A Randomised Controlled Trial of Scaffold InSertion and MIcrofracture Compared to Microfracture Alone for the Treatment of Chondral or Osteochondral Defects of the Knee (The SISMIC Study)

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Glossary / abbreviations

AE	Adverse event - any undesirable event in a subject receiving treatment according to the protocol, including occurrences which are not necessarily caused by or related to administration of the research procedures.
AMIC	Autologous matrix-induced chondrogenesis
AR	Adverse reaction – any undesirable experience that has happened a subject while taking a drug that is suspected to be caused by the drug or drugs
BTC	Bristol Trials Centre
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case report form
CTEU	Clinical Trials and Evaluation Unit
DMSC	Data Monitoring and Steering Committee
GCP	Good Clinical Practice
GP	General Practice
HES	Hospital Episode Statistics
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
IKDC	International Knee Documentation Committee
ITT	Intention-to-treat
KOOS	Knee injury and Osteoarthritis Outcome Score
LPLV	Last patient last visit
MCID	Minimal clinically important difference
MHRA	Medicines and healthcare products regulatory agency
MRC	Medical Research Council
MRI	Magnetic Resonance Imagining
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PEP-R	Patient Experience Partnership in Research
PIL	Patient information leaflet
PI	Principal Investigator
PSS	Personal social services perspective
RCT	Randomised controlled trial
REC	Research ethics committee
SAE	Serious adverse event - events which result in death, are life threatening, require hospitalisation or prolongation of hospitalisation, result in persistent or significant disability or incapacity.
SAR	Serious adverse reaction
SD	Standard deviation
SOP	Standard operating procedure
SSA	Site Specific Assessment
SSAR	Suspected serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction - an untoward medical occurrence suspected to be related to a medicinal product that is not consistent with the applicable product information and is serious.
TMF	Trial Master File
TMG	Trial management group
TSC	Trial steering committee
UKCRC	The UK Clinical Research Collaboration
WPAI	Work Productivity and Activity Impairment
QALYs	Quality adjusted life years

1. Trial summary

Knee injuries are common and can lead to pain and disability. Injuries to the smooth cartilage that lines the ends of the bone in joints can cause ongoing problems as the cartilage does not have a blood supply and rarely heals once injured. 10,000 people a year in the UK have a severe articular cartilage injury that warrants surgical treatment. There are two main ways in which these injuries can be treated surgically, the first is to try to address the symptoms without trying to restore the cartilage; such as cleaning (debriding) the area or replacing the damaged area with an implant. The other way is to try to repair or restore the cartilage in the damaged area. Cartilage does not grow back on its own, so an operation known as “microfracture” can be performed to encourage the cartilage to grow. A surgical tool is used to make perforations in the bone in the damaged area which allows blood and bone marrow to seep out of the holes, encouraging healing. A “scaffold”, which is usually made of the same material that makes up most of the cartilage (collagen), can be added, termed Autologous Matrix-Induced Chondrogenesis (AMIC). The scaffold is secured in place and acts as a template for new cartilage to form on. It is not clear if using a scaffold improves the outcome for patients. Using scaffold makes the operation more complex (approximately 20 minutes longer) and the cost of the scaffold is approximately £900, so it is important to establish if adding a scaffold results in a better outcome for patients and is cost-effective for the NHS.

The study will find out whether adding the scaffold is worthwhile or not for patients with knee articular cartilage injuries. Over 2 years we will aim to recruit 176 patients, who will be randomised into two equal sized groups from at least 16 hospitals. One group of patients will have microfracture alone and the other will have microfracture plus scaffold (AMIC). Everything else will be the same for all patients. Both groups will be followed for 2 years by clinical review. We will collect information about quality of life, symptoms and pain in the knee, complications of surgery, need for further surgery and costs to the NHS and patients.

2. Background

Up to 10,000 symptomatic articular cartilage injuries occur each year, mostly in patients under 35 years of age. There are two main treatment modalities, the first aims to restore cartilage with microfracture, with or without scaffold insertion, or cellular methods and the second aims to improve symptoms without restoring cartilage. For young patients, restoring cartilage is felt to be more appropriate. Microfracture involves penetrating the subchondral bone in the area of injury to release fibrin and stem cells, which leads to the development of some parts of normal cartilage, but not all. It has been suggested that results may be better if a scaffold is used to help the repair (AMIC). Scaffolds are safe to use but there is no definitive evidence that it improves results, as summarised in this most recent review.(1)

3. Rationale

Articular (hyaline) cartilage is a very specialised structure which allows low friction movement with very low wear rates.(2, 3) Injuries to the articular cartilage in the knee are common, particularly in patients under 35 years of age. The National Institute for Health and Care Excellence (NICE) estimates that around 10,000 patients per year in the UK suffer from cartilage damage warranting repair.(4) Unfortunately, as the cartilage is avascular with low cell density, the healing potential is low when injury occurs.(5) Cartilage damage can either occur spontaneously (osteochondritis dissecans(6)), due to acute injury or chronically due to injury to another structure such as the anterior cruciate ligament and secondary instability.

Treatment options are broadly divided into those that aim to restore cartilage, such as microfracture and microfracture with scaffold insertion (AMIC) and those that aim to reduce symptoms without restoring cartilage e.g. debridement, focal resurfacing, osteotomy or joint replacement. Microfracture involves penetrating the subchondral bone at the time of surgery to release fibrin and marrow stem cells with the intention of stimulating cartilage formation.(7) Microfracture increases type II collagen, matrix and protein formation but not all components of articular cartilage leading to the suggestion that the addition of scaffolds, which are typically made of collagen, may further improve outcomes.(8) NICE guidance states that although the addition of a scaffold is not associated with safety concerns, current evidence for its efficacy is lacking in quantity and quality.(9) This NIHR-HTA commissioned study aims to address this evidence gap.

This trial was developed in collaboration with the University of Bristol Musculoskeletal Research Unit patient involvement group; the 'Patient Experience Partnership in Research (PEP-R) comprises nine members who have had, or are having, treatment for musculoskeletal health conditions, several of whom have had knee surgery. They suggested that this research was taken to them for their views in a larger group setting, rather than members attending trial management group meetings. They therefore felt that their contribution would be most efficient in the following ways: A) The group should discuss the project 6 times over the 5 year grant, with 2 meetings in the first year. B) At the start of the project, they will discuss study background, research methods, methodology and ethics. C) They will review the information for participants, including invitation letters, information sheet and consent form. D) They will review the questionnaires/outcome measures. E) They will advise on keeping participants engaged, including reviewing newsletters and the summary of results for participants. F) They will monitor the progress and conduct of the study and work with the study team to identify and prioritise next steps. G) At the final meeting, they will discuss how to communicate the results to a lay audience. H) The meetings will be organised and facilitated by an experienced patient and public involvement coordinator, Amanda Burston (co-applicant). She will attend the trial management group meetings. The group were happy for her to represent the group and provide feedback to them. She will provide ongoing support and tailored development to PEP-R members and advise researchers on good practice.

4. Aims and objectives

We hypothesise that in patients with symptomatic chondral or osteochondral defects of the knee requiring treatment, microfracture with microstructural scaffold leads to a superior Knee Injury and Osteoarthritis Outcome Score (KOOS) outcome at 2-years compared with microfracture alone. The overall aim of this study is to evaluate the clinical and cost effectiveness of microstructural scaffold in patients undergoing microfracture for a chondral or osteochondral defect of the knee.

Specific objectives of the trial are:

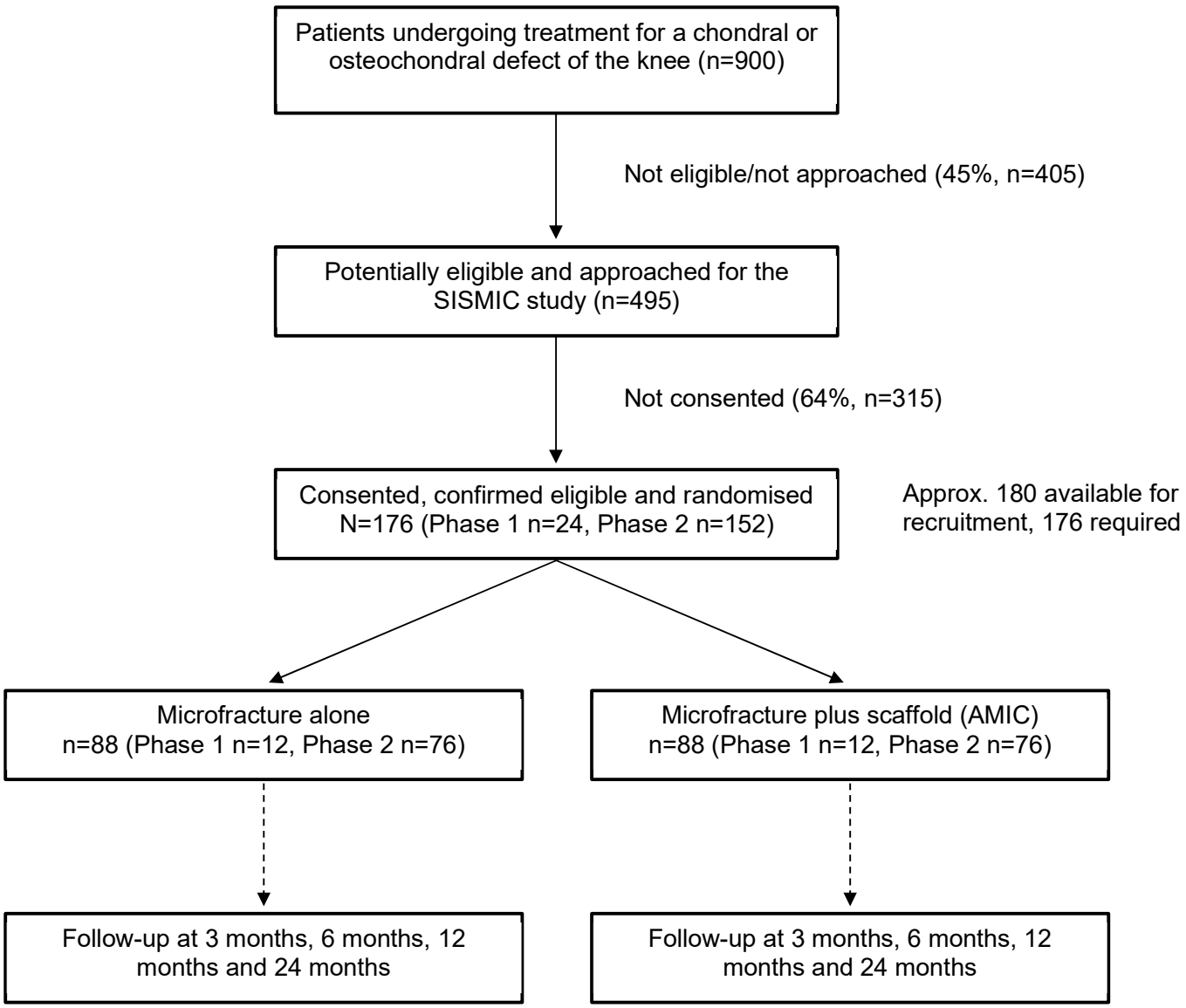
1. To estimate the difference between groups in mean Knee Injury and Osteoarthritis Outcome Score (KOOS) at 2 years
2. To estimate the difference between groups with respect to a range of secondary outcomes, including knee function, activity, Health Related Quality of Life (HRQoL), and return to work over a 2 year period
3. To estimate resource use and costs during the 2 year follow up and compare the cost-effectiveness of microfracture plus scaffold (AMIC) versus microfracture alone

4. Establish systems to allow collection of longer-term outcomes from routinely collected data (e.g. need for knee replacement identified from Hospital Episode Statistics (HES)).

5. Plan of Investigation

5.1 Trial schema

Figure 1 Trial schema



5.2 Trial design

Multicentre, parallel group, superiority randomised controlled trial (RCT) in which participants and clinical care teams (except for staff involved in the surgery) and members of the research team responsible for data collection will be blinded to allocation.

Phase 1 (internal pilot) will determine the feasibility to randomise once debridement of the chondral/osteochondral lesion has been performed. Progression to Phase 2 will depend on showing satisfactory recruitment in Phase 1. All participants from phase 1 to 2 will be followed up for 24 months. Progression will be contingent on meeting the criteria defined in section 7.4.

Further follow up may continue for up to 10 years subject to further funding.

5.3 Setting

Patients will be recruited from secondary and tertiary care NHS hospitals.

5.4 Key design features to minimise bias

(a) Selection bias/allocation bias (systematic differences between baseline characteristics of the groups that are compared)

This bias is ruled out by concealed randomisation (see section 6.1). The allocation will not be revealed until sufficient information to uniquely identify the participant and establish eligibility has been entered into the trial database.

(b) Performance bias (systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest).

This bias will be minimised by:

- blinding all participants and the clinical care team not directly involved in the surgery and assessing the success of blinding (see section 6.2);
- defining the intervention and comparator, as well as standard protocols for other procedures undertaken during the trial (see section 5.6);
- defining procedures for participant follow-up (see section 6.11);
- monitoring adherence to protocol (see section 8.1 and 8.2).

The patient information leaflet (PIL) and the process of obtaining informed consent will describe the uncertainty about the effects of scaffold insertion. Therefore, in the event of inadvertent unblinding of a participant, he or she should not have a strong expectation that any one method should lead to a more favourable result.

(c) Detection bias (systematic differences between groups in how outcomes are determined)

This bias will be minimised by:

- The primary outcome is patient reported and the patients will remain blinded;
- blinding individuals assessing outcomes (see section 6.2).

(d) Attrition bias (systematic differences between groups in withdrawals from a study)

This bias will be minimised by:

- Using established Bristol Trials Centre (BTC) methods to maximise the proportion of participants for whom all outcome data are available, and the proportion of participants who receive the intervention to which they were allocated (see section 6.3.2).
- Implementing measures to promote adherence to random allocations (see section 7.1)
- Documenting non-adherence to random allocations (see section 7.1)
- Using intention to treat analysis and investigating sensitivity to attrition bias in statistical and economic analyses, implementing appropriate imputations for missing data (see sections 7.1 and 7.5).

(e) Reporting bias

This type of bias will be minimised by having pre-specified outcomes (see section 5.7) and a pre-specified analysis plan (see sections 7.1 and 7.5).

5.5 Trial population

Adults with symptoms arising from a chondral or osteochondral defect of the knee.

5.5.1 Inclusion criteria

Participant may enter the study if ALL of the following apply

1. 18 years of age or older
2. Symptomatic chondral or osteochondral defect of the knee sited on the medial or lateral femoral condyles, trochlea or patella as confirmed by standard clinical practice.
3. Chondral or osteochondral lesion measuring no more than 4cm^2

5.5.2 Exclusion criteria

Participant may not enter the study if ANY of the following apply

1. Unstable, ligamentous injury to the knee that will not be treated
2. Unstable, meniscal tear that will not be treated
3. Less than 50% of native meniscal volume remaining in the knee following previous meniscal surgery
4. Knee alignment that in the opinion of the surgeon requires realignment surgery/osteotomy
5. Chondral or osteochondral lesion measuring >4cm^2 following operative debridement of the lesion to a stable chondral rim
6. Chondral or osteochondral lesion has been treated previously with one of the study interventions.
7. Defects occurring on the tibial chondral surface
8. Patient unable/unwilling to adhere to trial procedures
9. Unable to provide informed consent

10. Enrolled in another clinical trial and: a) co-enrolment is not permitted by the other trial; or b) co-enrolment would be burdensome for the patient; c) the intervention of the other trial could interfere with the SISMIC primary outcome.

5.6 Trial interventions

The surgery will be delivered in secondary or tertiary care facilities under the supervision of a Consultant Orthopaedic Surgeon. Participants will routinely have an MRI scan performed as part of their diagnostic/treatment pathway. All procedures will be performed in an operating theatre following preoperative assessment and appropriate consent, under general or regional anaesthesia according to the preference of the treating surgeon and anaesthetist.

Both trial interventions are stable, and it is not anticipated there will be significant change to the interventions during the trial. All study surgeons will deliver both study treatments.

A knee arthroscopy will be performed. The lesions will be identified and other pathology will be sought, assessed and recorded to ensure compliance with inclusion/ exclusion criteria. The chondral or osteochondral defect will be prepared according to the surgeon's standard technique, to ensure that the lesion is debrided adequately, removing all unstable chondral flaps to a stable chondral rim. The lesion will be measured to confirm it is not greater than 4cm^2 as per the eligibility criteria. A mini-arthrotomy (small incision) will be performed for access to the lesion where required. Microfracture will be performed to the exposed subchondral bone.

Surgeons that are already experienced in performing AMIC with an all arthroscopic technique will be permitted to continue to do so for patients randomised to the microfracture with microstructural scaffold (AMIC) arm of the trial. For those that are not experienced in performing AMIC with an all arthroscopic technique, the procedure will be performed through an arthrotomy. The specific technique used will be recorded

Intervention: microfracture of the chondral / osteochondral lesion with insertion of a bilayer collagen matrix microstructural scaffold (AMIC). The scaffold will be fixed either by stitching or using fibrin glue according to surgeon preference.

Control: microfracture alone.

5.6.1 Site and Surgeon Eligibility

If the study intervention (AMIC) is not routinely used at a site, the site's Trust Clinical Governance procedures should be followed to approve that the study intervention can be performed within the trust.

The techniques used in this study are stable clinical interventions that are in frequent and widespread use across the NHS. The skills required to perform the interventions are common to many of the procedures performed by the knee surgeons whom will deliver the study interventions. We recommend that the clinical expertise and competence of the Principal Investigator (PI) at each site to perform both study treatments is ensured by one of the following:

- Evidence of attendance of a surgical training day where arthroscopic chondral surgery was one of the techniques used within the last 2 years* or

- PI may provide confirmation of regular performance of arthroscopic chondral surgery (>4/year) in their clinical practice within the last 2 years.*
  * *excluding any period of cancelled or reduced activity in the NHS due to the effects of Covid19*

If required, the Chief Investigator (CI) or Clinical Lead will sign off the PI to confirm their competency and eligibility for participation in the trial. Once participation in the trial is initiated, the CI or clinical lead may, if required, reconfirm competency within the first 6 months by at least one of the following:

- attending the site to observe the performance of the study intervention or
- observing the surgeon perform the study intervention at a cadaveric (or alternative simulation environment) training session or
- review an intraoperative video of the technique being performed by the surgeon or
- observe videoed simulated delivery of the study intervention (either cadaveric or alternative simulation environment) or
- invite the PI to visit the sponsor site whilst study to observe the performance of the study intervention with training by the Clinical Lead

The site PI will confirm the competency of the other surgeons at their site. If any surgeon is not familiar with any part of the required interventions, face to face clinical training will be offered.

5.7 Primary and secondary outcomes

5.7.1 Primary outcome

Following the consensus statement recommendations of the International Cartilage Repair Society Recommendations,(10) the primary outcome is the participant-reported Knee injury and Osteoarthritis Outcome Score (KOOS) which is a validated score for articular cartilage repair 2 years post-randomisation.(11)

5.7.2 Secondary outcomes

Data will be collected to characterise the following secondary outcomes over the two year follow up period:

1. Knee function: International Knee Documentation Committee (IKDC) subjective knee evaluation score(12) at 2 years (range 0-100 with 100 representing the best level of symptoms, function and activity). Domains include symptoms experienced over the last 1-4 weeks and when undertaking particular activities, including sporting activities and activities of daily living. It is reliable and validated with a minimal clinically important difference (MCID) of 9 points.(13)

2. Activity: Tegner-Lysholm activity grading scale(14) (range 0-100 with 100 representing the best level of function/activity). There are 8 questions based on ability or symptoms including limp, support, pain, instability, locking, swelling, stair-climbing and squatting.

3. HRQoL: EQ-5D-5L, a validated, generalised and standardised instrument comprising a visual analogue scale measuring self-rated health and a health status instrument of 5 domains related to daily activities.(15) This instrument will be used to derived 2-year

quality-adjusted life years (QALYs), by attaching UK preference-based utility indices to the EQ-5D-5L health states and weighting them with survival over time.

4. Productivity: Work Productivity and Activity Impairment (WPAI), a validated instrument which measures the impact of health and symptom severity on work productivity and non-work activities.(16) Absenteeism and presenteeism will be valued using the human capital approach and estimates of average weekly earnings(17) to estimate productivity losses for the economic evaluation.

5. Complications: to include bleeding, infection, deep vein thrombosis or pulmonary embolism, need for further surgery (non-joint replacement and joint replacement).

6. Resources required to i) deliver the two treatments, ii) treat short- and long-term complications; iii) follow-up care in hospital, including rehabilitation, outpatient appointments, A&E, and re-admissions. Other health and social care resources required in the community and patient expenditures with their care will be collected from the participant using questionnaires. Resources will be valued using Department of Health and Social Care reference costs, and national unit costs for health and social care, where available(18, 19), or local sources otherwise.

5.8 Sample size calculation

The MCID for the KOOS at 2 years is 10 points(20, 21) and the standard deviation (SD) is approximately 18 in the population of interest.(20, 21) A total sample size of 176 participants (88 per group) will provide 90% power to detect an effect size of 10/18 (=0.56) SD with 5% statistical significance (two-tailed), allowing for up to 20% loss to follow-up.

The sample size calculation has not accounted for the repeated administrations of the KOOS after surgery. Assuming that each participant completes at least two questionnaires over the two years of follow-up (and at baseline) and that there is a moderate correlation of 0.7 between the repeated scores, the study will have 90% power to detect a difference of 0.25 SD in a longitudinal analysis.

6. Trial methods

6.1 Description of randomisation and code breaking

6.1.1 Randomisation

Randomisation will be carried out intraoperatively once debridement of the chondral / osteochondral lesion has been performed and the true size of the defect can be measured. Once the size of the lesion has been confirmed to be no more than 4cm^2, and therefore eligible for inclusion (see Section 5.5), randomisation will be performed. Consent and baseline assessment will be completed prior to surgery. Randomisation will be performed by a member of the local team not involved in data collection or participant follow-up using a secure internet-based randomisation system ensuring allocation concealment. The randomisation system will be available as part of the bespoke study database. Randomisation will be carried out by a member of the research team using their personal login details. Participants will be allocated in a 1:1 ratio to either microfracture plus microstructural scaffold (AMIC) or microfracture alone. The randomisation scheme will take into account important prognostic factors.

Any barriers to successfully randomising once debridement of the chondral/osteochondral lesion has been performed will be explored in phase 1 (internal pilot) of the RCT. Prospective surgeons have confirmed that there are not any foreseen issues around availability of instruments or materials with the above strategy.

6.1.2 Manual randomisation

Instructions on how to perform a manual randomisation will be provided to the research team should the online randomisation system fail.

6.2 Blinding

Randomisation will be performed by a member of the local team (e.g. unblinded research staff, theatre staff, surgical team or the operating surgeon) using an online system, after the size of the lesion has been confirmed to be no more than 4cm^2 and other inclusion/ exclusion criteria are satisfied hence the patient is eligible for inclusion. Anyone involved in the surgery who knows the patient's allocation will be asked not to discuss which operation the participant received. Research nurses responsible for data collection and participant follow-up will not randomise patients and will not be in the operating theatre.

Participants, their clinical care team (except for staff directly involved in the surgery) and research nurse(s) responsible for participant follow-up will not be informed of the allocation until the end of the study. This could be until at least 10 years post-randomisation pending further funding for follow up. If the patient is aware of their allocation before their follow up is finished, it is possible that knowing which treatment they received may influence their decision making regarding further treatment. The time period for blinding will be explained to patients in the PIL. The PIL clearly explains that it is not known which procedure is better. Therefore, in the event of inadvertent unblinding of a participant, it is unlikely that he or she would have a strong expectation that one or other method would lead to a more favourable result, but we would like to avoid taking this risk.

Microfracture and microfracture plus scaffold insertion (AMIC) can both be performed either arthroscopically or through an arthrotomy, these different approaches have different incision sizes. Arthrotomy is more likely to be performed in the scaffold group but we will ask the clinical care team to avoid defining that in the consent process. Patients will be consented for either approach as required. Therefore, we do not expect participants to be unblinded due to the scar size. The rehabilitation and other aspects of clinical care will be the same for both groups, so would not create unblinding. We will assess the success of blinding by asking the patient and all outcome assessors which treatment they think was received (Bang blinding index). Blinding of participants and study personnel will minimise performance bias.

We will provide sites with a study operation note template, which can be used to record the operation and details of the operation that are not blinded. The note will therefore not contain details about the study intervention. A copy of this can be kept in the medical notes, along with details of how to unblind, and another copy can be kept in the patient's CRF folder. The use of the operation note will be optional.

An unblinded CRF form will capture any details of the operation which could unblind staff members. This will be entered into the study database by an authorised unblinded member of staff and then placed in a sealed envelope. This will be stored in the study site file.

6.2.1 Unblinding

We do not anticipate unblinding will be requested on clinical grounds, e.g. to treat a complication. The intervention and control are similar surgical procedures with common risks, side effects and complications that occur at similar rates. The allocation of a patient to either arm of the study would not affect the management of the patient if a complication (e.g. infection or bleeding) were to occur meaning that the treating clinicians would not need to be aware of the allocation in order to deliver effective and appropriate treatment. However, for the rare occasion where unblinding is required, the unblinded CRF described in section 6.2 can be removed from the sealed envelope within the site file. Any member of staff accessing the documents in the sealed envelope will have to record the reason for accessing the documentation. This will provide a record of the staff who have been unblinded and the reason. Unblinding rates will be monitored throughout the trial by the study team and by the independent Data Monitoring and Safety Committee (DMSC) that will be established to oversee participant safety in the trial. Participants will be made aware before entering the study that they will not be told which treatment they will receive until the end of the trial.

6.3 Research procedures

6.3.1 Patient reported outcomes

Baseline comorbidity, KOOS, IKDC, HRQoL, Tegner-Lysholm activity grading scale and the WPAI questionnaires will be administered prior to randomisation. If the comorbidity questionnaire is not completed by the patient, this information should be sourced from the patients medical notes.

Questionnaires to capture clinical outcomes, HRQoL and resource use will be administered at approximately 3 months, 6 months, 1 year and 2 years when the participant attends the site for a clinical follow-up (up to 1 year) or research follow up (2 years), with alternative arrangements for participants who do not attend (e.g. postal, telephone or on-line data collection). If the patient does not complete the questionnaire at the site or if the questionnaire is not returned on time, then the site should follow this up with a phone call to the patient to ensure the questionnaire is returned. The completion rates of the questionnaires will be monitored via the study database and flagged to sites if missing.

6.3.2 Treatment adherence

Withdrawals during surgery should not occur due to the nature of the treatment; the duration of the intervention is the time taken to insert the scaffold. Problems with adherence (e.g. giving rise to cross-overs) are also expected to be low given randomisation will take place after debridement and confirmation that the lesion size is eligible. Operative details will be collected for all participants to allow adherence to be monitored.

6.3.3 Rehabilitation procedure – all participants

The rehabilitation protocol will be for all participants to mobilise protected weight bearing with crutches for 6 weeks post operatively and to use a brace limiting range of motion to 0-90 degrees flexion for 6 weeks. For patella and trochlea lesions there will be additional restriction of 0-30 degrees flexion for the first 2 weeks. Increased restriction will be at the discretion of the surgeon depending on lesion site, size and associated injuries.

6.4 Duration of treatment period

The duration of the treatment commences when the patient enters the operating room and concludes when the patient leaves the operating room after their surgery. The duration of the procedure will be between 30 minutes and 1 hour 30 minutes for both procedures. (experimental group 20 mins longer).

6.5 Definition of end of trial

Active data collection will continue up until 2 years post-randomisation. The patient's active involvement in the trial will end at this point. However, if we receive further funding we may continue follow up for at least 10 years. Data collection for the whole trial will be complete when the final randomised participant has completed the 2 year post randomisation. assessments. The end of the trial will be when the database is closed, all the data queries have been answered. This will allow time to process an amendment to continue with further follow up should further funding be awarded.

6.6 Data collection

Each patient will be assigned a unique study number. All data recorded on paper relating to the participant will be located in Case Report Form (CRF) folders, which will be stored securely at individual sites. Staff with authorisation to make changes to the study records, including the study database, will be listed on the study delegation log maintained at each specialty/centre. The baseline data will be collected after consent. Consenting patients will be seen by an authorised member of the local research team (as specified in the delegation log) who will answer any questions, confirm the patient's eligibility and take written informed consent if the patient decides to participate.

Patients who choose to consent using electronic consent methods will provide their email address to the local research team to receive a link to the electronic consent form.

Data collection will include the following elements:

(a) A screening log of all patients identified with a symptomatic chondral lesion will be invited to participate;

(b) Patients approached and assessed against the eligibility criteria and, if ineligible, reasons for ineligibility;

(c) Consent information collected prior to randomisation in all participating patients;

(d) Baseline information (e.g. sociodemographcs, history, planned operation and response to health, comorbidities and work status questionnaires) collected in all participating patients;

(e) Data relating to the participant's surgery and hospital stay collected in all participating patients;

(g) Data on health status, activity, knee function, productivity (collected via questionnaires), adverse events and resource use collected at 3, 6, 12 and 24 months post-randomisation for all participating patients.

(h) Bang Blinding Index from researchers and patients at 3 and 24 months

In the event that unforeseen circumstances prevent sites from being able to carry out their normal activities, they should contact the BTC who will do everything they can to help. This may include, but is not limited to, sending out questionnaires and reminders on their behalf.

To minimise bias, outcome measures are defined as far as possible on the basis of objective criteria and all personnel carrying out outcome assessment will be blinded.

Table 1 Data collection

Data item	*Baseline*	*Intra-operatively*	*Discharge*	*Post-randomisation*					
				3 months	*6 months*	*12 months*	*24 months*	*5 years**	*10 years**
Demography	✓								
Relevant medical history	✓								
Comorbidities	✓								
Operative details		✓							
Bang blinding index				✓			✓		
KOOS	✓			✓	✓	✓	✓	✓	✓
IKDC	✓			✓	✓	✓	✓	✓	✓
Activity grading	✓			✓	✓	✓	✓	✓	✓
Productivity	✓			✓	✓	✓	✓	✓	✓
HRQoL (EQ-5D)	✓			✓	✓	✓	✓	✓	✓
Post-operative complications			✓	✓	✓	✓	✓	✓	✓
Rehabilitation			✓	✓					
SAEs, including re-admissions¥			✓	✓	✓	✓	✓	✓	✓
Resource use		✓		✓	✓	✓	✓	✓	✓

* not costed as part of this study; events would be captured through routine data (HES)
¥ *SAEs will be subject to expedited reporting to the Sponsor up to 3 months post-randomisation. SAEs collected for later time points will not be subject to expedited reporting.*

To minimise bias, outcome measures are defined as far as possible on the basis of objective criteria. All personnel carrying out outcome assessment will be blinded; this will minimise detection bias.

6.7 Source data

The primary data source will be the participant's medical records, alongside the data collection forms for the study. The completed patient questionnaires will be the primary data source for information on the patients' health, knee function, productivity, comorbidities and activity.

6.8 Planned recruitment rate

6.8.1 Phase 1

Phase 1 recruitment will take place in up to 8 sites for 8 months. There will be a review of the progression criteria at the end phase 1. See section 7.4.

6.8.2 Phase 2

If the progression criteria are met, recruitment into Phase 2 will continue in an additional approximately 8 sites (at least 16 sites total). All participants will be followed up for 24 months.

6.9 Participant recruitment

All patients identified with a symptomatic chondral or osteochondral lesion will be invited to participate. Potential trial participants will be identified by clinical teams. Prior to screening, patients will be seen in specialist knee clinics or in consultation with a specialist knee surgeon, for example an orthopaedic elective knee clinic or acute knee clinic which patients are referred to from triage services (e.g. fracture clinic, GP or physiotherapy). During the clinic appointment the clinician will review the patient's MRI scan, if available, and once the patient is confirmed as requiring treatment for a symptomatic defect, they will be listed for surgery and could be on a waiting list for up to 9 months (waiting times will vary between centres). Patients may be informed of the study at the clinic, but due to long waiting times, it is anticipated that patients may be identified from surgery waiting lists and approached closer to their surgery date, for example at a pre-operative assessment clinic or consent clinic.

There will be a three-stage screening process. The initial stage of screening will take place once the patient is identified on the surgery waiting list or from a clinic virtual or face to face consultation. This will involve assessment of eligibility criteria, including preoperative imaging where the lesion size must be anticipated to be less than $4cm^2$ for the patient to be eligible. If none of the exclusion criteria have been met, the patient will be approached and given a PIL at this stage, either in person at a clinic or they will be sent the PIL in the post or via email by a member from the research team. If patients are sent a PIL in the post or via email, a member of the research team may have a telephone consultation or video call to explain the study and answer any questions (see 6.9.1 for further information). The PIL will include contact details for the research team in case the patient has any questions.

Following this, at 2 to 8 weeks before surgery the patient will attend a pre-operative assessment or other clinic (this will vary across sites). The surgeon will confirm the patient's preoperative eligibility and a member of the research team will gain consent (if the patient decides to participate). All individuals taking informed consent will be GCP trained. During the consultation potential participants will be fully apprised of the potential risks, benefits and burdens of the study. They will also be informed that if the lesion size is determined to be too big, they will not

be eligible for the study and will receive standard care. If a site is not able to take consent at a preoperative clinic, providing the patient has had time to consider the study and ask any questions, written consent can be taken on the day of surgery by a member of the research team. The patient will keep a copy of the consent form, the research team will file another copy in the patient CRF folder and a final copy will be stored in the patient's medical records. Details of all patients approached for the trial and reason(s) for non-participation (e.g. reason for being ineligible or patient refusal) will be documented.

The final stage of screening will occur in theatre when the patient's lesion size can be accurately measured following debridement of all loose and unstable cartilage to define the true lesion size, and eligibility can be fully confirmed. The patient will therefore be randomised in theatre.

6.9.1 Study information pack and consent provision

All potential patients will receive an invitation letter and PIL, approved by the HRA/NHS REC, describing the study as part of a study information pack. These documents may be given to the potential patient in person or sent via post or via email. The study information pack, if sent by post or email may also include the SISMIC patient consent form and baseline questionnaire for completion before surgery if the patient consents to join the trial. Whether the questionnaire is sent and completed before attending the hospital for surgery or is completed when the patient attends the hospital will depend on the local patient pathway.

Consent will be obtained either by face to face at a clinic appointment or remotely by telephone/video call or electronically using a purposed designed electronic database. The consent process will be described in detail in the study manual. Participants who consent via video call or telephone will be guided through the process of completing the consent form by the local research team. Participants will be asked to return their signed consent form by:

- scanning or taking a photograph of the form(s) and emailing the form(s)
- posting the form(s) to the research team
- bringing the form(s) to their next hospital visit

On receiving the consent form(s) the research team will check for errors, counter sign and date. Photocopies of the consent form(s) will be made and the research team will ensure that the participant is given a copy of their countersigned consent form(s) at a hospital visit or is sent copies by post or email as preferred. The counter-signed consent form will be retained at the study site, and a copy will be filed in the medical notes. Details of all participants approached for the study and reason(s) for non-participation (e.g. reason for being ineligible or participant refusal) will be documented. Eligibility will be confirmed by a clinician prior to randomisation.

6.10 Discontinuation/withdrawal of participants

Each participant has the right to withdraw at any time. It is unlikely for this trial that there would be any reason for the investigator to withdraw the participant from their allocated treatment, unless subsequent to randomisation, a clinical reason for not performing the surgical procedure is discovered. In the unlikely event that a participant loses capacity during the study they will be withdrawn. Any information already collected about them will be used, and where appropriate the collection of routine data for these patients will continue.

All withdrawals, including reasons (where given), will be recorded. If a participant wishes to withdraw, data collected up until that point will be included in the analyses. Passive data collection (e.g. from medical records) will also continue, unless the participant expresses a wish for this to stop. This is explained in the PIL.

6.11 Frequency and duration of follow up

Follow up will be face-to-face and via questionnaires. Questionnaires will be administered at at approximately 3, 6, 12 and 24 months post randomisation for information on knee function, activity, HRQoL, return to work and resource use.

Participants will attend the site for follow-up at approximately 3 months, 6 months, 1 year (all routine care) and at 2 years (research-specific follow-up). Data will be collected at these visits and with alternative arrangements for participants who do not attend (e.g. postal or on-line data collection, telephone follow-up at mutually agreed times).

All questionnaires will be administered by a research nurse at each participating centre in person, by post or online. Participating centres will be responsible for collecting these from patients and entering them into the study database. Reminders will be sent approximately 2 weeks after the initial contact if no reply has been received. A maximum of 3 reminders will be sent per time point. Participants can opt in to receive text message reminders. The SMS service will be provided by Three Cherries Limited, a third party vendor, contracted by the University of Bristol under a long-standing agreement to provide an SMS for research purposes.

Further follow up may continue for up to 10 years subject to further funding.

6.12 Likely rate of loss to follow-up

Until discharge from hospital, the only losses to follow-up will be due to death, a participant withdrawing or ceasing to engage in follow-up; these losses are expected to be very few. In estimating the target sample size for the study, a loss to follow-up of 20% has been allowed for.

6.13 Expenses

Participant travel expenses will not be reimbursed for the 3, 6 and 12 month follow up visits which are expected to occur as part of normal surgical follow up. Exceptions to these can be considered on a case by case basis. A limited amount of expenses will be available for the 24 month follow up visit which is a research-specific visit that would not be expected to occur as part of normal surgical follow up.

7. Statistical analyses

7.1 Plan of analysis – primary and secondary outcomes

Primary analyses will be by intention-to-treat (ITT) and will be directed by a pre-specified statistical analysis plan. Analyses will use data from all patients randomised. Primary and secondary outcomes will be compared using mixed model (continuous variables measured at multiple time points) regression, or logistic regression (binary variables). Mixed models allow all patients with data to be included in the analysis, i.e. partial missing data (assumed missing at random) is permitted. Interactions between treatment and time will be examined and if significant at the 10% level, results will be reported separately for each postoperative time point; otherwise overall treatment effects will be reported. Model validity will be checked using standard methods; if a model is a poor fit, alternative models or transformations will be explored. Outcomes analysed on a logarithmic scale will be transformed back to the original scale after analysis and results presented as geometric mean ratios. Analyses will be adjusted for baseline values and centre and surgeon will be fitted as a random effect. Findings will be reported as effect sizes with 95% confidence intervals, and in accordance with the CONSORT reporting guidelines.

7.2 Subgroup analyses

No subgroup analyses are planned

7.3 Frequency of analyses

The primary analysis will take place when follow-up is complete for all recruited patients, i.e. at 2 years. An analysis of outcomes at 1 year will also be conducted and reported. The value of including a closed formal interim analysis will be discussed with the DMSC. Safety data will be reported to the DMSC every 6 months, together with any additional analyses the committee request.

7.4 Criteria for the termination of the trial

There are two conditions that might lead the Trial Steering Committee (TSC) to recommend stopping the trial early:

A) A failure to recruit sufficient patients or open sufficient sites to meet the target sample size within the proposed duration of the grant and refusal of the funder to extend the duration of recruitment.

B) A failure to deliver the intervention as planned.

With respect to (A), we plan to recruit our target sample size of 176 participants over 24 months. After 8 months of active recruitment in the first 8 of our planned 16 study centres, opened in a staggered fashion, if our target recruitment rate is being met, we should have recruited 24 participants. Accepting recruitment typically starts slowly and increases over time as the trial gets established and that there is some variability from one month to the next (e.g. recruitment is typically lower over Christmas and in the summer holiday period than at other times of year) we will propose a recovery plan if:

A) Between 18 and 24 patients have been recruited within 8 months and
B) At least 5 sites have opened to recruitment

If these targets have not been met, i.e. fewer than 18 patients have been recruited or less than 5 sites have opened to recruitment, close down will be considered. Progression criteria are detailed in table 2.

The trial team will prepare a report for the TSC to consider and make a recommendation to the NIHR-HTA. With respect to (B), failure to deliver the intervention and rehabilitation as planned, we will monitor adherence to the protocol throughout the trial and will investigate all cases of nonadherence. We will prepare a report for the TSC to consider and we will propose halting the trial if the reasons for non-adherence cannot be addressed satisfactorily.

In addition to monitoring recruitment and adherence, the DMSC will monitor safety outcomes. The DMSC may recommend stopping the trial if the accrued data suggest that the trial is unsafe for one or both groups of participants.

Table 2 Progression criteria

	Red	Amber	Green
Trial recruitment	75%	75<100%	≥100%
Recruitment rate/ site/ month	0	0-1	≥1
Number of sites opened	<5	5<8	8
Total number of participants recruited	<18	18<24	24

7.5 Health Economics

A prospective within-trial economic evaluation will be conducted from an NHS and personal social services perspective (PSS) at 2 years, following NICE guidelines.(22) Given the important economic consequences to society of delivering treatments to this younger patient group, we will also report productivity losses of absenteeism and presenteeism captured within the WPAI, and privately incurred costs separately. The economic evaluation will estimate the differences in the costs and health benefits between the two groups within a cost-consequences framework. Consequences of interest are quality adjusted life years (QALYs) and the primary and secondary outcomes.

The cost-effectiveness analyses will be by ITT and follow closely the statistical analysis in terms of methods to adjust for stratification and baseline variables. Costs and QALYs in the second year of treatment will be discounted using the discount rates advised in NICE guidelines (currently 3.5%).(22) It is likely that there will be a relationship between costs and outcomes and data are not missing completely at random but can be predicted by known confounders. Missing cost and QALY data will be jointly imputed using multiple imputation methods with chained equations assuming data and the primary economic analyses will use complete datasets with imputed data.

We will also report all available cost and outcomes, including QALY data, in a cost-consequences table for transparent decision-making, with costs aggregated by secondary care and community based NHS resources, PSS, productivity losses, and private expenses, and further aggregate the NHS plus PSS for the main analysis. The primary economic result will be the incremental net monetary benefit statistic, which represents the monetary value of an

intervention. Using NICE recommend thresholds of willingness-to-pay between £20,000 and £30,000 for a QALY, we will estimate how much the UK society is willing to pay for the incremental QALYs gained or lost from adding scaffolding to microfracture and deduce its cost over the 2 years. If the value is positive it means that the addition of the scaffold represents good value for money in the UK. The difference in costs, QALYs, and incremental net monetary benefit will be bootstrapped and adjusted for baseline and stratification variables and follow closely the statistical analysis assumptions. We will perform a range of sensitivity analyses to assess the methodological and costing assumptions, including reporting productivity losses and how these may or may not influence decision-making from a societal perspective. The probability of microfracture with insertion of a microstructural scaffold being cost-effective compared to microfracture alone will be depicted in a cost-effectiveness acceptability curve.(23) If no treatment is dominant, we will also report the incremental cost per QALY gained ratio.

Subject to securing further funding, we will assess the economic consequences of inserting a microstructural scaffold from an NHS perspective over the first 5 and then 10 years of follow-up. NHS secondary care data will be retrieved from linked HES data and NHS costs derived from resource use healthcare resource group codes. HRQoL measured by the EQ-5D-5L would be sought at 5 and 10 years and QALYs estimated in a similar way to the main 2-year analysis. For comparison with future economic evaluation results, we will produce economic results in the 2-year economic evaluation using secondary care resource use data only. In the likelihood that the health benefits would extend beyond 5 years, we will explore the possibility of using Markov decision economic models to estimate the lifetime cost-effectiveness of the two treatment options.

8. Trial management

North Bristol NHS Trust will act as Sponsor. The trial will be managed by the Clinical Trials and Evaluation Unit (CTEU), Bristol Trials Centre (BTC). The BTC is built on the experience of the Bristol Clinical Trials and Evaluation Unit and the Bristol Randomised Trials Collaboration, both fully registered UKCRC Units. BTC will prepare all the trial documentation and data collection forms, specify the randomisation scheme, develop and maintain the study database, check data quality as the trial progresses, monitor recruitment and carry out trial analyses in collaboration with the clinical investigators.

8.1 Day-to-day management

Appropriately qualified persons by training will be responsible for identifying potential trial participants, seeking informed participant consent, randomising participants, collecting trial data and ensuring the trial protocol is adhered to.

The core research team will meet approximately every 6 weeks to manage the trial and monitor progress. The core team are regular collaborators on a large number of different projects and in the case of the clinicians work together in both elective and trauma capacities. There are well established lines of communication and such communication will be continuous throughout the life of the project rather than being constrained to formal meetings only, this will facilitate rapid response to any issues raised.

8.2 Monitoring of sites

8.2.1 Site Initiation

Before the study commences training session(s) will be organised by BTC. These sessions will ensure that personnel involved fully understand the protocol, CRFs and the practical procedures for the study. These sessions will either be completed face to face or via teleconference.

8.2.2 Site monitoring

BTC will carry out central monitoring and audit of compliance of centres/surgical specialties with the principles of Good Clinical Practice (GCP) and data collection procedures. The study database will have extensive in-built validation and the core research team and TMG will review the completeness and consistency of the data throughout the trial. BTC will not check CRFs against the data entered or against source data, unless there are good reasons to visit the site to complete a monitoring visit (e.g. the central monitoring highlights a problem or as requested by the sponsor).

8.3 Trial Steering Committee and Data Monitoring and Safety Committee

8.3.1 Trial Steering Committee

An independent TSC will be established to oversee the conduct of the study. It is anticipated that the TSC will comprise the lead investigators, an independent chair and at least three additional independent members, including a statistician or methodologist, an orthopaedic knee surgeon, an experienced clinical researcher and a patient/public representative. The TSC will develop terms of reference outlining their responsibilities and operational details. The TSC will meet before recruitment begins and regularly (at intervals to be agreed with the Committee) during the course of the study. The TSC will formally review recruitment at the end of phase 1 and make recommendations.

8.3.2 Data Monitoring and Safety Committee

An independent DMSC will be established to review safety data during the course of the study and will review the assumptions underpinning the sample size calculation. The DMSC will develop a charter outlining their responsibilities and operational details. The DMSC will meet (jointly with the TSC) before the trial begins and they will meet regularly thereafter (at intervals to be agreed with the Committee).

9. Safety reporting

Serious and other adverse events will be recorded and reported in accordance with Good Clinical Practice (GCP) guidelines and the Sponsor's SOP (see Figure 2). Please see Table 3 for definitions.

BTC will report SUSARs to regulatory authorities and copy all reports to the sponsor within the expected time frames. Sites will report SAEs to the BTC within 24hrs of the study team becoming aware of the event. Events that are anticipated of surgery will not require expedited reporting to the Sponsor unless they are deemed to be related to the intervention, otherwise all unexpected serious events will be reported to the Sponsor as detailed in 0.

Elective surgery during the follow-up period that was planned prior to recruitment to the trial will not be reported as an unexpected SAE.

If the event is ongoing, there is no mandatory requirement regarding the frequency which follow-up reports should be submitted. As a minimum, a report should be submitted when the event resolves/ends.

Table 3 Definitions

Term	Definition
Adverse Event (AE)	An AE can be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the research procedure, whether or not considered related. AEs require continuous assessment.
Adverse Reaction (AR)	The distinguishing feature between an AR and AE is whether there is evidence to suggest there is a causal relationship between the event and the research procedure.
Serious Adverse Event (SAE)	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.
Serious Adverse Reaction (SAR)	Any SAE that is classed in nature as serious and there is evidence to suggest there is a causal relationship between the event and the research procedure, but where that event is expected.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any SAE that is classed in nature as serious and there is evidence to suggest there is a causal relationship between the event and the research procedure, but where that event is unexpected.

9.1 Expected Events of a Bilayer Collage Matrix

There are no known expected events associated with the insertion of a bilayer collagen matrix.

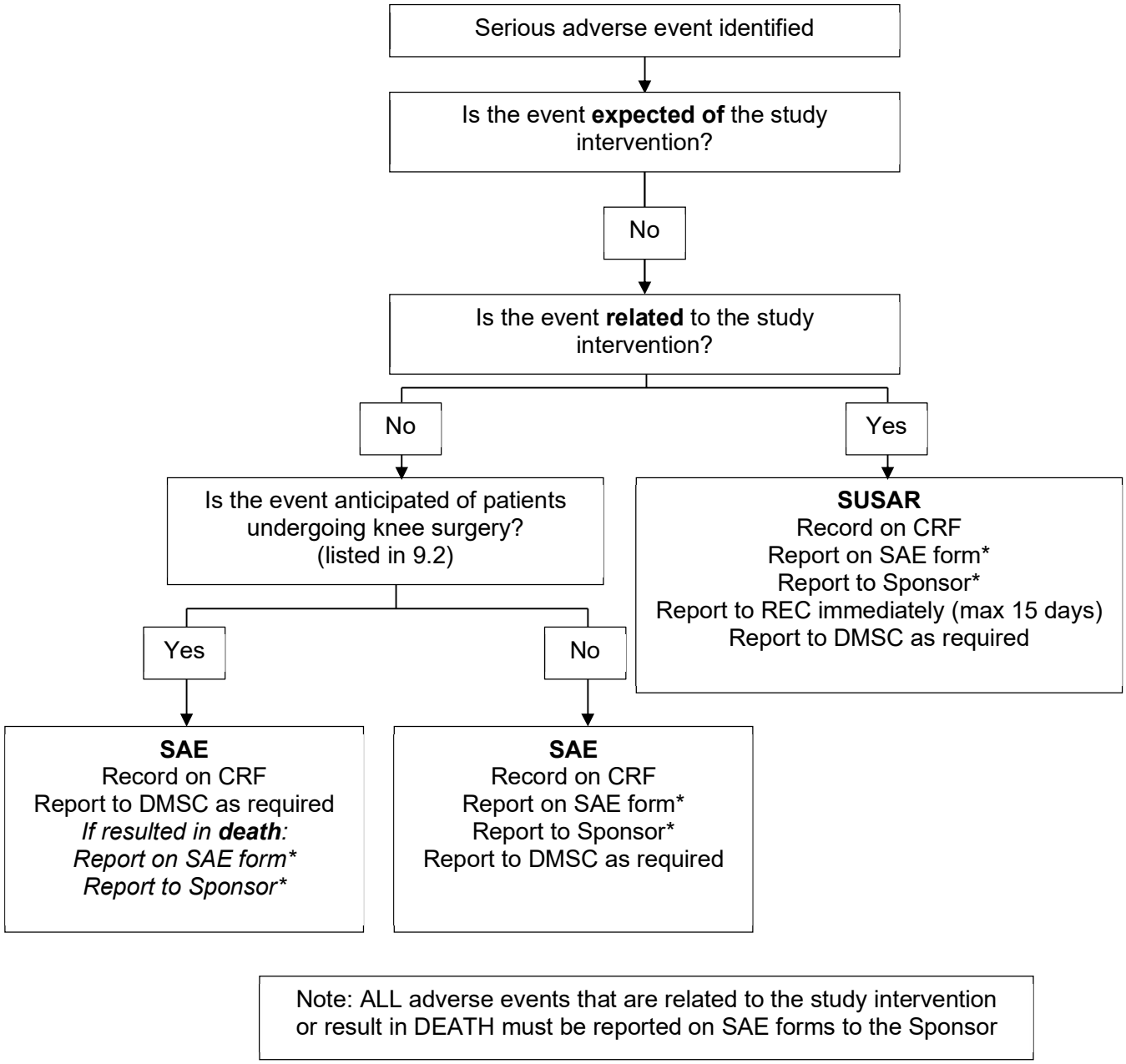
9.2 Anticipated Events of Knee Surgery

The following adverse events occur frequently in patients undergoing knee surgery and therefore will be considered anticipated:

- Swelling that meets the criteria of a serious event, or requires further surgical intervention (e.g. further arthroscopic or open surgery)
- Pain that meets the criteria of a serious event, or requires further surgical intervention (e.g. further arthroscopic or open surgery)
- Stiffness that meets the criteria of a serious event, or requires further surgical intervention (e.g. further arthroscopic or open surgery or a manipulation under anaesthetic)
- Infection as confirmed by positive microbiological samples from the operated knee or requiring washout or debridement for infection
- Bleeding requiring washout in theatre
- Scarring - excessive scarring leading to stiffness or another problem that requires further surgical intervention (e.g. further arthroscopic or open surgery or a manipulation under anaesthetic)
- Nerve damage - leading to a persistent (>2 weeks) alteration in motor function of a peripheral nerve or sensory disturbance
- DVT/PE
- Further knee surgery

Data on these adverse events collected during the trial will be reported regularly to the trial DMSC and to the Sponsor for review. If an anticipated event meets the criteria for seriousness (as outlined in Table 3) and is deemed by the Principal Investigator (or delegated individual) to be possibly, probably or definitely related to the bilayer collagen matrix this event would be reported as a SUSAR.

Figure 2 Serious adverse event reporting flow chart



** SAEs will be subject to expedited reporting to the Sponsor up to 3 months post-randomisation, unless the SAE is related. Related SAEs will be subject to expedited reporting to the Sponsor up to 24 months post-randomisation. Beyond the 3 month time point, aggregated reports will be provided to the Sponsor.*

9.3 Period for recording serious adverse events

Data on adverse events will be collected from randomisation to hospital discharge. All serious adverse events (SAEs) will be collected from consent up to 24 months. SAEs will be subject to expedited reporting to the Sponsor up to 3 months post-randomisation, unless the SAE is related. Related SAEs will be subject to expedited reporting to the Sponsor up to 24 months post-randomisation. Beyond the 3 month time point, aggregated reports will be provided to the Sponsor.

10. Ethical considerations

10.1 Review by an NHS Research Ethics Committee

The research will be performed subject to a favourable opinion from an NHS REC and Health Research Authority (HRA), including any provisions of Site Specific Assessment (SSA), and local site capacity and capability confirmation. Ethics review of the protocol for the trial and other trial related essential documents (e.g. PIL and consent form) will be carried out by a UK NHS REC. Any subsequent amendments to these documents will be submitted to the REC and HRA for approval prior to implementation.

10.2 Risks and anticipated benefits

Potential benefits of taking part in the study include that if either of the treatment arms is found to be superior, of which there is no current robust evidence, then patients allocated to that arm would receive a superior treatment. Conversely, those allocated to the other arm would not receive this benefit.

Participation in research studies may offer benefit to patients in terms of outcomes experienced for the treatments they undergo.(24)

The risks, side effects and potential complications associated with participation in the study are the same between the control and experimental intervention being used, as such, it is not anticipated that participation in the study would represent an increased risk for participants. Patients deemed to be eligible for inclusion will have symptomatic articular cartilage lesions that require treatment as defined by NICE, therefore the surgical treatment rate would not be increased for participants. Potential adverse effects of the types of surgery being used in this study include infection, bleeding, pain, stiffness, swelling, deep vein thrombosis, pulmonary embolism, scarring, numbness and reoperation.

The conduct of this study will allow us to determine which of the treatments is the most clinically and cost effective, as such, this study will allow us to make evidence-based recommendations for the treatment of this patient population.

10.3 Informing potential study participants of possible benefits and known risks

Information about possible benefits and risks of participation will be described in the PIL.

10.4 Obtaining informed consent from participants

All participants will be required to give written informed consent. This process, including the information about the trial given to patients in advance of recruitment, is described above in section 6.9. The PI or delegate will be responsible for the consent process.

10.5 Co-enrolment

Co-enrolment with another study will be considered on a case-by-case basis. Generally, co-enrolment will be allowed if the intervention is not expected to influence the primary outcome, it is permitted by the other study and if participation in both studies does not present an excess burden to the participant.

11. Research governance

This study will be conducted in accordance with:

- Good Clinical Practice (GCP) guidelines
- UK Policy Framework for Health and Social Care Research

11.1 Sponsor approval

Any amendments to the trial documents must be approved by the sponsor prior to submission to the REC/HRA.

11.2 Confirmation of Capacity and Capability

Confirmation of capacity and capability from the each NHS Trust is required prior to the start of the study at that site.

Any amendments to the study documents approved the REC and the HRA will be submitted to the study sites, as required by the HRA.

11.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and study manual and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or BTC or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their trial team of any amendments to the trial documents approved the REC/HRA that they receive and ensure that the changes are complied with.

11.4 Monitoring by sponsor

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the UK Policy Framework for Health and Social Care Research and the Medicines for Human Use (Clinical Trials) Regulations 2004. All study related documents will be

made available on request for monitoring and audit by the sponsor (or BTC if they have been delegated to monitor see 8.2.2), the relevant REC/HRA and for inspection by the MHRA or other licensing bodies.

11.5 Indemnity

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

12. Data protection and participant confidentiality

12.1 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 2018.

12.2 Data handling, storage and sharing

12.2.1 Data handling

Full details will be provided in the data management plan which will also define how personal, identifiable and non-identifiable patient information is used in the study.

Data will be entered into a purpose-designed server database hosted on the NHS network. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to SISMIC study staff at the participating site and the co-ordinating centre. Information capable of identifying participants will not be made available in any form to those outside the study.

Access to the database will be via a secure password-protected web-interface (NHS clinical portal). Study data transferred electronically to the University of Bristol network for statistical analyses will be pseudonymised and transferred via a secure network. The participants will be identified using their name and unique study identifier on the secure NHS hosted database.

Data will be entered promptly and data validation and cleaning will be carried out throughout the trial. The trial manual will cover database use, data validation and data cleaning. The manual will be available and regularly maintained.

12.2.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and for 5 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. In compliance with the MRC Policy on Data Sharing, and with participant agreement, relevant ‘meta’-data about the trial and the full dataset, but without any participant identifiers other than the unique participant identifier, will be held indefinitely (University server). These will be retained because of the potential for the raw data to be used subsequently for secondary research.

Archiving will be done as per BTC SOPs in agreement with the Sponsor. Sites will be expected to archive their own documents as per site agreements and BTC will archive the TMF and central coordinating centre documents for five years after the end of the study.

12.2.3 Data sharing

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review.

13. Dissemination of findings

The results of the study will be made publicly available within 12 months of last patient last visit (LPLV). The findings will be disseminated by usual academic channels, i.e. presentation at international meetings, as well as by peer-reviewed publications (including a full report to the NIHR-HTA programme) and through patient organisations and newsletters to patients, where available. Patients who state they would like to be updated on the results of the study will receive a summary of results at the end of the study.

14. References

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15. Amendments to protocol

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
0	1.0	23rd March 2021	2.0	24th May 2021	Updated SAE reporting flow chart due to error	

Appendix 1

Collaboration with the National Joint Registry (NJR) and the International Cartilage Regeneration and Joint Preservation Registry (ICRS).

An initial agreement is in place with the ICRS to gather consent from patients to be part of the registry. At an agreed time, we will share a data set of patients who gave consent for their data to be shared with the registry. This will not involve us registering patients onto the registry as part of the study, however we will not stop sites registering patients if this is part of their usual protocol.
We anticipate that a similar agreement with the NJR will be formed, however this is yet to be put in place.