Signature:_____

Date: _____

RESEARCH PROTOCOL SUMMARY

TITLE:	A multi-centre, randomised, single-blinded trial assessing patient and clinical outcomes of Viscoseal injection after meniscal repair surgery
Short title:	HIKE trial (Hyaluronate [Viscoseal] Injection after Knee surgery; an Evaluation)
IRAS number	272362
Device description	'Viscoseal' , a 0.5% sodium Hyaluronate solution in a 10 ml bottle. To be administered intra-articularly. Active ingredient - Sodium hyaluronate Excipients - Sodium chloride, Sodium monohydrogenphosphate, sodium dihydrogenphosphate, water for injection. Duration of treatment: Single instillation at the end of arthroscopy and after completion of normal irrigation process. Current usage: Licensed and widely used throughout the UK and Europe for arthroscopic procedures. Viscoseal is devoid of animal proteins and hence has negligible allergenic potential.
Study type	Medical device randomised controlled trial, involving CE-marked devices used for intended purpose.
Study design	Single-centre, two-arm (1:1 allocation), single-blinded, prospective randomized trial.
Patient population	Total of 52 patients, aged 18-59 and BMI < 35, with MRI-confirmed meniscal injury who are eligible for meniscal repair surgery due to associated pain and impaired knee joint functionality. Previous knee surgery on index leg, accompanying ligament injury, and advanced knee osteoarthritis are the main exclusion criteria. For MRI imaging pilot sub-study, a total of 24 patients (out of the above 52 patients) will be enrolled.
Primary objective	To assess the efficacy of Viscoseal for reduction of post-operative pain after arthroscopic meniscal repair surgery when compared with standard care.
Secondary objectives	To assess the efficacy of Viscoseal for reduction of post-operative swelling after arthroscopic meniscal repair surgery when compared with standard care. To assess the efficacy of Viscoseal for improvement of post-operative patient-reported outcome measures, including pain upon walking and knee functionality, after arthroscopic meniscal repair surgery when compared with standard care.

	To evaluate, as part of a pilot sub-study, if there are any differences in terms of meniscus and knee joint recovery by means of radiological examination using MRI.
Sponsor	North Cumbria Integrated Care NHS Foundation Trust
Manufacturer & research grant provider	Manufacturer and distributor: TRB CHEMEDICA (UK) LTD MED IC3, KEELE UNIVERSITY SCIENCE PARK KEELE, STAFFORDSHIRE, ST5 5NP
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Organisations where research will take place	North Cumbria Integrated Care NHS Foundation Trust Orthopaedics Department, Cumberland Infirmary, Carlisle CA2 7HY, UK / Westcumberland hospital, Whitehaven, CA28 8JG, UK [CI Mr Cristian Nita] The Royal Orthopaedic Hospital NHS Foundation Trust, Bristol Road South, Northfield, Birmingham B31 2AP [PI Mr Tanweer Ashraf] Warrington & Halton Hospitals NHS Foundation Trust, Lovely Ln, Warrington WA5 1QG [PI Mr Curtis Robb]
Planned timeline	Recruitment start date (first patient, first visit) 1 Jan 2020 Recruitment end date (last patient, first visit): 1 July 2022 Recruitment end date (last patient, last visit): 1 Jan 2023
Protocol version, date	Version 1.3, dd 21 May 2021

1. CONTENTS

1. LAY SUMMARY

Arthroscopic, or keyhole, surgery of the meniscus in the knee joint has benefits over open surgery. Nonetheless, there is scope to further improve outcomes for patients by reducing pain and discomfort and promoting enhanced recovery of knee joint functionality. The medical device Viscoseal contains hyaluronan and is designed to replenish levels of this compound in the knee joint following arthroscopic repair of the meniscus. Naturally, synovial fluid in the knee joint contains hyaluronan, but a lot of it is washed away when surgeons flush the knee joint during surgery to remove loose pieces of meniscus, cartilage, or bone. Previous studies, both in laboratory studies and patient trials, have demonstrated that Viscoseal can promote re-establishment of biological structure in the knee joint to allow it to return to a normal physiological state and protect cartilage. This present prospective, randomised, controlled trial aims to build on this evidence by comparing standard care versus the injection of Viscoseal (26 vs 26 patients) at the end of arthroscopic meniscus surgery. The degree of pain, leg swelling and knee functionality experienced by patients after surgery will be measured using validated patient surveys focused on the meniscus. The main objective is to determine if Viscoseal can achieve a minimal clinically important difference in pain relief after meniscal repair surgery when compared to standard care.

2. INTRODUCTION

Arthroscopic surgery confers significant benefits on the recipient over and above those associated with open surgical procedures. The technique offers less insult to the structures being operated on and the surrounding architecture, decreases the risk of complication and infection, and reduces pain, hospitalisation time, and recovery time. The knee is the largest synovial joint, with a shared capsule enveloping the medial tibio-femoral (MTF), lateral tibio-femoral (LTF), and patella-femoral (PTF) compartments. The knee affords a number of congruent articulations where degenerative or traumatically induced changes may manifest. Arthroscopic knee surgery is a widely practised operation used to remove osteophytes, calcium pyrophosphate dehydrate (CPPD) deposition, and loose bodies. Debridement of irregular condylar surfaces may also be effected during this type of procedure. The knee houses meniscal structures composed of fibrochondrocytes enveloped in a matrix containing highly oriented Type 1 collagen fibres. Damage to these structures can be treated, the objective of meniscal repair being to obtain not only a stable but also a completely healed tear. However, where repair is not possible or practicable, meniscectomy can also be carried out arthroscopically.

As with any surgical intervention there can be side effects associated with arthroscopy, primarily these are pain, swelling and loss of joint mobility; surgical trauma can contribute to this [1,2,3] Usually 1 -2 litres of saline is used as an irrigating medium during a simple arthroscopic procedure. Because the irrigation solution washes out the synovial fluid (SF) that resides in all synovial joints, the protective and lubricating functions of the SF are temporarily absent, and several days may elapse before the joint begins to replace the fluid that has been lost. Additional problems arise due to the fact that irrigation solutions may have a negative effect on the metabolism of articular cartilage (1-3), and reduced mobility due to arthroscopy may lead to decreased production of endogenous hyaluronan. Further deleterious processes, brought about by the commonly practised instillation of intra articular local anaesthetic at the end of the procedure, reportedly deplete cartilage integrity, and compromise chondrocyte synthesis and disrupt collagen structures in hyaline matrices. (4-7).
Hyaluronan is a normal vital constituent of both articular cartilage and synovial fluid. It is an unbranched high molecular weight polysaccharide belonging to the family of glycosaminoglycans. A major role of Hyaluronic Acid (HA) is to maintain the structural and functional characteristics of the extra-cellular matrix of articular cartilage, and - in its unaggregated form – polymerise the synovial fluid. It is ubiquitous throughout the human system in the interstitial space [8]. Viscoseal (TRB Chemedica) is a 0.5% concentration, isotonic solution of hyaluronan of fermentative origin. It is designed as a synovial fluid substitute for use following arthroscopic surgery or joint lavage. Instilled into the joint immediately after surgery, Viscoseal purportedly acts as a temporary substitute for the synovial fluid (SF) that has been lost during arthroscopy, performing the lubricating, shock absorbing and filtering functions of this fluid. In addition, it displaces any irrigating solution left in the joint space, preventing impairment of cartilage metabolism.

The introduction of Viscous Sodium Hyaluronate into the joint space re-establishes the protective coating of Hyaluronan over the surface of the articular cartilage and synovial membrane. By replacing the superficial layer of viscous Hyaluronan on the intima of the synovium, potential innervation of pain receptors is reduced. This reduction in pain helps to enhance joint mobility, which in turn promotes the production of endogenous Hyaluronan.

Sodium Hyaluronate has been used extensively in the treatment of osteoarthritic joints. Intra-articular injection of exogenous hyaluronan has been demonstrated to be useful in relieving pain and improving function in degenerative knee joints in randomised controlled trials. The benefits persist for approximately 6 months, with no serious adverse effects. [8,11,12,13,14]. In addition, reports have shown that exogenous hyaluronan promotes tissue healing [15,16] and protects articular cartilage and synovial membrane from damage following the experimental initiation of joint disease [17]. Exogenous hyaluronan has been used following arthroscopy in other joints, demonstrating significant benefits with no reported complications [18,19]. Randomised trials involving the administration of Viscoseal in meniscal repair and meniscectomy surgery also demonstrated positive effects. Early and medium term pain experienced by patients was lower in those treated with Viscoseal. Furthermore, post-operative leg swelling was reduced in the two weeks following the procedure when compared to patients who had not received Viscoseal [20-21]. One study failed to see an effect of HA on recovery after partial meniscectomy [22]; however, patients only received 24 mg of HA (Hymovis 24 mg/3 mL; Fidia Farmaceutici SpA) whereas the Viscoseal dose is 50 mg (10ml at 0.5%). Another limitation of that particular study is that some of the outcome measures were not optimal for meniscal surgery, such as the Knee injury and Osteoarthritis Outcome Score (KOOS) which is primarily used for knee replacement surgery. The same measure was used by Thein et al [20], and they could not detect a difference between control and Viscoseal cohorts either. HA, through application of Hymovis, may even contribute to reduced pain and a degree of meniscal tear healing when it is administered as a conservative treatment without surgical intervention [23]

This present study further investigates the effects of instilling 10ml of a 0.5% Sodium Hyaluronate of fermentative origin (Viscoseal) into the capsule at the end of arthroscopic meniscal surgery. By displacing residual saline and debris from the surrounding soft tissue and exposed cancellous bone, and establishing a viscous, protective barrier over localised nociceptors, it is hypothesised that a more favourable patient outcomes – as evinced by meniscus-specific validated scoring instruments - will be achieved.

3. INVESTIGATIONAL DEVICE & INTERVENTION

3.1 Investigational device

'Viscoseal' is a 0.5% sodium hyaluronate solution in a 10 ml bottle. It is administered intra-articularly as a single instillation at the end of arthroscopy and after completion of normal irrigation (lavage) process. The active ingredient is sodium hyaluronate, and the excipients are sodium chloride,

sodium monohydrogenphosphate, sodium dihydrogenphosphate, and water. The product is licensed and widely used throughout the UK and Europe for arthroscopic procedures. Viscoseal is devoid of animal proteins and hence has negligible allergenic potential.

3.2 Intervention

3.2.1 Standard care (control) arm

All patients receive general anesthesia and a pneumatic tourniquet is used. Patients are already randomised prior to surgery to avoid delays with surgery and allow a vial of Viscoseal to be ready for the relevant patients. Joint irrigation is performed with the assistance of a manual arthroscopic pump using 0.9% NaCl solution at room temperature. Then, the remaining fluids are drained from the knee. At the end of the surgery, local anaesthetics is applied to the soft tissue of the arthroscopic portals [either 20 ml 0.5% Levobupivacaine (Chirocaine®), or 20 ml 0.75% Ropivocaine (Naropin®), or equivalent product], and the knee is dressed, while the tourniquet is still inflated. All surgeries are intended to be performed in a day-surgery facility with the patient being discharged the same day. Postoperatively, partial weight bearing with crutches is allowed. Crutches are recommended for the first 48 hours, primarily for patient safety by minimising the risk of a fall.

3.2.2 Viscoseal (intervention) arm

Apart from the difference in terms of Viscoseal administration to the intervention group, the surgical protocol for the Viscoseal arm is identical to that of the standard care group. At the end of the surgery, again all the remaining fluids are drained from the knee, but this is followed by injection of 10 mL of Viscoseal preparation. Used Viscoseal product and syringes will be disposed of in line with local guidelines on disposal of clinical waste.

3.2.3 Magnetic Resonance Imaging

A subset of 24 participants will also undergo an additional MRI at 26 post-surgery to determine the morphology and status of the meniscus radiologically. This MRI will be as the one that all patients undergo as part of diagnosing the meniscal injury prior to surgery. Apart from consenting to the MRI sub-study as part of HIKE, patients will also provide consent separately for the MRI procedure itself. The protocol for meniscus imaging has been described previously [24]. A 1.5-Tesla Siemens Avanto scanner will be used for this purpose to obtain sagittal T1, sagittal PDFS, coronal STIR, coronal PDFS and axial T2 GRE images.

4. STUDY HYPOTHESIS

4.1 Primary objective

- To assess the efficacy of Viscoseal for reduction of post-operative pain after arthroscopic meniscal repair surgery when compared with standard care.

4.2 Secondary objective

- To assess the efficacy of Viscoseal for reduction of post-operative swelling after arthroscopic meniscal repair surgery when compared with standard care.
- To assess the efficacy of Viscoseal for improvement of post-operative patient-reported outcome measures, including pain upon walking and knee functionality, after arthroscopic meniscal repair surgery when compared with standard care.
- To evaluate, as part of a pilot sub-study, if there are any differences in terms of meniscus and knee joint recovery by means of radiological examination using MRI

5. STUDY PROTOCOL

5.1 Study design, recruitment sites and timeline

This concerns a single-centre, controlled prospective randomized study of CE-marked medical devices. The study will be carried out in the following NHS Trust:

- North Cumbria University Hospitals NHS Trust, both Cumberland Infirmary, Carlisle, and West Cumberland Hospital, Whitehaven. CI/PI Mr Cristian Nita

The study will take place in a hospital setting with support and oversight from the treating orthopaedic surgeon, nursing staff and research staff. Where appropriate, research delivery staff will be delegated to provide support with data collection and processing.

Table 1. Anticipated timeline

Month	Setup	Recruitment	Analysis	Finalise
Oct-19	Submission for HRA approval			
Dec-19	NIHR portfolio adoption			
Dec-19	HRA and Trust approval			
Jan-20		Start recruitment		
Jul-22		Finish recruitment		
Jan-23			Follow-up complete; Analyse data.	
Feb-23				manuscript & report writing complete

5.2 Participant identification and research setting

Participants will be recruited from orthopaedics clinics and all eligible patients will be invited to take part until the required numbers have been achieved. Identification will be by the orthopaedics

clinical team, who are supporting the study. A screening form will be completed for potentially eligible patients to confirm that they indeed meet the trial criteria.

To summarise, the orthopaedic team will:

- Identify potentially eligible patients and ask verbal consent for them being approached about the study by a member of the R&D team
- Complete the incl/excl criteria part of the screening form (if a patient has given verbal consent to being approached by the research team then they can complete the screening form)

5.3 Consent and recruitment

Those eligible will be approached and provided with an information pack and consent form, which will be signed to indicate that informed consent has been given. Patients will be given ample time to consider taking part, more than 24 hours if they wish. The study will be first mentioned at an orthopaedics out-patient clinic visit. The direct healthcare professional will first approach a patient about the study, and after verbal consent by the patient the healthcare professional themselves or a member of the research team can go through the informed consent process.

Patients are also allowed to consent to taking part when first approached as long as the study has been discussed with the patient and they have been given time to read the patient information leaflet and opportunity to ask any questions that they may have. Participants will receive no incentives and consent will be regarded as a process and not a one-off event. Participants are free to withdraw from the study at any time without the need to give any reasons for withdrawal. Their standard of care will not be affected by either declining to participate in the study or withdrawing during participation. Data collected up to the date of withdrawal will be retained for analysis.

Participants will be randomised to either the treatment as usual (TaU) or the intervention group (Viscoseal) any time up until the day of surgery. Study subjects who subsequently require additional significant surgical intervention, primarily ligament reconstruction, will be withdrawn from the study.

The MRI sub-study will be offered to all patients consecutively, and this will be done until the 24 required patients for said sub-study have been recruited.

5.4 Follow-up

Patients are in the study for a period of 26 weeks. Thereafter, the patient will be followed up as they would be in normal clinical practice. Two study follow-up visits are aligned to hospital/clinic visits and the other are done remotely. Baseline data can be collected on the day of surgery (prior the actual operation), and 48 hrs, 7 days, 14 days and 12 weeks post-surgery data can be collected when the patient attends for standard follow-up in the orthopaedics out-patient department. The data at week 26 falls outside these dates. In these instances, data can be collected over the phone, via e-mail or by mail (whichever is preferred by the patient – mail is by use of freepost, to avoid patients incurring any costs). The researcher will ask/phone/e-mail/mail the participant at each follow-up time point to check on any adverse event reporting, and if consented by the patient can

also send reminders to the participant regarding the completion of certain outcome data at the aforementioned follow-up time points.

5.5 Outcome measures

5.5.1 Primary outcome measures

To determine the level of index leg related pain experienced at day 7 post-operation and to compare the average pain scores of patients in the control and Viscoseal arm respectively, through administration of 100 mm visual descriptor scale (VDS) for pain at rest.

The study is powered to detect the established minimal clinically important difference (MCID) of 15 mm on a 100 mm VDS pain.

5.5.2 Secondary outcome measures

All the outcome measures are summarised in Table 2.

Table 2. Overview of measurements

Weeks	-12 weeks to day of surgery	48 hours	7 days*	14 days*	12 weeks#	26 weeks~
VDS pain scale for knee (at rest)	X	X	X	X	X	X
VDS pain scale for knee (walking)	X				X	X
McGill pain questionnaire (at rest)	X	X	X	X		
Limb girth measurement (index leg)	X			X	X	
Lysholm scale	X				X	X
WOMET tool	X				X	X
Use of analgesics / anti-inflammatories	X	X	X	X	X	X
Patient satisfaction questionnaire re surgery						X
MRI scan (sub-study; not all participants)						X

** Allowed to be up to 2 days early or late*

 # Allowed to be up to 2 weeks early or late

~ Allowed to be up to 4 weeks early or late

5.5.3 MRI sub-study outcomes measures

Assessment of length and depth of meniscal tears will be performed by a radiologist using MRI at baseline and 26 weeks after surgery. The radiologist will be blinded to the patients' study allocation. The following standard grading system will be used to describe abnormal intrameniscal signals: Grade 1 – the signal is oval or globular in appearance and does not communicate with any meniscal surface; Grade 2 – the signal is a more linear but, similarly, does not communicate with the articular surfaces; Grade 3 – the signal, located within the meniscus, is linear and should communicate with either the superior or the inferior articular surfaces. Grade 1 and 2 signals are consistent with intrasubstance myxoid degeneration, whereas a Grade 3 signal is consistent with a tear.
Tear patterns will be classified as longitudinal (located anywhere along the meniscus), horizontal (begins at the inner margin of the meniscus and extends towards the capsule), radial (begins at the inner margin and extends towards the capsule) or flap (either a vertical flap tear or a horizontal flap tear). By comparing the follow-up MR images with the baseline images, the presence or absence of a reduction in length and depth of the lesion can be identified. The occurrence of a new lesion with respect to baseline will be considered as a deterioration/recurrence and recorded as an adverse event. Reductions in the length and depth of the meniscal tear subsequent to baseline, assessed radiologically, were measured in relation to the index tear evaluated at baseline.

6. SUBJECTS

6.1 Anticipated number of research subjects

The sample size calculation does take into account a 10% patient attrition rate (withdrawal and loss to follow-up), since this involves a study with multiple time points for data collection up to 26 weeks. Patients will be recruited from the adult population routinely seen by the evaluating clinical staff members. The primary outcome measure is based on knee/leg (ie wound site) pain experienced 7-days post-surgery based on the VDS pain scale (with leg at rest). The hypothetical difference in pain perception, based on a previous publication involving meniscal repair and Viscoseal, is 15mm on a 100 mm scale which equates to a significant 'minimally clinically important difference' for pain (Kelly 2001; Lee et al 2003; Tashjian et al 2009).

The non-parametric two-sided Mann-Whitney u-test is applied because the data is ordinal; 80% power and 5% significance is also applied. A priori power calculations using GPower 3.1 software, result in the following sample size summarized in Table 3.

It involves a minimum total of **52 participants**, who undergo meniscal repair surgery. Randomised 1:1, therefore 26 patients per arm.

Table 3, Sample size calculation

	Mean pain score (mm) at 7 days post-op~	**Standard Deviation (hypothetical)**
Viscoseal	28	20
Standard care	43	20

	Power beta of 80%, Alpha p-value of 0.05, Effect size 0.75 Sample size required without any drop-out: 48 samples. Sample size with 10% attrition rate included: 52 **Total of 52 patients:** • **26 Patients to receive standard care** • **26 Patient to receive Viscoseal**
~Based on Thein et al, 2010	

For the MRI imaging sub-study a total of 24 patients will be recruited, 12 controls and and 12 viscoseal patients. This is in line with guidelines on pilot studies [25].

The CONSORT guidelines require a statement on the number of patients assessed for eligibility (Schulz, Altman & Moher 2010). The number of patients screened but who did not meet the inclusion criteria or who declined to participate will be recorded, as will any patients who are lost to follow-up (Appendix 3).

6.1.1 Randomisation

Following written consent, participants are allocated at random to the control or Viscoseal intervention group, using a randomised sequence from the freeware randomisation programme, see https://www.randomizer.org/ .

To take into account that not all patients will consent to taking part in the MRI sub-study, two randomisation sequences will be produced. One for patients who consent to both trial and MRI sub-study and one for patient who only consent to the main trial. This means:

- 24 patients for main trial + MRI sub-study (12 control and 12 Viscoseal)
- 28 patients for main trial only (14 control and 14 Viscoseal).

In this manner both control and Viscoseal arms are equally represented in the MRI sub-study and the remaining patients for the main trial are also equally distributed amongst the two study arms.

If one of the two randomisation blocks is full, then only the remaining block will be recruited to. However, North Cumbria Integrated Care is the only NHS Trust to conduct the MRI-substudy.

Sequential envelopes with each next randomisation allocation (for each randomisation block) will be used to achieve concealment and these will be kept in the research department. The researcher or regular healthcare professional for the participant in question can e-mail (research@ncic.nhs.uk) or phone the R&D Dept (01228 602173) to determine which treatment the next participant has been allocated to.

6.2 Eligibility criteria

6.2.1 Inclusion criteria

- Patients has mechanical symptoms and pain and MRI evidence of meniscal tear, amenable to surgical repair
- Meniscal surgical repair of the knee for meniscal tear grade III
- Proficient in English (reading and writing, due to surveys being sent electronically)
- Adult patients aged > 18 years and < 60 years
- Mental capacity to give written informed consent and follow trial measurements

6.2.2 Exclusion criteria

- Under the age of 18 years or over 59 years
- Unable to fully understand the consent process and provide informed consent due to either language barriers or mental capacity
- Menisectomy
- Previous surgery on affected knee
- Progressive joint disease (osteoarthritis of the affected knee, Kellgren & Lawrence grade 3 or above),
- Accompanying hip osteoarthritis of sufficient severity to interfere with the functional assessment of the knee;
- Known or suspected infection of the affected joint;
- Painful knee conditions other than osteoarthritis, such as rheumatoid diseases (RA, gout);
- Other joint diseases or previous management of the operated knee within the last year that might interfere with the assessment of the meniscal repair
- Limited life expectancy, i.e. undergoing palliative care
- Any condition that is associated with excessive bleeding, coagulation abnormalities or any other significant haematological condition (e.g. Factor V Leiden, haemophilia).
- Patients who are participating in another interventional research study involving an investigational product related to the knee surgery procedure and its aftercare.
- The patient has concurrent (medical) conditions that in the opinion of the investigator may compromise patient safety or study objectives.
- BMI > 35 (Patients with BMI>35 are not suitable for day surgery and their pathway of care would differ significantly from the majority group BMI<35 hence the restriction)
- Known hypersensitivity to hyaluronic acid, other constituents of Viscoseal, marcaine, codydramol
- Any auto-immune disease that affects the limbs, such as rheumatoid arthritis, treated with immune-modulating drugs.
- Inflammatory arthropathy.
- Co-existing condition that significantly impacts on usual daily activities (including, but not limited to, lower limb amputation, cancer, neurodegenerative disease, or other condition that leaves patient invalid or to use a wheelchair) as assessed by recruiting clinician.
- Contraindications for MRI diagnostics (see https://radiology.ucsf.edu/patient-care/patient-safety/mri/absolute-contraindications) since qualifying meniscal injury pre-surgery needs to be demonstrated by MRI.

6.3 Early withdrawal of subjects

Patients have the right to withdraw from the trial at any time and without giving any reason. If a patient withdraws from the trial, any and all information gathered prior to the withdrawal will be excluded in the analysis, no further data collection will occur. If a patient does not attend a planned follow-up appointment then two more attempts will be made to contact the patient regarding the study. If still no contact can be made then the patient is deemed lost to follow-up and any collected study data will be retained.

As mentioned in section 5.3, study subjects who subsequently require additional significant surgical intervention, primarily ligament reconstruction, will be withdrawn from the study.

7. SAFETY

7.1 Potential risks & benefits to study participants

There is no anticipated personal safety risk associated with taking part in this study. If the research team learns of important new information that might affect the patient's desire to remain in the study, he or she will be told. Appropriate precautions are in place to ensure medical and personal information is kept safe through adhering to appropriate governance regulations. Any adverse events will be recorded, as outlined in sections below.

For the participants in the control group there is no direct benefit in taking part in this study. They will be cared for in exactly the same manner as they normally would. For participants in the Viscoseal intervention group, there may be benefits in terms of improved recovery and reduced pain compared to normal standard care. Although there is initial evidence that this is indeed the case, this has not yet been proven and established through a prospective randomised trial, and this study is aimed to assess this. Participants cannot claim payments, reimbursement of expenses or any other benefits or incentives for taking part in this research.

7.2 Safety definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or other clinical investigation participant taking part in a trial of a medical device, which does not necessarily have to have a causal relationship with the device under investigation. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the device, whether or not considered related to the device.
Serious Adverse Event	A serious adverse event is any untoward medical occurrence that: - results in death - is life-threatening

- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

7.3 Procedures for recording adverse events

All SAEs need to be reported to the sponsor/host Trust R&D **within one working day** of the investigator team becoming aware of them – AEs should be reported on within two weeks of becoming aware of them. For this purpose an AE report form is completed by the researcher and/or Chief Investigator

The relationship of each adverse event to the trial must be determined by the Chief Investigator, a medically qualified individual, according to the following definitions:

- **Related**: The adverse event follows a reasonable temporal sequence from swabbing. It cannot reasonably be attributed to any other cause.
- **Not Related**: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.
- **Severity grading**: the Chief Investigator will also record if it concerns an AE or SAE.

This is recorded on the aforementioned AE reporting form. The forms are stored in the study site file.

Pseudo-anonymised copies of all adverse events forms will be shared with TRB CHEMEDICA (UK) LTD as soon as causality reporting has been performed and concluded.

8. STATISTICAL CONSIDERATION AND DATA ANALYSIS PLAN

8.1 Analysis of baseline characteristics

To determine the demographics and characteristics of the patients in the two arms the following data will be collated:

- Age (yrs)
- Gender

- Height (kg), weight (cm), BMI

Distribution of data will be summarised but no inferential statistics will be applied in line with guidance [26].

Data concerning the actual meniscal repair procedure will also be collected, including:

- Exact meniscal surgery carried out (repair, partial meniscectomy, complete meniscectomy)
- Length of operation (min) and blood loss (ml) during operation
- Details on lavage procedure, if deviation from standard procedure.
- Type of anaesthetic and analgesics prescribed post-surgery
- Hospital length of stay (days)
- Moment physiotherapy and early recovery initiated, if applicable
- Any analgesics and/or anti-inflammatories administered and/or prescribed.

Any differences in distribution will be established with Chi-squared test or Mann-Whitney U-test/t-test (depending on distribution of data) as indicated.

8.2 Primary outcome statistics

To determine the level of operation-site related pain – at rest - experienced at day 7 post-operation (plus day 2, day 14, week 12 and week 26) and to compare the average pain scores of patients in the control and Viscoseal arm respectively, through administration of 100 mm visual descriptor scale (VDS) for pain. To compare the groups, the Mann-Whitney U-test will be applied.

The study is powered to detect the established minimal clinically important difference (MCID) of 15 mm on a 100 mm VDS pain.

In addition, VDS scale will be used for pain upon walking.

To avoid relying on one outcome measure related to pain, at 7 and 14 days post-surgery pain perception will also be measured using the short form McGill pain questionnaire. Again, to compare groups the Mann-Whitney U-test will be applied.

8.3 Secondary outcome statistics

The average baseline demographics for participants in each group will be compared to ascertain that randomisation has indeed led to comparable distribution of participants:

Sex, age, height, weight, BMI, length of stay, type of anaesthetic for surgery and type of analgesics post-surgery.

To compare outcomes between the two groups (standard vs Viscoseal), student t-test, Mann-Whitney U-test or Chi-squared test will be applied as applicable, depending on type and distribution of data .

Cox proportional hazards regression analysis will be conducted to investigate the role of Viscoseal and other covariates (as mentioned above) in post-surgery related pain, swelling and knee function.

The statistics apply to:

At least 2 weeks prior to surgery, and 7 days and 14 days post-surgery

- Indication of degree of swelling by measurement of thigh, suprapatellar and calf girth.

Up to 12 weeks prior to surgery, 12 weeks and 26 weeks post-surgery, knee function measurements: Lysholm and WOMET tools.

Descriptive safety overview post-surgery up to 26 weeks:

- Readmitted to theatre and/or hospital
- Infection of wound site
- Diagnosed with pulmonary embolism or deep vein thrombosis.

Patient satisfaction survey at 12 weeks and 26 weeks post-surgery – any difference in outcome will be determined with Mann-Whitney U-test

MRI diagnostics outcomes:

Descriptive statistics, primarily frequencies and averages, to summarise per intervention arm

- Type of injury
- Size of injury
- Grading of injury
- Any recurring or new meniscal injury

9. DATA HANDLING AND MONITORING

Data arising from this study is confidential. Identifiable information can only be accessed by delegated members of the study team. Anyone in the research team who does not have a substantive contract with North Cumbria Integrated Care NHS Trust or one of the recruiting NHS Trusts will need to apply for a letter of access via the NIHR research passport scheme, should they require access to identifiable study data.

Patient identifiable data will only be used within each respective Trust and by the core research team. All identifiable data is stored on password protected NHS computer systems. Anonymised data will be shared and stored using security-enabled systems such as password-protection and encryption of e-mails and files. The requirements of the Data Protection Act and NHS Code of Confidentiality will be followed at all times. All researchers will be fully trained in NHS Confidentiality and GCP. Participants' GP practices will be informed that they are taking part in the study.

All paper data will be held in secure locked environments in the office of the Research & Development department at the Cumberland Infirmary, Carlisle, North Cumbria Integrated Care. Data released (e.g. by publication) will contain no information that could lead to the identification of an individual participant. Upon completion of the study the site files will be archived for a period of 15 years in line with local archiving policy and procedures. Direct access to data only will be granted to authorised representatives from the sponsor / host institution, grant funder and medical device provider (TRB Chemedica UK) and the regulatory authorities to permit trial-related monitoring, audits and inspections.

This investigator-initiated trial will be monitored in terms of conduct of the study by the in-house research team, led by the Chief Investigator, who will convene on a monthly basis in person or via phone/e-mail. A formal trial steering committee will not be convened for this trial – however, when data is available for 50% of the sample an interim analysis will take place to assess if there are any points of concern to consider. The study can be audited by the in-house R&D department as part of their rolling audit programme of sponsored and hosted research studies. As part of the research grant agreement, anonymised study data will be shared with TRB Chemedica UK for review and for potential publication purposes. No identifiable data, including on potential exemplar case photos, will be contained in any of this data.

10. GOVERANCE OF STUDY

10.1 Approvals

This study will be conducted in compliance with the protocol approved by the Health Research Authority, National Research Ethics Service, and local Trust R&D Approval, and according to Good Clinical Practice standards including the Declaration of Helsinki (1964, Amended Oct 2013). No deviation from the protocol will be implemented without the prior review and approval of the aforementioned review bodies, except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported according to policies and procedures

10.2 Sponsor & Indemnity

North Cumbria Integrated Care NHS Trust is the sponsor of this study and therefore NHS indemnity applies for design, conduct and management of the study. TRB CHEMEDICA (UK) LTD has provided a grant for this study by means of provision of the Viscoseal medical devices and a non-restricted grant worth £6,000.

Patients will not be given financial incentives for taking part in the study. Travel expenses are not offered in this study since patients are not seen in clinic more frequently than they would normally attend as part of their normal care pathway.

11. PUBLICATION AND DATA-SHARING POLICY

The study will be registered on ISRCTN or Clinical Trials Gov website, in line with CONSORT guidelines on good practice in clinical research.

The results of this study are planned to be disseminated through:

- Peer-reviewed manuscript in scientific journal
- Internal report to the funder of the trial, TRB CHEMEDICA (UK) LTD

As stated in the PIL and ICF, anonymised study data will be shared with TRB CHEMEDICA (UK) LTD as part of the research grant agreement.

A summary of the main findings can be supplied to participants on request and this will be stated in the informed consent form.

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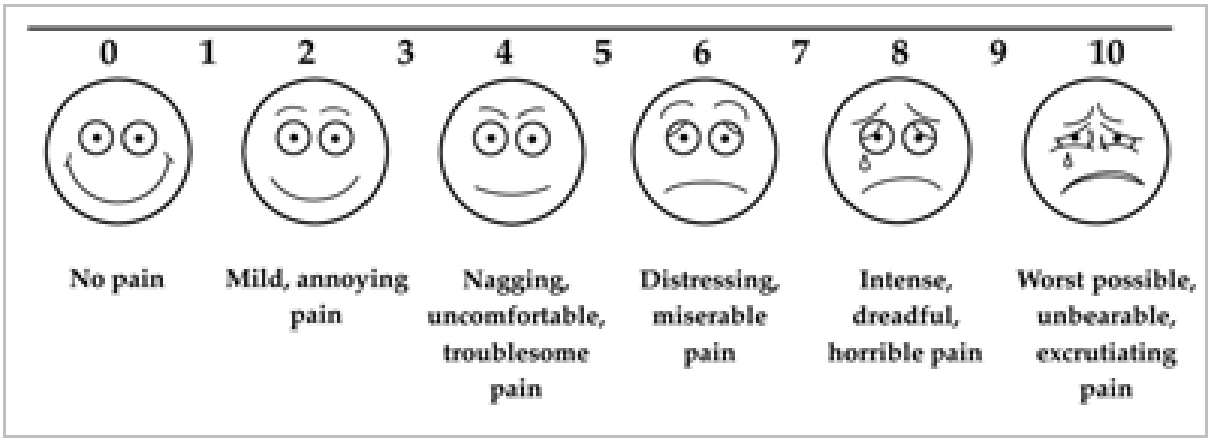
APPENDIX 1. TOOLS AND ASSESSMENTS

This appendix contains:

- Visual Descriptor Pain scale
- Short-form McGill pain questionnaire [27]
- Lysholm scale [28]
- Limb girth measurement
- WOMET tool – enclosed as a separate document [29]

Visual Descriptor Pain score

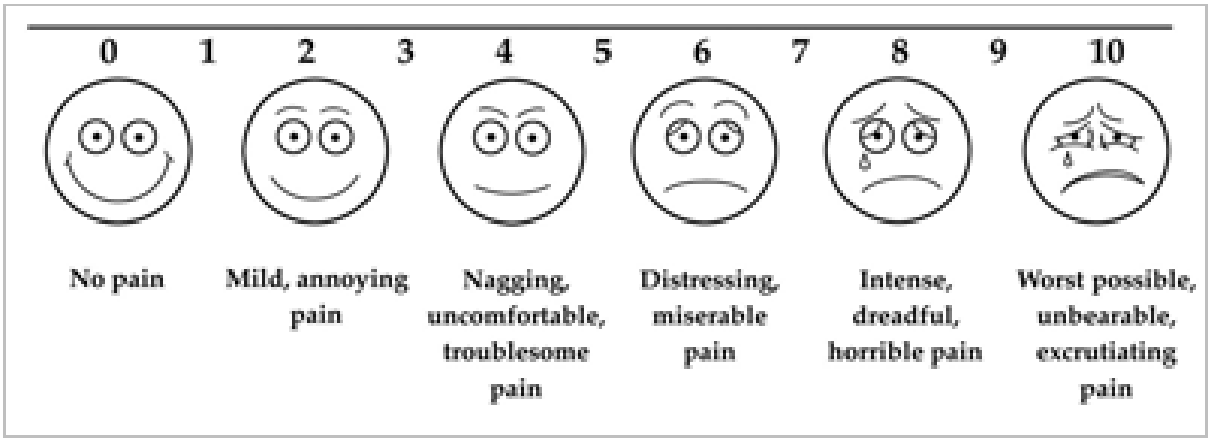
How painful has your leg, the one has been operated on, been in the last **2 days when resting**:



Please put a vertical line on the numbered bar above. We kindly ask you consider the affected knee when you answer this question.

Visual Descriptor Pain score

How painful has your leg, the one has been operated on, been in the last **2 days when walking**:



Please put a vertical line on the numbered bar above. We kindly ask you consider the affected knee when you answer this question.

Short-form McGill pain questionnaire

PATIENT'S NAME: _____ DATE: _____

	NONE	MILD	MODERATE	SEVERE
THROBBING	0) _____	1) _____	2) _____	3) _____
SHOOTING	0) _____	1) _____	2) _____	3) _____
STABBING	0) _____	1) _____	2) _____	3) _____
SHARP	0) _____	1) _____	2) _____	3) _____
CRAMPING	0) _____	1) _____	2) _____	3) _____
GNAWING	0) _____	1) _____	2) _____	3) _____
HOT/BURNING	0) _____	1) _____	2) _____	3) _____
ACHING	0) _____	1) _____	2) _____	3) _____
HEAVY	0) _____	1) _____	2) _____	3) _____
TENDER	0) _____	1) _____	2) _____	3) _____
SPLITTING	0) _____	1) _____	2) _____	3) _____
TIRING/EXHAUSTING	0) _____	1) _____	2) _____	3) _____
SICKENING	0) _____	1) _____	2) _____	3) _____
FEARFUL	0) _____	1) _____	2) _____	3) _____
PUNISHING/CRUEL	0) _____	1) _____	2) _____	3) _____

VAS NO PAIN ——— WORST POSSIBLE PAIN

PPI

0 NO PAIN _____
1 MILD _____
2 DISCOMFORTING _____
3 DISTRESSING _____
4 HORRIBLE _____
5 EXCRUCIATING _____

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The short-form McGill Pain Questionnaire (SF-MPQ). Descriptors 1–11 represent the sensory dimension of pain experience and 12-15 represent the affective dimension. Each descriptor is ranked on an intensity scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe. The Present Pain Intensity (PPI) of the standard long-form McGill Pain Questionnaire (LF-MPQ) and the visual analogue scale (VAS) are also included to provide overall intensity scores.

The McGill Pain Questionnaire: Major properties and scoring methods . Melzack, 1987

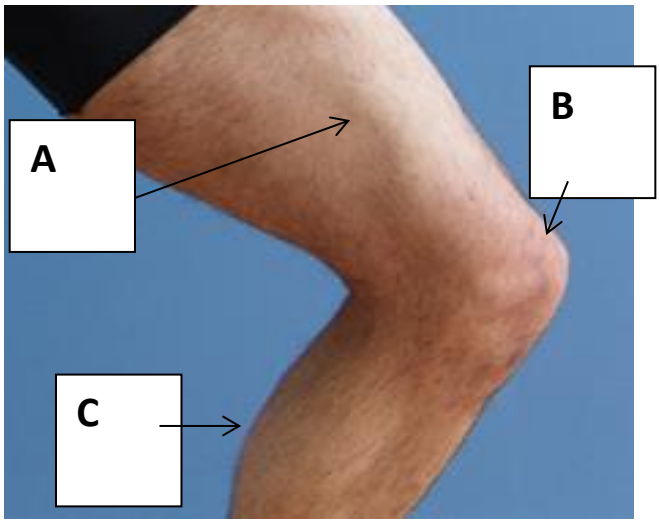
Limb girth measurement

There are three places to measure the leg please, see picture below for reference points. Before your surgery, the first measurements will be done by the researcher, so that you can see where exactly the measurements are done. Once done and recorded, please return the completed form with other completed questionnaires to the HIKE study team, using provided FREEPOST envelope (no stamp needed) :

A- **Thigh –** from top of your kneecap, move up 10 cm and then measure around your thigh **(**ie thigh circumference 10 cm above suprapatellar border)**_____(cm)**

B- **Top of kneecap** – with leg stretched, or if not possible in position as in picture below, find top of kneecap and measure knee circumference (ie top of patella, with leg stretched**)** **_____(cm)**

C- **Calf –** find widest part of calf, usually about 10-15 cm down from kneecap, and measure calf circumference **_____ (cm)**



Lysholm questionnaire

Chart 1 *- Lysholm Questionnaire (Scale).*

Limping (5 points)
Never = 5
Mild or periodically = 3
Strong and continuous = 0

Support (5 points)
No support = 5
Walking stick or crutches = 2
Impossible = 0

Restraining (15 points)
No restraining or restraining feeling = 15
Has the feeling, but no restraining = 10
Occasional restraining = 6
Frequent = 2
Joint restrained at examination = 0

Instability (25 points)
Never miss a step = 25
Seldom, during athletic activities or other strong-effort exercises = 20
Frequently during athletic activities or other strong-effort exercises (or unable to participate) = 15
Occasionally in daily activities = 10
Frequently in daily activities = 5
At each step = 0

Pain (25 points)
No pain = 25
Intermittent or mild during strong-effort exercises = 20
Marked during strong-effort exercises = 15
Marked during or after walking more than 2 Km = 10
Marked during or after walking less than 2 Km = 5
Continuous = 0

Swelling (10 points)
No swelling = 10
Upon strong-effort exercises = 6
Upon usual exercises = 2
Continuous = 0

Climbing stairs (10 points)
No problem = 10
Slightly damaged = 6
One step at a time = 2
Impossible = 0

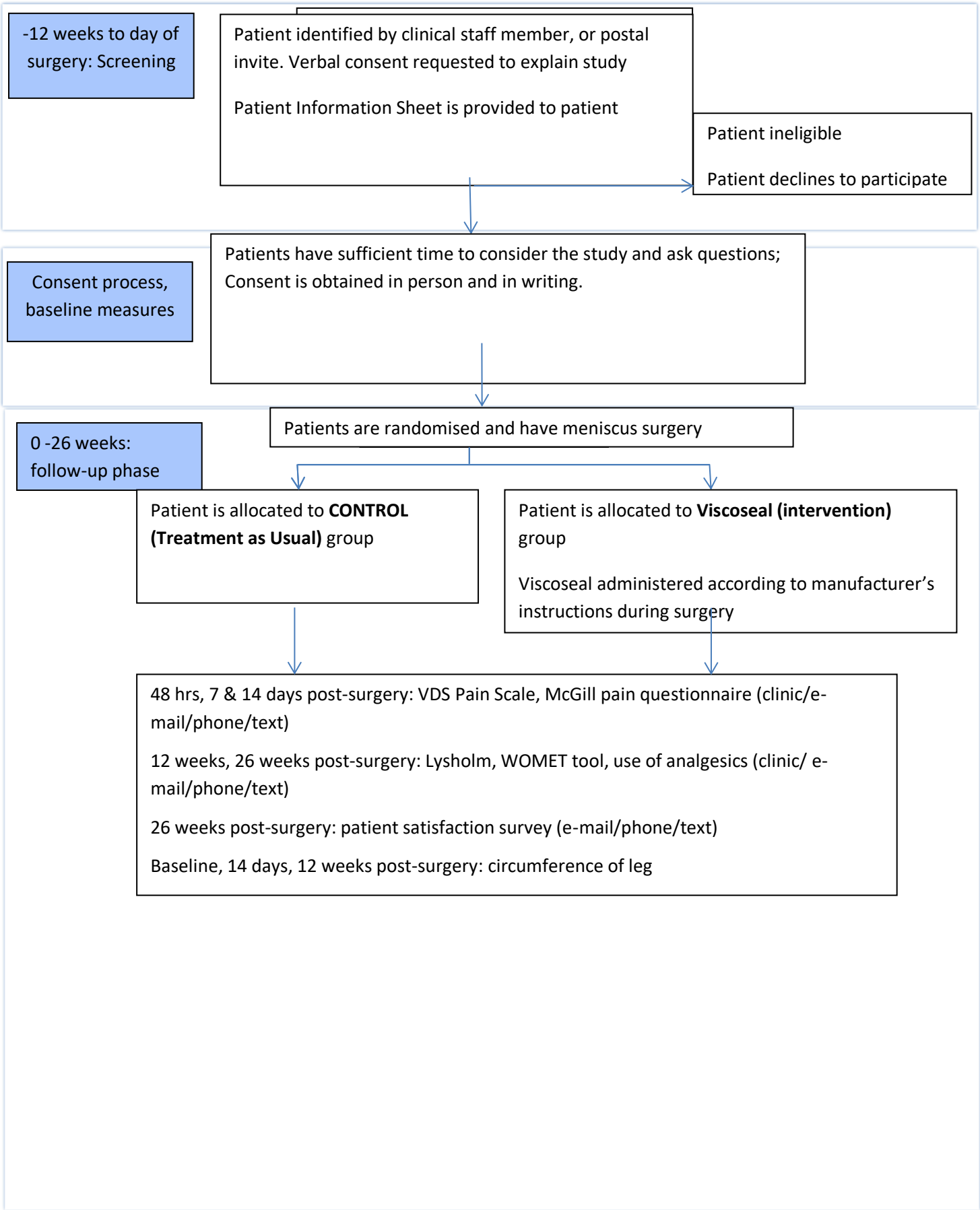
Squatting (5 points)
No problem = 5
Slightly damaged = 4
Not exceeding 90 degrees = 2
Impossible = 0

Total score: _____

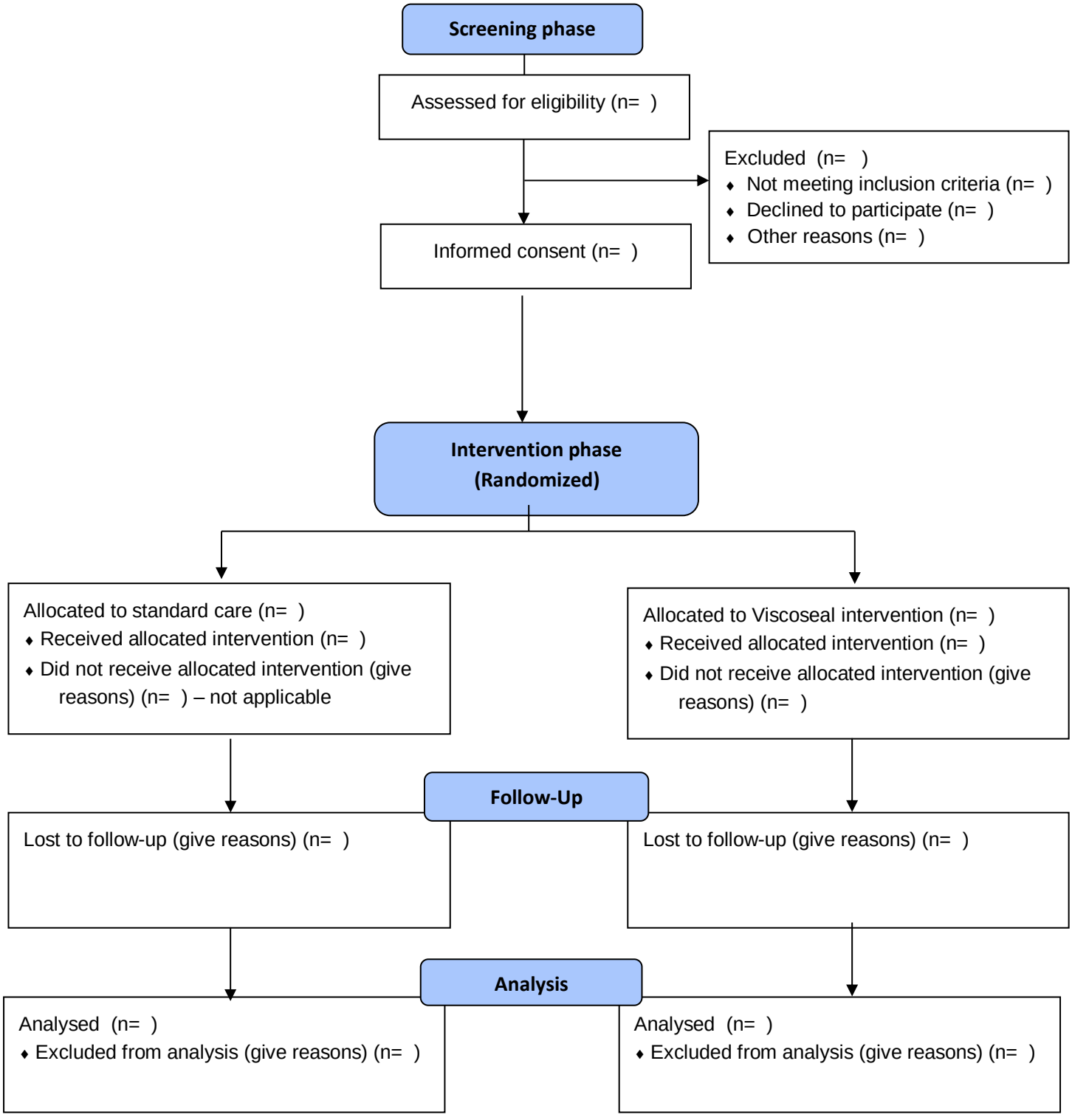
Score table: Excellent: 95 – 100; Good: 84 – 94; Fair: 65 – 83; Poor: < 64

All the outcome measures are summarised in Table 2.

APPENDIX 2. STUDY PARTICIPANT FLOWCHART



APPENDIX 3. CONSORT FLOWCHART



**Based on CONSORT Flowchart [28]*