North Cumbria Integrated Care NHS Foundation Trust

CASK trial

Compression After Surgery of the Knee trial

CASK trial, A single-centre, two-arm, controlled, prospective randomized trial comparing standard crepe bandaging with Andoflex TLC Calamine Lite (25-30 mmHg) compression bandaging after knee surgery.

Version 1.1, dd 31 August 2021

Chief Investigator's Statement of Ownership and Content.

I, Mr Matt Dawson, 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:	CASK trial, A single-centre, two-arm, controlled, prospective randomized trial comparing standard crepe bandaging with Andoflex TLC Calamine Lite (25-30 mmHg) compression bandaging after knee surgery.
Short title:	CASK trial; Compression After Surgery of the Knee trial
IRAS number	288969
Device description	AndoFlex TLC Calamine Lite Two-Layer Compression System. Compression of 25-30 mmHg. Layer 1 is a soft foam roll impregnated with calamine that is designed to soothe and calm skin. Layer 2 is a non-latex short stretch compression bandage that sticks to itself and features Easy HandTear Technology, eliminating the need for scissors. It provides a two-step short stretch performance with high working pressure and low resting pressure. Visual indicators are provided for ease of application - ovals become circles when the intended compression is achieved.
Study type	Medical device trial, involving CE-marked devices used for intended purpose.
Study design	Single-centre, two-arm, controlled, prospective randomized trial.
Patient population	Adult participants who have knee surgery – specifically knee replacement or osteotomy - and who meet the study inclusion criteria (including being medically fit to have compression bandaging). Participants must have the capacity to provide informed written consent and complete patient reported outcome measures. The study has the following sample parameters: standard deviation of 2 cm per cohort, power beta of 80%, alpha p-value of 0.05. Sample size takes into account 20% attrition rate, effect size of 0.75 (mean difference of 1.5cm on 10cm visual analogue scale) based on previous ROBOT trial results. Total of 74 patients per surgery type: - 37 Patients to receive non-compression bandaging - 37 Patient to receive Andoflex TLC Calamine Lite dual-layer compression bandaging Therefore total is: - 74 knee replacement cases - 74 osteotomy cases

	Overall trial sample size: 148
Primary objective	To determine the level of operation-site related pain experienced at day 5 post-operation and to compare the average pain scores of patients in the control and Andoflex TLC Calamine Lite arm respectively, through administration of 10 cm visual descriptor scale (VDS) for 'at rest' pain.
Secondary objectives	Post-operative patient-reported outcome measures: Prior to surgery and 3, 5, 12 days, and 6 weeks post-surgery - Pain perception, using VDS pain (at rest and walking) and short form McGill pain questionnaire Prior to surgery as baseline, and 6 and 12 weeks post-surgery, knee function and quality of life measurements - Knee and Osteoarthritis Outcome Score (KOOS) - Range of motion of the affected limb Descriptive safety overview at 30 days and 12 weeks post-surgery: - Readmitted to theatre and/or hospital - Infection of wound site - Diagnosed with pulmonary embolism or deep vein thrombosis. Patient satisfaction survey at 12 days post-surgery
Sponsor	North Cumbria Integrated Care NHS Foundation Trust
Manufacturer & research grant provider	Milliken Healthcare Inc
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Organisation where research will take place	North Cumbria Integrated Care NHS Foundation Trust Orthopaedics Department Newtown Road, Carlisle CA2 7HY, UK
Planned timeline	Recruitment start date (first patient, first visit) 1 July 2021, Recruitment end date (last patient, first visit): 31 July 2022 Recruitment end date (last patient, last visit): 31 Oct 2022
Protocol version, date	Version 1, dd 11May2021

1. CONTENTS

1. LAY SUMMARY

Medial osteoarthritis – wearing of the inside of the knee joint – can be treated with either knee replacement or osteotomy procedures. With the former, either part or the whole of the knee joint is replaced. With the latter, it involves cutting the tibial and or femoral bone and introducing an opening wedge to change the angle of the knee joint and thereby shift the patient's weight from the medial to the lateral side (outside) of the knee. For all major knee operations, post-surgery the site of operation can be painful. Increased pain may limit a patient's progress with post-operative mobilisation. Therefore, research is already ongoing in the field of knee surgery to determine if different type of bandaging of the affected leg post-surgery may improve patient and clinical outcomes. A new method is now available which involves bandaging that compresses the leg. This may reduce pain. This present study aims to assess if compression bandaging is better than standard non-compression bandaging in terms of keeping a patient comfortable by reducing pain and possibly improving other clinical outcomes too. A total of 148 patients will be recruited and allocated to either standard bandaging (74 patients) or Andoflex TLC Calamine Lite compression bandaging (also 74 patients); follow-up of patients will be up to 12 weeks post-surgery. Apart from clinical outcomes such as the degree and type of pain experienced by patients, safety data such as incidence of infection and deep vein thrombosis/pulmonary embolism, plus readmission to hospital will be recorded too. The main objective of the study is whether Andoflex TLC Calamine Lite compression bandaging (worn for 5 days post-surgery) is significantly better than standard bandaging (worn for up to 48 hours post-surgery) at day 5 post-surgery when measured on a visual display pain scale.

2. INTRODUCTION

Major knee surgery is associated with post-surgery pain. The surgical site is subject to bleeding and inflammation-related fluid build-up in the intraarticular tissues (Holm et al, 2020). Pain may impact negatively on recovery time and active early rehabilitation due to physical impairment that it may cause ((Mizner & Snyder-Mackler, 2005). This in turn may increase hospital length of stay and poor patient reported-outcomes (Moretti et al, 2012; Williams et al, 2013). Many service improvement programmes and techniques have been introduced in knee surgery over the years, including means to reduce intra-articular bleeding, tourniquets and medication (Martin et al , 2014). Initiatives in post-surgical management of patients have been less successful. These include methods such as the use of a cold compress (Morsi 2002), cryotherapy (Adie et al, 2012), elastic bandaging (Hughes et al, 1995) and some types of compression bandaging (Anderson et al, 2008; Charalambides et al, 2005).

Compression bandage therapy is established treatment of venous ulcers and lymphoedema (Franks et al, 2004, Pike 2011). It is hypothesised that the application of this external compression aids venous return and reduces hydrostatic pressure in the leg by (i) improving the efficacy of the calf muscle pump and (ii) moving blood from the superficial to deep venous system, subsequently allowing movement of fluid from the interstitial space. The use of inelastic bandages are preferred in arthroplasty as they have a low, tolerable resting pressure but a more effective activation of the deep venous system and calf muscle pump with ambulation compared to their elastic counterparts (Spence & Cahall, 1996).
The efficacy in total knee arthroplasty is still unclear due to conflicting results in the literature and heterogeneous methodology (Munk et al, 2013; Pinsornsak P & Chumchuen, 2013; Cheung et al, 2014). An acute pain study by Andersen et al (2008) utilised a compression bandage consisting of a double layer of soft padding and an outer elastic adhesive dressing compared with standard bandage in a randomised controlled trial of 48 patients. The intervention group had significantly reduced pain at 8 hours compared to a control group, though the bandage was combined with local anaesthetic infiltration.

Direct evidence on the role that different bandaging may play in improving post-operative outcomes after high tibial, distal femoral or double osteotomy is limited. Most osteotomy studies focus heavily on post-operative accuracy achieved in correcting the knee joint angle at circa 6 months post-surgery onwards (Amendola & Bonasia, 2010; Khoshbin et al, 2017). Other surgery-related findings have been reported as an incidental finding, such as 2 DVTs in a sample of 47 HTO patients by Miller et al (2009). In a recent study involving osteotomy patients, we showed a marked change in the type and temporal profile of pain experienced by patients post-surgery, see Table 1 (Jonker et al, 2020).

Table 1, At rest pain level related to affected leg post-surgery, measured using 10-cm visual display scale (Jonker et al, 2020)

Time point	**Standard care arm (n = 18)**	**Coban™ 2 arm (n = 18)**	**p-value**
5 days post-surgery, median (IQR)	5.5 (2.5-7.0)	2.5 (1.5-6.5)	0.068
12 days post-surgery, median (IQR)	4.0 (3.0-5.3)	2.3 (1.4-5.6)	0.39
6 weeks post-surgery, value (IQR)	2.0 (1.5-2.5)[#]	2.8 (1.0-5.8)*	0.21

[#] n = 16; * n=17

Taken together, preliminary data suggests that the use of an inelastic, short-stretch 2-layer compression bandage following knee surgery is a safe technique that may improve health outcomes. Therefore, we aim to assess its effectiveness and safety in a knee surgery patient population and we will focus on outcome measures up to 12 weeks post-surgery.

3. INVESTIGATIONAL DEVICE & INTERVENTION

3.1 Intervention

3.1.1 Standard care (control) arm

As soon as the operation is finished and a wound dressing has been applied, the standard bandaging is applied. One layer of soft synthetic bandage , stretching from proximal tibia to distal femur covered by a further layer of crepe bandage prior to or after tourniquet deflation, with 50% overlap of each layer (cryotherapy can be applied over this if standard of care). The bandaging will be removed approximately 48 hours post-operatively whilst leaving the dressing in situ. The bandages can be removed sooner than 48 hours if the patients find them very uncomfortable, or in the event of any adverse events that would require their removal, or if a cryocuff is applied post-operatively.

3.1.2 Andoflex TLC Calamine Lite compression bandaging (intervention) arm

As with standard bandaging, the Andoflex TLC Calamine Lite compression bandage will be applied over the routine surgical wound dressing. A foam inner bandage (Andoflex TLC Calamine Lite 2, Milliken Healthcare) is applied from the toe to the groin on the affected leg with minimal overlap. The second layer, which is the actual compression bandage (Andoflex TLC Calamine Lite 2, Milliken Healthcare) is applied at full stretch and with a 50% overlap of bandage to ensure adequate

compression in the application. The mode of action of this two layer compressive bandage kit is of particular practical use, since it is tolerable for patients overnight due to its low resting pressure. Furthermore, it produces high pressure compression with movement to stimulate the calf muscle pump. The bandage is applied from the toes upwards. The application of bandage from thigh to groin requires removal of the tourniquet first and so the leg is kept elevated until the bandaging is complete. There is a training video available on correct application of the bandages : https://www.youtube.com/watch?v=pal0pY_cTRc (Andoflex is known as Coflex in some other countries such as the USA).

The compression bandage has been shown to effect compression for up to a week. To balance compression and comfort, patients are asked to continue wearing the bandage for 5 consecutive days after surgery. The bandages can be removed sooner if the patients find them very uncomfortable (which will be classed as an adverse event) or in the event of any other adverse events that would require their removal – this will be recorded on the Case Report Form and in medical notes. If requested by the patient, they are allowed to return to a hospital clinic to have the Andoflex TLC Calamine Lite bandaging reapplied if for any reason the first set needed to be taken off. To maintain consistency, clinical healthcare professionals who apply a new Andoflex TLC Calamine Lite bandage need to sign a declaration that they have watched the training video and are comfortable complying with the instructions. Full product information on the Andoflex TLC Calamine 2-layer compression system can be found on the Andover Healthcare Inc website https://andoverhealthcare.com/product/coflex-tlc-calamine/

There are two pressure options: compression of either (standard compression) 35-40 mmHg or ('Lite' compression) 25-30 mmHg, for patients with an ABPI of ≥ 0.8 or ≥ 0.5 respectively. Layer 1 is a soft foam roll impregnated with calamine that is designed to soothe and calm skin with multiple wounds or other skin conditions. Layer 2 is a non-latex short stretch compression bandage that sticks to itself and features Easy HandTear Technology, eliminating the need for scissors. Absorbs 20xs its dry weight vs. traditional Unna Boot, and 50% more active ingredients than traditional Unna Boot. It provides a two-step short stretch performance with high working pressure and low resting pressure. Visual indicators are provided for ease of application - ovals become circles when the intended compression is achieved.

Apart from the difference in type of bandage, the protocol for the Andoflex TLC Calamine Lite arm is identical to that of the standard care group (cryocuff can be applied to this treatment arm, but will be applied over the bandaging). Used bandaging will be disposed of in line with local guidelines on disposal of clinical waste if in clinical location, or by patient in home setting.

Figures 1 & 2. Standard wool and crepe bandaging (top) vs Andoflex TLC Calamine Lite dual layer compression bandaging (bottom)

Figure 1 Standard wool and crepe bandage.

4. STUDY HYPOTHESIS

4.1 Primary objective

- To assess the efficacy of Andoflex TLC Calamine Lite compression bandaging for reduction of post-operative pain after knee surgery compared with standard care bandaging.

4.2 Secondary objective

- To assess the type of pain experienced by patients wearing either Andoflex TLC Calamine Lite compression bandaging or crepe bandaging.
- To assess the efficacy of Andoflex TLC Calamine Lite compression bandaging for improvement of post-operative patient-reported outcome measures, including knee functionality, after knee surgery when compared with standard care bandaging.
- To determine if there is a difference in pain outcomes dependent on the knee surgery sub-cohort (knee replacement, osteotomy).

5. STUDY PROTOCOL

5.1 Study design, recruitment sites and timeline

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

- North Cumbria Integrated Care NHS Foundation Trust (both Cumberland Infirmary, Carlisle, and West Cumberland Hospital, Whitehaven. CI Mr Matt Dawson)

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 2. Anticipated timeline

Month	Setup	Recruitment	Analysis	Finalise
May 2021	Submission for NRES/ HRA approval			
Jun 2021	NIHR portfolio adoption			
Jun 2021	NRES/HRA and Trust approval			
Jul 2021		Start recruitment		
Jul 2022		Finish recruitment		
Oct 2022			Follow-up complete; Analyse data.	
Nov 2022				manuscript & report writing

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 control bandage group (TaU) or the intervention group (Andoflex TLC Calamine Lite) any time up until the day of surgery.

5.4 Follow-up

Patients are in the study for a period of 12 weeks. Thereafter, the patient will be followed up as they would be in normal clinical practice. Study visits are aligned to hospital/clinic visits where possible. Baseline data can be collected on the day of surgery (prior the actual operation), and 12 day and 12 week post-surgery data can be collected when the patient attends for standard follow-up in the orthopaedics out-patient department. The data at day 3, 5, day 12 and week 3 falls outside these dates. For all outcome measures, 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 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 operation-site related pain experienced at day 5 post-operation and to compare the average pain scores of patients in the control and Andoflex TLC Calamine Lite arm respectively, through administration of 10 cm visual descriptor scale (VDS) for pain.

The study is powered to detect the established minimal clinically important difference (MCID) of 1.5 cm on a 10 cm VDS pain.

5.5.2 Secondary outcome measures

All the outcome measures are summarised in Table 3.

Table 3. Overview of measurements

Weeks	-12 weeks to day of surgery	0 surgery	3 days##	5 days##	12 days#	6 weeks*	12 weeks *
Application bandage straight after surgery		X					
VDS pain scale (at rest)	X		X	X	X	X	
VDS pain scale (walking)	X		X	X	X	X	
McGill pain questionnaire	X		X	X	X	X	
Limb range of motion	X					X	
KOOS score	X					X	X
Patient satisfaction questionnaire re bandaging					X	(X, if not returned yet at 12 days)	

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

 # Allowed to be up to 3 days early or late

Allowed to be up to 1 day early or late

6. SUBJECTS

6.1 Anticipated number of research subjects

The sample size calculation does take into account a 20% patient attrition rate (withdrawal and loss to follow-up), since this involves a study with multiple time points for data collection up to 12 weeks. Patients will be recruited from the adult (age 18+) population routinely seen by the evaluating clinical staff members. The primary outcome measure is based on knee/leg (ie wound site) pain experienced 5-days post-surgery based on the VDS pain scale 'at rest'. The hypothetical difference in pain perception is 1.5 on a 10 cm scale which equates to a significant 'minimally clinically important difference' for pain (Kelly 2001; Lee et al 2003; Tashjian et al 2009). The values and differences observed in the ROBOT trial will be used for reference.

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.

Analysis will be performed on an intention-to-treat basis, although the number of days that a participant has worn a bandage will be recorded.

Data will be analysed as one cohort and also stratified by surgery type (knee replacement, osteotomy) in the resulting analysis.

Table 4, Sample size calculation

	Mean pain score at 5 days post-op	Standard Deviation
Arm A (*hypothetical*)	*5.0*	*2*

Arm B (*hypothetical*)	*3.5*	*2*
	Power beta of 80%, Alpha p-value of 0.05, Effect size 0.75 Sample size required without any drop-out: 62 samples. Sample size with 20% attrition rate included: 74 Total of 74 patients per surgery type: - 37 Patients to receive non-compression bandaging - 37 Patient to receive Andoflex TLC Calamine Lite dual-layer compression bandaging Therefore total is: - 74 knee replacement cases - 74 osteotomy cases **Overall trial sample size: 148**	

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 Andoflex TLC Calamine Lite intervention group, using a randomised sequence from the freeware randomisation programme, see https://www.randomizer.org/ . No stratified or block randomisation will be undertaken, apart randomisation per surgery type.

Sequential envelopes with each next randomisation allocation 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@cumbria.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

- Patient who is listed for:
    - Knee arthroplasty (replacement) surgery, either partial or total knee replacement (single or double).
    - Unilateral high tibial osteotomy (HTO) or distal femoral osteotomy (DFO) or a double osteotomy (HTO and DFO) at one of participating NHS Trusts.
    - In case of double procedure patients, one leg will be classed as the index leg and all outcomes measures will focus on said leg.
- Clinical indication, in the opinion of the treating surgeon, that dual-layer compression bandaging may be of benefit to the patient

- Adult patients aged > 18 years
- Mental capacity to give written informed consent

6.2.2 Exclusion criteria

- Under the age of 18 years
- Unable to fully understand the consent process and provide informed consent due to either language barriers or mental capacity
- Revision of previous knee replacement or osteotomy on the index leg.
- 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).
- Cardiovascular or vascular condition that in the opinion of the treating surgeon contraindicates the use of compression bandaging, including moderate to severe peripheral arterial disease, venous leg ulcer, high dose anti-coagulant medication
- Any skin or other condition that contraindicates the use of compression bandaging, including diabetic foot ulcer or peripheral neuropathy.
- Patients who are participating in another interventional research study involving an investigational product related to the knee procedure and its aftercare.
- The patient has concurrent (medical) conditions that in the opinion of the investigator may compromise patient safety or study objectives.
- Patient has practical or mobility issues which will prevent them from removing the bandage themselves

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.

7. SAFETY

7.1 Potential risks & benefits to study participants

There are no major anticipated personal safety risks associated with patients taking part in this study, though it is recognised that the – particularly incorrect – application of (compression) bandaging can result in skin reactions and discomfort and can affect blood flow. 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 Andoflex TLC Calamine Lite intervention group, there may be benefits in terms of improved DFU healing 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 Milliken 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

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

- Type of surgery
    - Including type of medical device used and which leg operated on
- Length of operation (min) and blood loss (ml) during operation
- Type of anaesthetic and analgesics prescribed post-surgery
- Hospital length of stay (days)
- Moment physiotherapy and early recovery initiated
- Type of standard bandaging applied if control patient.

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 experienced at day 5 post-operation and to compare the average pain scores of patients in the control and Andoflex TLC Calamine Lite arm respectively, through administration of 10 cm visual descriptor scale (VDS) for pain.

The study is powered to detect the established minimal clinically important difference (MCID) of 1.5 cm on a 10 cm VDS pain.

The average difference between time points will be calculated per group, 5 days post-surgery weeks being the primary endpoint. Three days, 12 days and 6 weeks post-surgery will also be analysed. To compare the groups, the Mann-Whitney U-test will be applied.

To avoid relying on one outcome measure related to pain, at 3, 5, 12 days, and 6 weeks 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 Andoflex TLC Calamine Lite bandaging), 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 bandaging and other covariates (as mentioned above) in post-surgery related pain and knee function.

The statistics apply to:

Up to 12 weeks prior to surgery, and 12 weeks post-surgery, knee function and quality of life measurements: Knee and Osteoarthritis Outcome Score (KOOS), and range of movement of the affected limb (goniometer)

Descriptive safety overview at 30 days and 12 weeks post-surgery:

- Readmitted to theatre and/or hospital
- Infection of wound site
- Diagnosed with pulmonary embolism or deep vein thrombosis
- All monitored remotely by review of patients' hospital notes.

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

For all outcome measures and statistics, both whole cohort and surgery-specific stratification analysis will be conducted.

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 Cumbria Partnership NHS Trusts 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 in the Cumberland Infirmary, Carlisle. 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 (Milliken Healthcare) 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 Milliken Healthcare 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 Foundation Trust is the sponsor of this study and therefore NHS indemnity applies for design, conduct and management of the study. Milliken has provided a grant for this study by means of provision of the Andoflex TLC Calamine Lite bandaging material worth £1,000.

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, Milliken

As stated in the PIL and ICF, anonymised study data will be shared with Milliken 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.

12. REFERENCES

Adie S, Kwan A, Naylor JM, Harris IA, Mittal R. Cryotherapy following total knee replacement. Cochrane Database Syst Rev. 2012;9:CD007911.

Amendola, A. and Bonasia, D.E., 2010. Results of high tibial osteotomy: review of the literature. *International orthopaedics*, *34*(2), pp.155-160.

Andersen LO, Husted H, Otte KS, Kristensen BB, Kehlet H. A compression bandage improves local infiltration analgesia in total knee arthroplasty. Acta Orthop. 2008;79:806–11.

Brock TM, Sprowson AP, Muller S, Reed MR. Short-stretch inelastic compression bandage in knee swelling following total knee arthroplasty study (STICKS): study protocol for a randomised controlled feasibility study. Trials. 2015;16(1):87.

Charalambides C, Beer M, Melhuish J, Williams RJ, Cobb AG. Bandaging technique after knee replacement. Acta Orthop. 2005;76:89–94.

Cheung A, Lykostratis H, Holloway I. Compression bandaging improves mobility following total knee replacement in an enhanced recovery setting. J Perioper Pract. 2014;24(4):84-6.

Fahrer H, Rentsch HU, Gerber NJ, Beyeler C, Hess CW, Grunig B. Knee effusion and reflex inhibition of the quadriceps. A bar to effective retraining. J Bone Joint Surg. 1988;70:635–8.

Franks PJ, Moody M, Moffatt CJ, Martin R, Blewett R, Seymour E, et al. Randomized trial of cohesive short-stretch versus four-layer bandaging in the management of venous ulceration. Wound Repair Regen. 2004;12:157–62.

Holm B, Kristensen MT, Bencke J, Husted H, Kehlet H, Bandholm T. Loss of kneeextension strength is related to knee swelling after total knee arthroplasty. Arch Phys Med Rehabil. 2010;91:1770–6.

Hughes DL, Crosby AC. Treatment of knee sprains: modified Robert Jones or elastic support bandage? J Accid Emerg Med. 1995;12:115–8.

Jonker L, Bell L, Robinson K, Davidson K, Dawson M. Application of compression bandaging post-osteotomy results in altered pain profile; results of a single-centre randomised controlled trial. International Journal of Orthopaedic and Trauma Nursing. 2020 Nov 12:100833.

Kelly, A.M., 2001. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. *Emergency Medicine Journal*, *18*(3), pp.205-207.

Khoshbin, A., Sheth, U., Ogilvie-Harris, D., Mahomed, N., Jenkinson, R., Gandhi, R. and Wasserstein, D., 2017. The effect of patient, provider and surgical factors on survivorship of high tibial osteotomy to total knee arthroplasty: a population-based study. *Knee Surgery, Sports Traumatology, Arthroscopy*, *25*(3), pp.887-894.

Lee, J.S., Hobden, E., Stiell, I.G. and Wells, G.A., 2003. Clinically important change in the visual analog scale after adequate pain control. *Academic Emergency Medicine*, *10*(10), pp.1128-1130

Martin JG, Cassatt KB, Kincaid-Cinnamon KA, Westendorf DS, Garton AS, Lemke JH. Topical Administration of Tranexamic Acid in Primary Total Hip and Total Knee Arthroplasty. J Arthroplasty. 2014;29(5):889–94

Melzack, R., 1987. The short-form McGill pain questionnaire. *Pain*, *30*(2), pp.191-197.

Miller, B.S., Downie, B., McDonough, E.B. and Wojtys, E.M., 2009. Complications after medial opening wedge high tibial osteotomy. *Arthroscopy: The Journal of Arthroscopic & Related Surgery*, *25*(6), pp.639-646.

Mizner RL, Snyder-Mackler L. Altered loading during walking and sit-to-stand is affected by quadriceps weakness after total knee arthroplasty. J Orthop Res. 2005;23:1083–90.

Moher D, Schulz KF, Altman DG, Group C. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. The Lancet. 2001;357(9263):1191-4.

Moretti B, Notarnicola A, Moretti L, Setti S, De Terlizzi F, Pesce V, et al. I-ONE therapy in patients undergoing total knee arthroplasty: a prospective, randomized and controlled study. BMC Musculoskelet Disord. 2012;13:88.
Morsi E. Continuous-flow cold therapy after total knee arthroplasty. J Arthroplasty. 2002;17:718–22.

Munk S, Jensen NJ, Andersen I, Kehlet H, Hansen TB. Effect of compression therapy on knee swelling and pain after total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc. 2013;21:388–92.

Pike C. Using Actico bandaging for chronic oedema/lymphoedema management. Br J Nurs. 2011;20:1246, 8–51.

Pinsornsak P, Chumchuen S. Can a modified Robert Jones bandage after knee arthroplasty reduce blood loss? A prospective randomized controlled trial. Clin Orthop Relat Res. 2013;471:1677–81.

Richards, K. C., O'Sullivan, P. S., & Phillips, R. L. (2000). Measurement of sleep in critically ill patients. *Journal of Nursing Measurements, 8*(2), 131–144.

Rosso F, Margheritini F. Distal femoral osteotomy. Current reviews in musculoskeletal medicine. 2014 Dec 1;7(4):302-11

Spence RK, Cahall E. Inelastic versus elastic leg compression in chronic venous insufficiency: a comparison of limb size and venous hemodynamics. J Vasc Surg.

1996;24:783–7.

Tashjian, R.Z., Deloach, J., Porucznik, C.A. and Powell, A.P., 2009. Minimal clinically important differences (MCID) and patient acceptable symptomatic state (PASS) for visual analog scales (VAS) measuring pain in patients treated for rotator cuff disease. *Journal of Shoulder and Elbow Surgery*, *18*(6), pp.927-932.

Williams DP, O'Brien S, Doran E, Price AJ, Beard DJ, Murray DW, et al. Early postoperative predictors of satisfaction following total knee arthroplasty. Knee. 2013;20:442–6.

Yu GV, Schubert EK, Khoury WE. The Jones compression bandage. Review and clinical applications. J Am Podiatr Med Assoc. 2002;92:221–31.

APPENDIX 1. TOOLS AND ASSESSMENTS

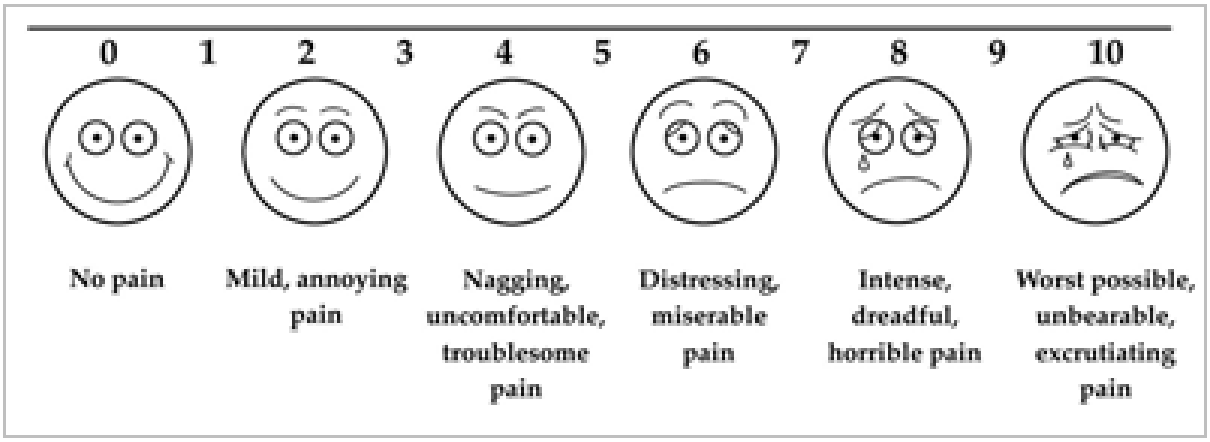
This appendix contains:

- Visual Descriptor Pain scale
- Short-form McGill pain questionnaire

The KOOS score and Bandage Patient Satisfaction Questionnaire are enclosed separately to this protocol.

Visual Descriptor Pain score

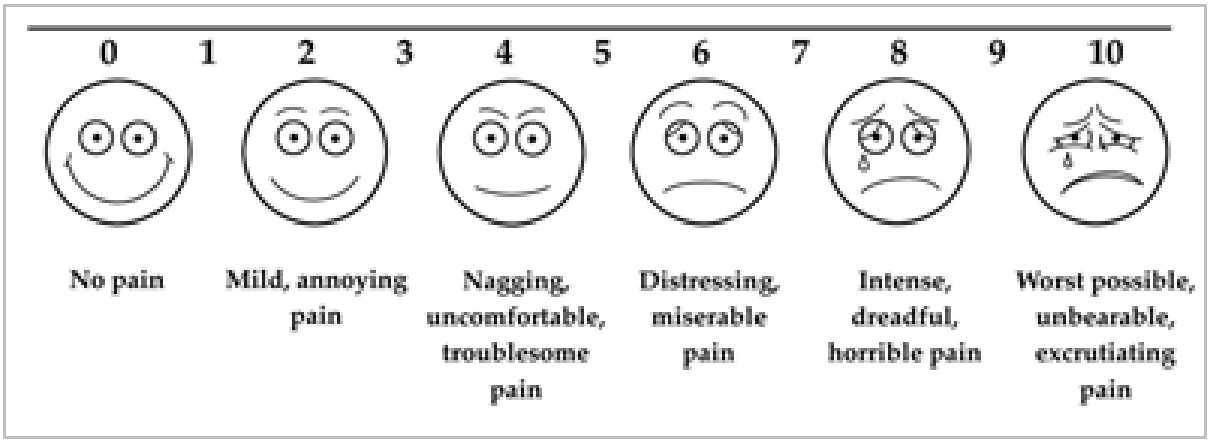
How painful has your leg, the one has been operated on, been **in the last day when resting**:



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 day 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

How painful has your leg, the one has been operated on, been **generally in the last day**

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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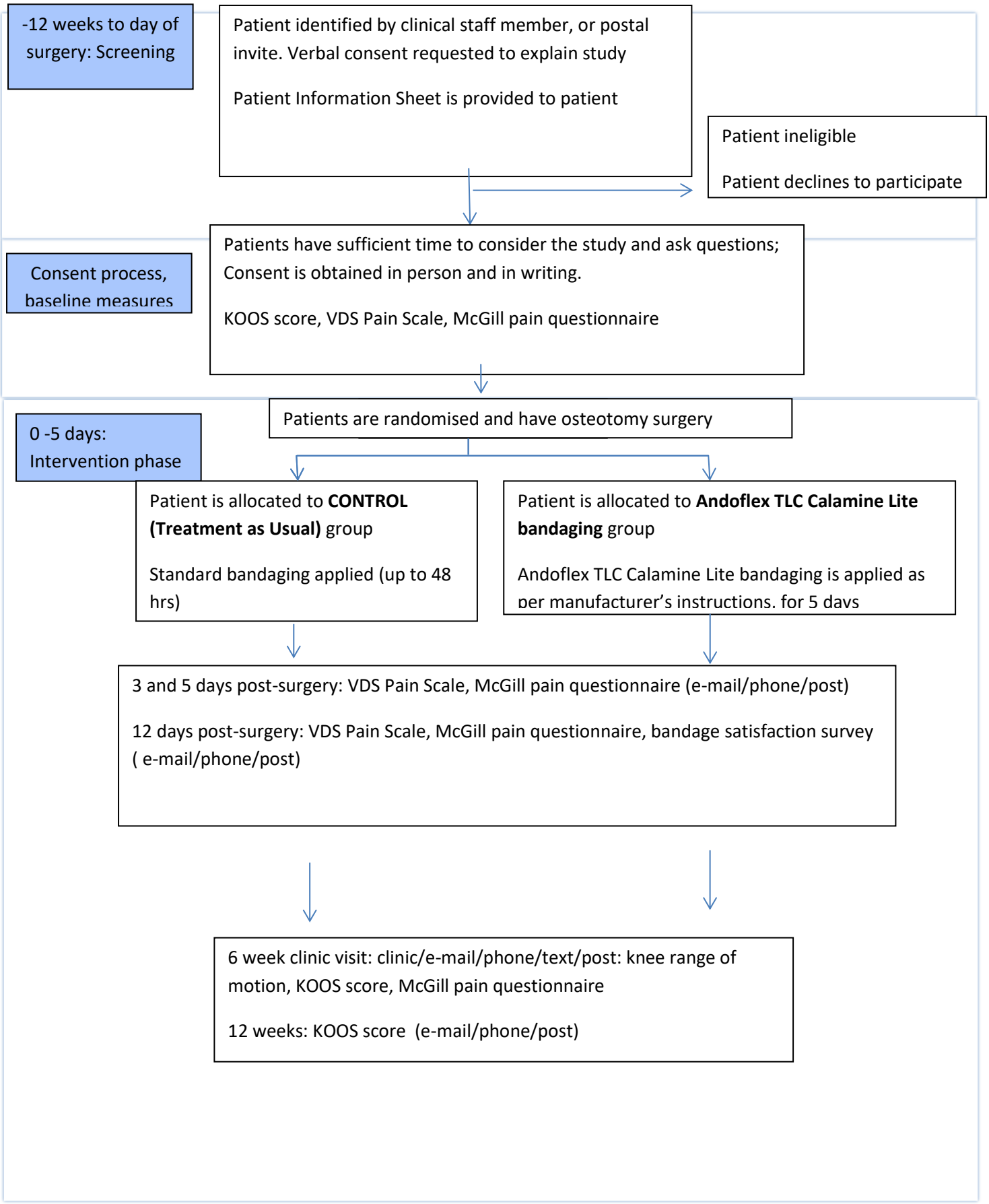
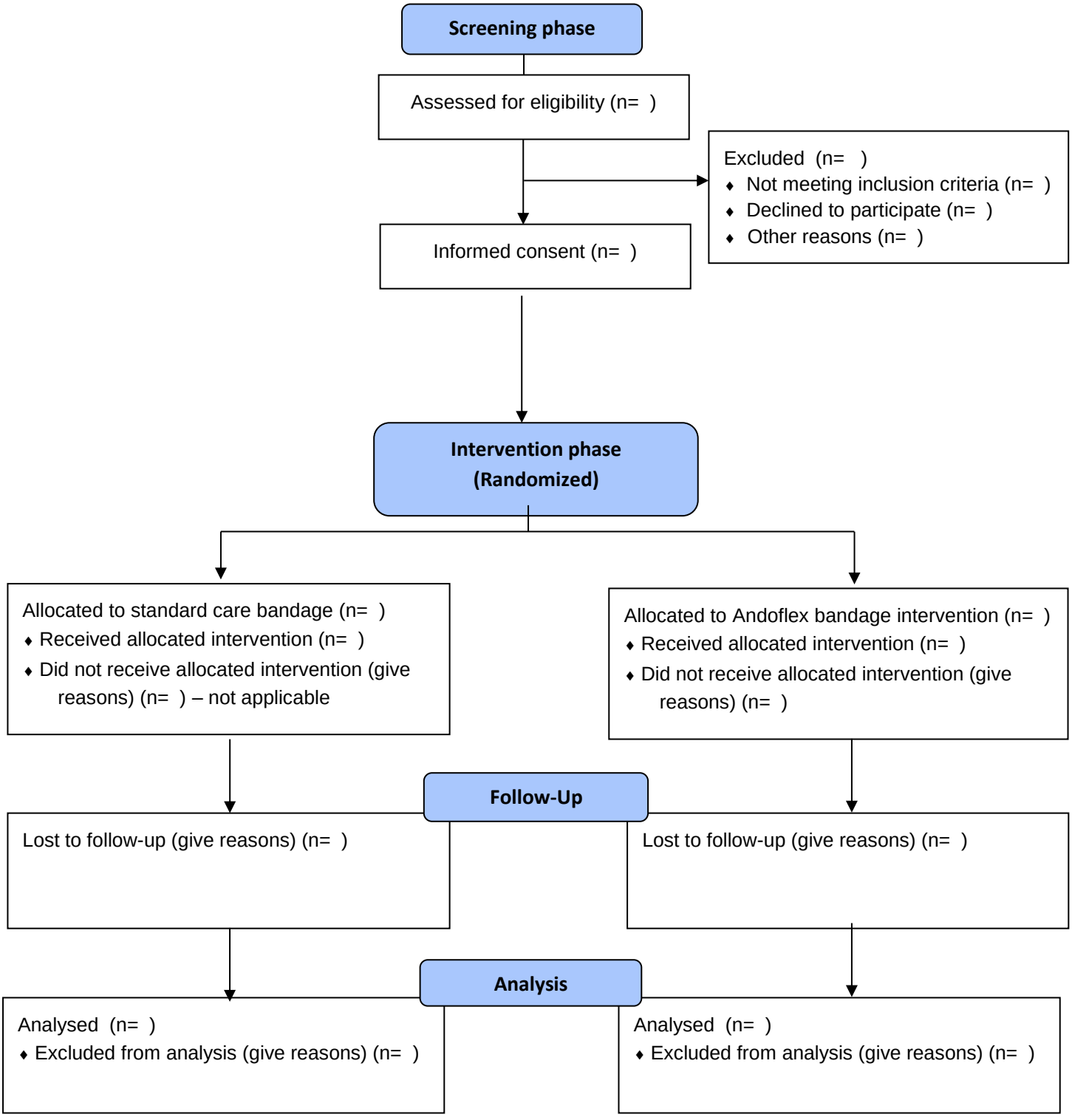
The short-form McGill Pain Questionnaire (SF-MPQ). Descriptors 1–11 represent the sensory dimension of pain experience and 12-15 represent the affective dimension. Each descriptor is ranked on an intensity scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe. The Present Pain Intensity (PPI) of the 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

APPENDIX 2. STUDY PARTICIPANT FLOWCHART



APPENDIX 3. CONSORT FLOWCHART



**Based on CONSORT Flowchart (Moher et al, 2001)*