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Synopsis

# Microfracture with or without collagen scaffold insertion for adults with chondral or osteochondral defects of the knee: the SISMIC RCT and its challenges during and after the COVID-19 pandemic

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Published October 2025
DOI: 10.3310/BRTS2415

## Abstract

**Background:** Around 10,000 symptomatic knee articular cartilage injuries requiring repair occur annually in the United Kingdom, mostly in people under 35 years of age. Microfracture surgery aims to restore cartilage. Adding microstructural scaffolds made of collagen may further improve outcomes.

**Objectives:** To evaluate the clinical and cost-effectiveness of microstructural scaffold in patients undergoing microfracture for a symptomatic chondral or osteochondral defect of the knee.

**Design:** Multicentre, parallel two-group, superiority randomised controlled trial with blinding of participants, research staff and clinical care teams not involved in the surgery.

**Setting** National Health Service hospitals offering arthroscopic chondral surgery.

**Participants:** Adults aged 18 years or older with symptomatic chondral or osteochondral defects of the knee on the medial or lateral femoral condyles, trochlea or patella and a chondral or osteochondral lesion measuring no more than 4 $cm^2$. Exclusions were: unstable ligamentous injuries or meniscal tears that would not be treated; a knee with defects on the tibial chondral surface, < 50% native meniscal volume or requiring realignment surgery/osteotomy; and a lesion previously treated with microfracture.

**Interventions:** Lesions were debrided, and microfracture was performed on the exposed subchondral bone.
Intervention: microfracture of the chondral or osteochondral lesion with insertion of a bilayer collagen matrix microstructural scaffold, fixed with stiches or fibrin glue.
Comparator: microfracture alone.
Postoperative physiotherapy was standardised.
Participants were randomised 1 : 1 between intervention and control.

**Main outcome measures:** Primary outcome was the Knee Injury and Osteoarthritis Outcome Score at 24 months post randomisation. Secondary outcomes included International Knee Documentation Committee knee evaluation score; Tegner-Lysholm activity grading scale; EuroQol-5 Dimensions, five-level version; Work Productivity and Activity Impairment; complications and resource use measured at 3, 6, 12 and 24 months.

**Results** Twenty-two patients were screened across 8 sites, 20 of whom were eligible on screening. Of the 20 patients considered initially eligible, 2 patients were not interested and 1 opted for chondroplasty; the remaining 17 all consented to participate. Between November 2021 and October 2022, 10 participants were randomised, 5 to

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microfracture and 5 to microfracture with scaffold. Three patients failed the final in-surgery eligibility check (lesions had healed), one decided not to have surgery and three were still waiting when the study was closed. The median age was 38 years, and four participants were female. Most participants (seven) had damage to the lateral femoral condyle, and six had a medial and/or lateral meniscal tear. All participants received the allocated treatment and are included in the reported results. When a scaffold was used, the surgery took on average 10 minutes longer. There were three serious adverse events, knee pain and swelling in one participant, and a suspected anaphylactic reaction in another.

**Limitations:** The SISMIC randomised controlled trial did not progress beyond the internal pilot phase due to insufficient recruitment. The target number of sites were opened, but recruitment was only 42% of the target 24 participants randomised. Insufficient data were collected to answer the research question.

**Conclusions:** The SISMIC randomised controlled trial was severely impacted by the COVID-19 pandemic, the limited resources available at sites and the reduced elective orthopaedic surgical activity.

**Future work:** To reflect contemporary practice, we recommend that a future trial evaluates three treatments: chondroplasty, chondroplasty with a microstructural scaffold and autologous chondrocyte implantation.

**Funding:** This synopsis presents independent research funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme as award number NIHR127849.

A plain language summary of this synopsis is available on the NIHR Journals Library Website https://doi.org/10.3310/BRTS2415.

## Introduction

### *Background*

The National Institute for Health and Care Excellence (NICE) estimates approximately 10,000 symptomatic knee articular cartilage injuries requiring repair occur annually in the UK,[1] mostly in patients under 35 years of age. Articular (hyaline) cartilage is a specialised structure, allowing low-friction movement with very low wear rates.[2] Unfortunately, cartilage is avascular with low cell density, so it has low healing potential.[3] Cartilage damage can either occur spontaneously (osteochondritis dissecans),[4] due to acute injury or chronically due to injury to instability (e.g. anterior cruciate ligament injury).

Treatment options either aim to restore cartilage [e.g. microfracture, microfracture with scaffold insertion (autologous matrix-induced chondrogenesis – AMIC)] or aim to reduce symptoms without restoring cartilage (e.g. debridement, focal resurfacing, osteotomy, joint replacement). For young patients, restoring cartilage is considered more appropriate. Microfracture involves penetrating the subchondral bone in the area of injury to release fibrin and marrow stem cells with the intention of stimulating cartilage formation.[5] Microfracture increases type II collagen, matrix and protein formation, but not all components of articular cartilage, leading to the suggestion that the addition of microstructural scaffolds, typically made of collagen, may further improve outcomes.[6] During the procedure, a microstructural scaffold is secured over the affected area, acting as a template upon which new cartilage forms. Scaffolds are safe, but they make the operation more complex (approximately 20 minutes longer) and cost approximately £900 each. There is no definitive evidence that using microstructural scaffolds improves outcomes.[7]

### *Rationale*

Evidence of microstructural scaffold's efficacy is lacking,[8] so it is important to establish if their use result in better outcomes for patients and whether it is cost-effective for the NHS. This NIHR Health Technology Assessment (HTA)-commissioned study aimed to address this evidence gap.

### *Aims and objectives*

#### Aim

The aim was to evaluate the clinical and cost-effectiveness of microstructural scaffold in patients undergoing microfracture for a symptomatic chondral or osteochondral defect of the knee. We hypothesised that microfracture with microstructural scaffold would lead to a superior Knee Injury and Osteoarthritis Outcome Score (KOOS) at 2 years compared with microfracture alone.

#### Objectives

Specific objectives were:

1. To estimate the difference between groups in mean KOOS at 2 years.
2. To estimate the difference between groups over a 2-year period with respect to secondary outcomes [knee function, activity, health-related quality of life (HRQoL), return to work].
3. To estimate resource use and costs over 2 years 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).

## Methods

### *Study design*

The SISMIC study was a 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 were blinded to the allocation. The study schema is shown in *Figure 1*.

An internal pilot phase (Phase 1) was incorporated to determine the feasibility of randomising participants during surgery once debridement of the chondral or osteochondral lesion had been performed (see *Criteria for the termination of the trial* for details of the progression criteria). Participant follow-up was planned for 24 months.

### *Setting*

National Health Service hospitals in the UK offering microfracture surgery for a symptomatic chondral or osteochondral defect of the knee.

### *Participants*

Adults with symptomatic chondral or osteochondral defects of the knee.

### Eligibility criteria

#### *Inclusion criteria*

Participants were eligible if *all* of the following applied:

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 4 $cm^2$.

#### *Exclusion criteria*

Participants were ineligible if *any* of the following applied:

1. unstable ligamentous injury to the knee that would not be treated
2. unstable meniscal tear that would 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 required realignment surgery/osteotomy

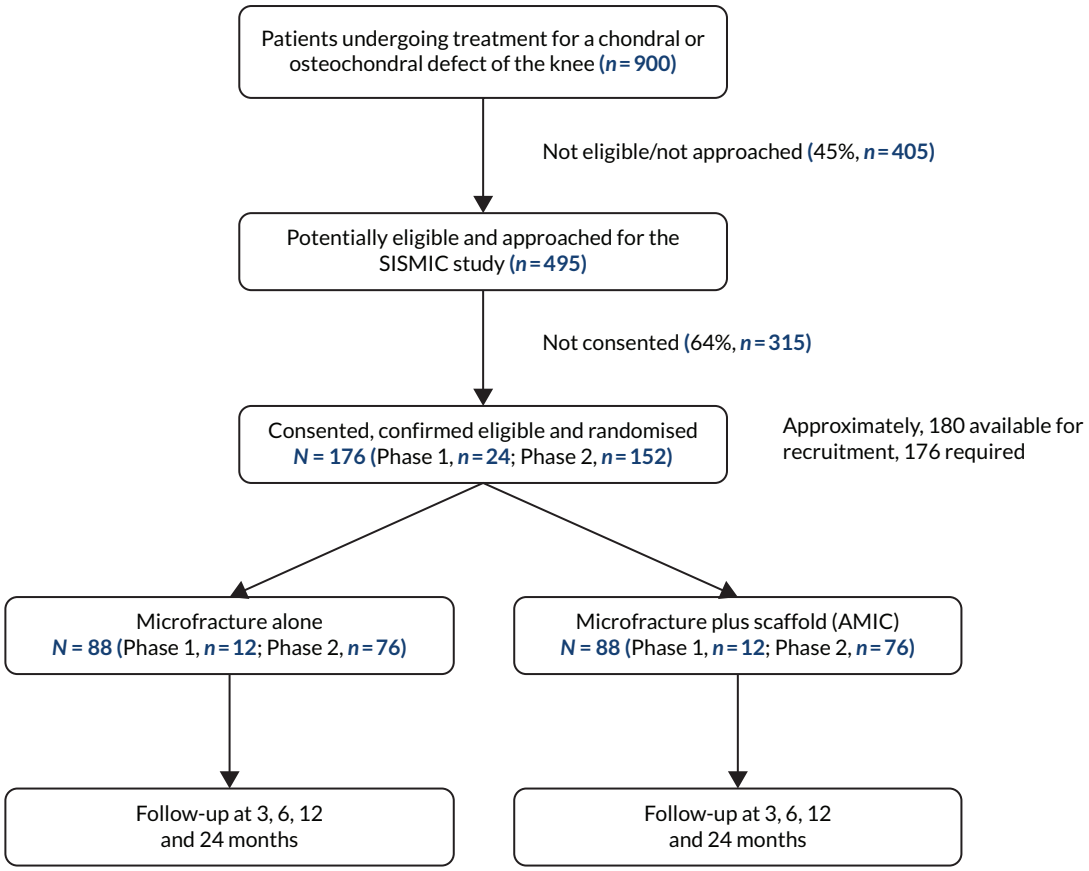


**FIGURE 1** Study schema.

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5. chondral or osteochondral lesion measuring > 4 $cm^2$ following operative debridement of the lesion to a stable chondral rim
6. chondral or osteochondral lesion that had previously been treated 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: (1) co-enrolment is not permitted by the other trial or (2) co-enrolment would be burdensome for the patient or (3) the intervention of the other trial could interfere with the SISMIC primary outcome.

### *Conduct (screening and consent process)*

Patients identified by clinical teams with a symptomatic chondral or osteochondral lesion were invited to participate. Initially, patients were seen in specialist knee clinics or in consultation with a specialist knee surgeon. Once patients were confirmed as requiring treatment for a symptomatic defect, they were listed for surgery.

A three-stage screening process was employed. The initial screening stage took place from surgical waiting lists or clinic consultations, where eligibility criteria was assessed, including preoperative imaging to anticipate the lesion size. If none of the exclusions applied, the patient was approached and given a Health Research Authority and NHS Research Ethics Committee (REC) approved invitation letter and participant information leaflet (PIL), either in person, via post or via e-mail, by a research team member. If the information was sent via post or e-mail, a research team member scheduled a telephone consultation or video call to explain the study and answer any questions. The PIL also included the research team's contact details. The postal/e-mail pack may also have included the participant consent form and baseline questionnaire for completion before surgery if the local patient pathway was such that potential participants could be consented remotely and may not attend the hospital before their surgery.

If the patient agreed to participate, a research team member obtained written informed consent. All research team members taking informed consent were Good Clinical Practice trained. During the consultation, potential participants were fully appraised of the potential risks, benefits and burdens of the study, and they were also informed that if the lesion size was found to be too large during surgery, they would not be eligible and would instead receive standard care. If patients did not attend a preoperative clinic, it was permitted for written consent to be taken on the day of surgery, providing that the patient had sufficient time to consider the study and ask questions.

Participants who consented via video call or telephone were guided through the process of completing the paper consent form by the local research team. Participants were asked to return their signed consent form by either scanning or taking a photograph of the form and e-mailing it, posting the form to the research team or bringing the form to their next hospital visit. On receiving the consent form, the research team checked for errors, countersigned and dated it. Photocopies were made, and the research team ensured that the participant was given a copy of the countersigned form. The countersigned form was retained at the study site, and a copy filed in the medical notes. Alternatively, consent could be captured electronically using a purposed designed electronic consent facility (REDCap eConsent, Vanderbilt University, Nashville, Tennessee, USA). The eConsent facility was created to adapt the study to a post-pandemic world.

The final stage of screening occurred during surgery when the patient's lesion size was accurately measured following debridement. Once eligibility was confirmed, participants were randomised in theatre.

### *Study site and surgeon eligibility*

#### Study sites

Any secondary or tertiary NHS hospital offering microfracture surgery for a symptomatic chondral or osteochondral defect of the knee was eligible to participate. If AMIC (the study intervention) was not in routine use at the hospital at the time of joining the study, the hospital trust's clinical governance team was required to approve its use prior to opening.

#### Study surgeons

The techniques used in SISMIC are stable clinical interventions in frequent and widespread use across the NHS. The skills required to perform the interventions are common to many of the procedures performed by knee surgeons. We recommended that the clinical expertise and competence was ensured by one of the following:

- evidence of attendance within the last 2 years (excluding any period of cancelled or reduced activity in the NHS due to the effects of COVID-19) of a surgical training day where arthroscopic chondral surgery was one of the techniques used or
- 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 COVID-19).

The chief investigator (CI) or clinical lead confirmed the site principal investigator's (PI's) competency and eligibility for participation in the trial. The site PI was responsible for confirming the competency of the other study surgeons at their site. If any surgeon was not familiar with any part of the required interventions, face-to-face clinical training was offered. All study surgeons delivered both study treatments.

If the PI of a site did not meet the eligibility criteria above, then the CI or clinical lead would confirm competency within 6 months by one or more of the means below:

- attending the site to observe the performance of the study intervention
- observing the surgeon perform the study intervention at a cadaveric (or alternative simulation environment) training session
- reviewing an intraoperative video of the technique being performed by the surgeon
- observing videoed simulated delivery of the study intervention (either cadaveric or alternative simulation environment)
- inviting the PI to visit the sponsor site to observe the performance of the study intervention with training by the clinical lead.

## *Trial interventions*

Prior to surgery, all participants routinely had a magnetic resonance imaging (MRI) scan performed as part of their diagnostic/treatment pathway.

All procedures were performed in an operating theatre under general or regional anaesthesia according to the preference of the treating surgeon and anaesthetist. The surgery was delivered under the supervision of a consultant orthopaedic surgeon. Lesions were identified and other pathology sought, assessed and recorded to ensure compliance with inclusion/exclusion criteria. Each chondral or osteochondral defect was prepared according to the surgeon's standard technique to ensure that the lesion was debrided adequately, removing all unstable chondral flaps to a stable chondral rim. Lesions were measured to confirm the size was not > 4 $cm^2$ as per the eligibility criterion. A mini-arthrotomy (small incision) was performed for access to the lesion where required. Microfracture was performed on the exposed subchondral bone.

Surgeons were permitted to use an all-arthroscopic technique for AMIC or perform the procedure through an arthrotomy, according to preference. The specific technique used was recorded in the case report forms (CRFs).

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

*Comparator*: microfracture alone.

### Standard care

Both treatments are routinely used within the NHS. Patients found to be ineligible during surgery (after debridement of the lesion to determine its true size) were treated according to their local hospital's and surgeon's standard care. All other treatment was according to local hospital standard care, with the exception of post-operative physiotherapy, which was standardised across participating centres (see below).

### Rehabilitation procedure

All participants were mobilised using protected weight-bearing with crutches for 6 weeks postoperatively and a brace limiting range of motion to 0–90 degrees of flexion for 6 weeks. For patella and trochlea lesions, there was additional restriction of 0–30 degrees of flexion for the first 2 weeks. Increased restriction was at the discretion of the surgeon depending on lesion site, size and associated injuries.

## *Outcomes*

### Primary outcome

Following the consensus statement of the International Cartilage Repair Society Recommendations,[9] the primary outcome was the participant-reported KOOS, a validated score for articular cartilage repair, at 2 years post randomisation.[10]

### Secondary outcomes

Planned secondary outcomes were:

1. Knee function: International Knee Documentation Committee (IKDC) subjective knee evaluation score[11] at 2 years (range 0–100, with 100 representing the best level of symptoms, function and activity). It is reliable and validated with a minimal clinically important difference (MCID) of 10 points.[12–14]
2. Activity: Tegner-Lysholm activity grading scale[15] (range 0–100, with 100 representing the best level of function/activity).
3. HRQoL: EuroQol-5 Dimensions, five-level version (EQ-5D-5L), a validated, generalised and standardised instrument comprising a visual analogue scale (VAS) measuring self-rated health and a

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health status instrument of five domains related to daily activities.[16] Planned use to derive 2-year quality-adjusted life-years (QALYs) by attaching UK preference-based utility indices to the EQ-5D-5L health status 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.[17] Absenteeism and presenteeism will be valued using the human capital approach and estimates of average weekly earnings[18] to estimate economic productivity losses.
5. Complications: bleeding, infection, deep-vein thrombosis (DVT) or pulmonary embolism, need for further surgery (non-joint replacement and joint replacement).
6. Resources required to (1) deliver treatments, (2) treat short- and long-term complications and (3) follow up care in hospital (rehabilitation, outpatient appointments, emergency department, re-admissions). Other health and social care resources required in the community and patient expenditures with their care were collected from the participant using questionnaires. Resources were intended to be valued using Department of Health and Social Care (DHSC) reference costs, and national unit costs for health and social care, where available,[19,20] or local sources.

### *Adverse events*

No known expected events were associated with the insertion of a bilayer collagen matrix, but a number of adverse events (AEs) were expected as a result of surgery. The list of expected events are listed in the study protocol.

Data on non-serious adverse events (non-SAEs) were collected from randomisation until hospital discharge. Data on all SAEs were planned to be collected from consent up to 24 months post randomisation.

### *Sample size*

We used a MCID for the KOOS at 2 years of 10 points and a standard deviation (SD) of 18 as reported by previous work.[13,14] A planned sample size of 176 participants (88 per group) would have provided 90% power to detect an effect size of 10/18 (= 0.56) SD with 5% statistical significance (two-tailed), allowing for up to 20% lost to follow-up.

### *Randomisation*

Randomisation was performed intraoperatively once debridement of the chondral or osteochondral lesion had taken place and its true size measured. If the size of the lesion was confirmed to be no more than 4 $cm^2$, an unblinded member of the local team randomised the participant using a secure internet-based randomisation system that ensured allocation concealment. Participants were allocated in a 1 : 1 ratio to either microfracture plus microstructural scaffold (AMIC) or microfracture alone. The allocation was stratified by centre and blocked with blocks of varying sizes.

Instructions on how to randomise in the event the online randomisation system failed were provided to the research team.

### *Blinding*

Personnel involved in surgery who were aware of the participant's random allocation were asked not to discuss which operation the participant received. Research nurses responsible for data collection and participant follow-up did not randomise participants and were not present 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 were made aware that they would not be informed of the allocations until the end of the study. If the participant became aware of their allocation before completing follow-up, the PIL explains that it is unknown which procedure is better, so it is unlikely that they would have a strong expectation that one or other method would lead to a more favourable result.

Microfracture and microfracture plus scaffold insertion can both be performed either arthroscopically or through an arthrotomy, resulting in different incision sizes. Arthrotomy is more likely to be performed in the scaffold group, but the clinical care teams were asked to avoid discussing this during consent so not to unblind participants. Rehabilitation and other aspects of clinical care were the same for both groups. We planned to assess the success of blinding by asking the patients and outcome assessors which treatment they thought was received.

Sites were provided with a template study operation note to record details of the operation that are not blinded (i.e. no details about the study intervention). This was not mandated but provided as an aide to prevent accidental unblinding by theatre staff recording details of the intervention in the participant's medical notes. Sites that used this operation note kept a copy in the medical notes, along with details of how to unblind.

A separate CRF captured details of the study intervention and was entered into the study database by an authorised

unblinded member of staff. It was then placed in a sealed envelope and stored in a file.

### Unblinding

Requests for unblinding were not anticipated (e.g. to treat a complication) as the intervention and comparator are similar surgical procedures with common risks, side effects and complications that occur at similar rates. Allocation would not affect the management if a complication (e.g. infection or bleeding) were to occur. However, if unblinding was required, the unblinded CRF form could be removed from the aforementioned sealed envelope. Members of staff who accessed the unblinded CRF(s) were required to record the reason for doing so. Unblinding rates were monitored by the study team and by the independent Data Monitoring and Safety Committee.

## *Data collection and follow-up schedule*

Each patient screened was assigned a unique study number, and data were collected using purpose-designed paper CRFs and participant-completed questionnaires. Data collection at scheduled points are shown in *Table 1*. CRF data were collected face-to-face or remotely via telephone or video call, depending on time point and patient follow-up pathway at the hospital. Questionnaires were administered in person if the participant attended a hospital follow-up visit, or by post, telephone or completed online if the participant did not have a hospital visit. If the participant did not complete the questionnaire at the site or if the questionnaire was not returned on time, then the site telephoned the participant to remind them.

Data collection included the following elements:

1. Screening log of all patients identified with a symptomatic chondral lesion, including details of approach; assessment against the eligibility criteria, including reasons for ineligibility.
2. Consent information.
3. Baseline information (e.g. sociodemographics, history, planned operation, response to health, comorbidities and work status questionnaires).
4. Surgical and hospital stay information.
5. Data study outcomes, AEs and resource use collected at 3, 6, 12 and 24 months post randomisation. To maximise questionnaire completion rates, we developed an electronic facility for the validated questionnaires to be completed online via a web interface.
6. Bang Blinding Index to assess potential bias in researchers and participants at 3 and 24 months.

## *Criteria for the termination of the trial*

Two conditions were considered for stopping the trial early:

1. Failure to recruit a sufficient number of participants or open a sufficient number of sites to meet the target sample size within the proposed duration of the study and refusal of the funder to extend the duration of recruitment.
2. Failure to deliver the intervention as planned.

We planned to recruit our target sample size of 176 participants over 24 months, with an assessment of the progression criteria (*Table 2*) after 8 months. Progression to Phase 2 required 24 participants to be recruited by the end of Phase 1 across eight sites (assumed it would be opened in a staggered fashion).

We proposed a recovery plan if:

1. between 18 and 24 patients were recruited within 8 months and
2. at least five sites have opened to recruitment.

If the targets were not met, close-down would be considered.

Intervention delivery adherence was monitored and cases of non-adherence investigated. The Trial Steering Committee (TSC) would consider halting the trial if the reasons for non-adherence could not be addressed satisfactorily.

## *Analysis methods*

### Planned statistical and health economic analyses

Primary analyses were planned to be by intention to treat, using data from all participants randomised and directed by a pre-specified statistical analysis plan. The intention was to report the study findings as effect sizes with 95% confidence intervals and in accordance with the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. Details of the proposed analyses are outlined in the study protocol. The data collected in the trial were insufficient to support these analyses; therefore, descriptive data are presented. Categorical data are presented as counts and percentages, and continuous data are summarised as means and SDs, or medians and interquartile ranges (IQRs) if the distribution is skewed.

A prospective within-trial economic evaluation from an NHS and personal social services perspective at 2 years, in line with NICE guidelines,[21] within a cost–consequences framework was planned. Consequences of interest were

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**TABLE 1** Standard Protocol Items: Recommendations for Interventional Trials diagram of assessments and data collection

| | | Study period | | | | | |
|---|---|---|---|---|---|---|---|
| | | | Post randomisation | | | | |
| | Enrolment | Randomisation, day of surgery | Hospital discharge | + 3-month follow-up | + 6-month follow-up | + 12-month follow-up | + 24-month follow-up |
| Time point | $-t_1$ | 0 | $t_1$ | $t_2$ | $t_3$ | $t_4$ | $t_5$ |
| ***Enrolment*** | | | | | | | |
| First-stage eligibility assessment | X | | | | | | |
| Informed consent | X | | | | | | |
| ***Interventions*** | | | | | | | |
| Surgery | | X | | | | | |
| Second-stage eligibility confirmation | | X | | | | | |
| Allocation determined | | X | | | | | |
| ***Assessments/data collection*** | | | | | | | |
| Demography | X | | | | | | |
| Relevant medical history | X | | | | | | |
| Comorbidities | X | | | | | | |
| Operative details | | X | | | | | |
| Postoperative complications | | | X | | | | |
| Rehabilitation | | | X | X | | | |
| KOOS | X | | | X | X | X | X |
| IKDC | X | | | X | X | X | X |
| Activity grading | X | | | X | X | X | X |
| Productivity | X | | | X | X | X | X |
| EQ-5D | X | | | X | X | X | X |
| SAEs, including re-admissions | | | X | X | X | X | X |
| Resource use | | X | | X | X | X | X |

**Note**
X indicates that this assessment/data collection was carried out at this timepoint, for example at enrolment.

**TABLE 2** Progression criteria

| | Status | | |
|---|---|---|---|
| **Criteria** | **Red** | **Amber** | **Green** |
| Trial recruitment | < 75% | 75 < 100% | ≥ 100% |
| Recruitment rate/site/month | 0 | 0–1 | ≥ 1 |
| Sites opened | < 5 | 5–7 | 8 |
| Participants recruited | < 18 | 18–23 | 24 |
| Outcome | Consider study closure | Propose and implement recovery plan | Continue to full trial |

QALYs and the primary and secondary outcomes. The data collected in the trial were insufficient to support these analyses, and health economic analyses were not undertaken.

### *Patient and public involvement*

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 treatment for musculoskeletal health conditions, several of whom have had knee surgery. The group felt that they would like to contribute by: (1) discussing the project six times over the 5-year study, with two meetings in the first year; (2) at the start of the project, discussing the study background, research methods, methodology and ethics; (3) reviewing the information for potential participants, including invitation letters, information sheet and consent form; (4) reviewing the questionnaires/outcome measures; (5) advising on keeping participants engaged, including reviewing newsletters and the summary of results for participants; (6) monitoring the progress and conduct of the study and working with the study team to identify and prioritise next steps; (7) discussing how to communicate the results to a lay audience. The meetings were to be organised and facilitated by an experienced patient and public involvement (PPI) co-ordinator (Amanda Burston and Catherine Jameson). A patient member, supported by the PPI co-ordinator (Amanda Burston and Catherine Jameson), sat on the TSC.

## Results

### *Study sites*

Eight sites opened to recruitment over a 9-month period from October 2021 to July 2022 (*Table 3*). The sites had good geographical spread; there were sites in south of England, the midlands and the north and a site in Scotland.

### *Screening and first-stage eligibility*

Twenty-two patients underwent initial screening, of which 20 were considered eligible (2 patients had a lesion > 4 $cm^2$ on MRI).

### *Approach and consent*

Of the 20 patients considered initially eligible, 2 patients were not interested and 1 opted for chondroplasty; the remaining 17 all consented to participate. Of the 17 patients who consented to take part, 11 completed the paper consent form face-to-face, and 6 completed it via video/telephone call. Two of the six returned the completed form by post, three by scanning or taking a photograph and e-mailing, and one in person at their next hospital visit.

### *Second-stage eligibility*

Three of the 17 initially eligible consenting patients failed the second-stage eligibility check because they were found to have healed articular cartilage lesions and did not proceed to randomisation. Four other patients were not randomised, three because the study closed before they had a date for surgery (see *Assessment of trial progress against the progression criteria and the impact of COVID-19*) and the other decided not to proceed with surgery.

### *Randomised participants*

Between 26 November 2021 and 19 October 2022, 10 participants were randomised across 6 sites, 5 to microfracture with AMIC and 5 to microfracture alone. Five participants were followed up to 3 months and 3–6 months (*Figure 2*). The remaining two had not reached the 3-month time point when the study closed (see Notification of study closure) and follow-up ceased.

### *Assessment of trial progress against the progression criteria and the impact of COVID-19*

Recruitment was due to begin in May 2020, that is, 2 months after the start of the COVID-19 pandemic. The

This synopsis should be referenced as follows:
Whitehouse MR, Howells N, Dabner L, Thirard R, Culliford L, Marques E, *et al*. Microfracture with or without collagen scaffold insertion for adults with chondral or osteochondral defects of the knee: the SISMIC RCT and its challenges during and after the COVID-19 pandemic [published online ahead of print October 29 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/BRTS2415

**TABLE 3** Site activation dates

| Site | Date open to recruitment |
|---|---|
| Royal Cornwall Hospitals NHS Trust | 28 October 2021 |
| Walsall Healthcare NHS Trust | 9 November 2021 |
| North Bristol NHS Trust | 11 November 2021 |
| North Cumbria Integrated Care NHS Foundation Trust | 5 January 2022 |
| NHS Lanarkshire | 13 January 2022 |
| Somerset NHS Foundation Trust | 5 July 2022 |
| Maidstone and Tunbridge Wells NHS Trust | 25 July 2022 |
| Chesterfield Royal Hospital NHS Foundation Trust | 27 July 2022 |

disruption to health services due to the pandemic, with elective orthopaedic services being particularly hard hit and research teams being reallocated to support urgent public health studies, resulted in a 17-month delay, with the first site not opening until October 2021. Five sites were opened in 3 months to January 2022, but then, following communication from the DHSC that the NIHR portfolio was under review and that studies may be closed, no further sites opened in the 6 months between January 2022 and June 2022. The feedback we had from potential PIs and sites was that this information from the DHSC had a significant negative impact on their ability to open and recruit. Three more sites opened to recruitment in July 2022 (see *Table 3*).

The 8-month internal pilot phase (Phase 1) finished in June 2022. The TSC met to discuss trial progress

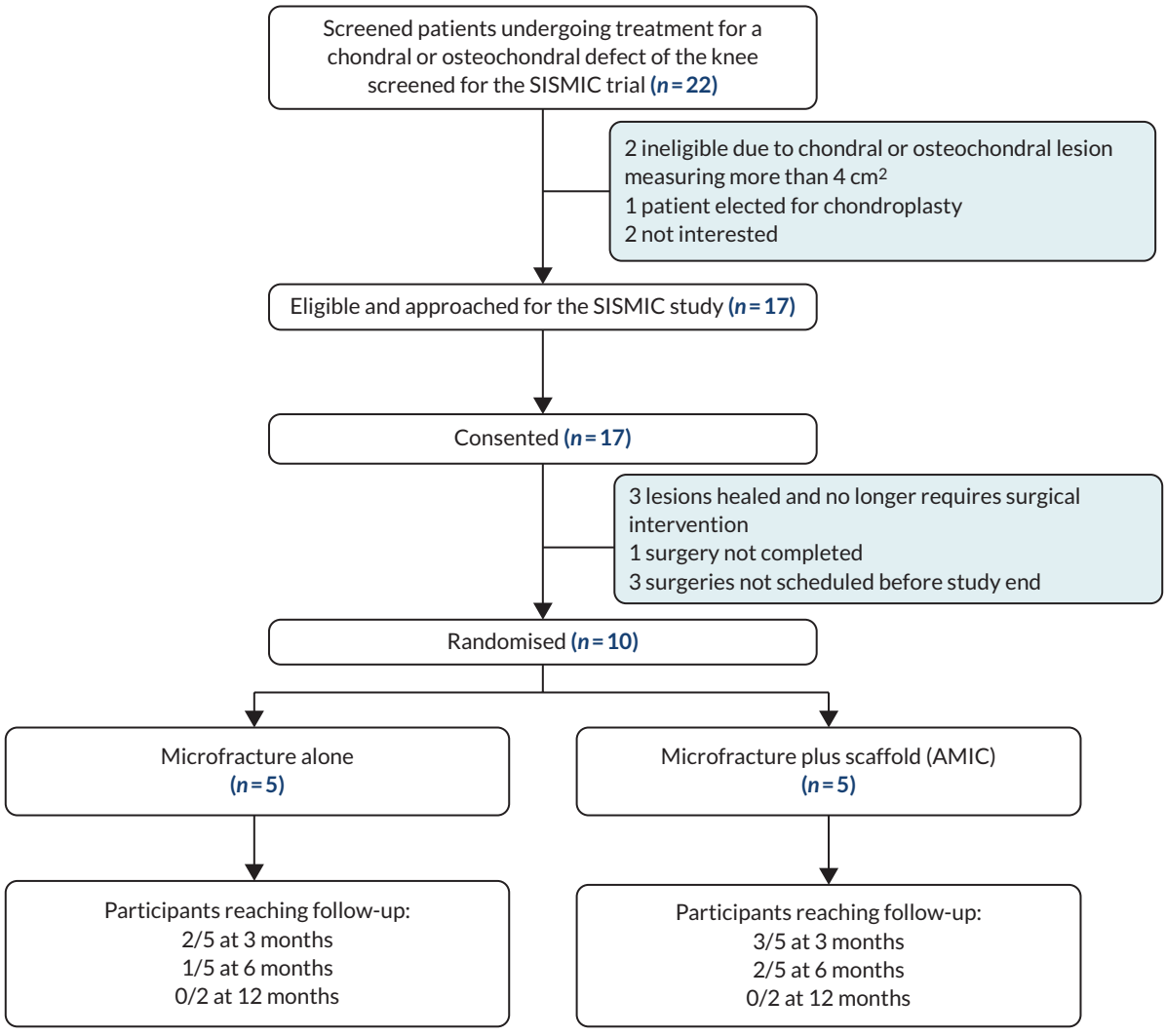


**FIGURE 2** Trial CONSORT diagram.

in July 2022 when six of the target eight sites were open. They recommended that the trial be given a further opportunity to recruit sufficient numbers of participants, as the sixth site had been open less than a month. At the time of the TSC meeting, 13 participants had consented to take part, and 6 participants had been randomised, which was one quarter of the target 24 randomised participants.

Eight sites were open to recruitment at the time the progression criteria were assessed by NIHR HTA in August 2022 (green status). At that time, 17 participants had consented and 10 participants randomised (red status). Although these numbers were an improvement on the figures reviewed by the TSC, they fell significantly short of the numbers expected when the study was conceived, and targets were set based on pre-pandemic orthopaedic elective surgery numbers. The study team expected the recruitment rate to increase as elective surgery numbers increased, and a recovery plan was submitted to both the TSC and NIHR HTA proposing a 9-month extension to the pilot phase, with revised lower recruitment rates reflecting elective surgical activity at the time. This was to give a fair chance of assessing the likely success of recruitment as NHS-wide surgical activity increased and the recently opened sites had an opportunity to recruit to the study. However, following a meeting with the NIHR HTA in October 2022, a recommendation was made to close the study with immediate effect because the review committee felt there was insufficient evidence to suggest we could achieve our revised recruitment targets, and uncertainty remained as to when elective orthopaedic services would resume pre-pandemic levels and, therefore, when sites could recruit to the expected levels.

### *Notification of study closure*

In October 2022, all sites were notified of the study closure. Open sites were instructed to halt recruitment so that no further patients were consented into the study and site resources were not unnecessarily directed to recruitment activity. Participants who had already consented to take part but had not yet undergone surgery were not randomised, as the lead time for surgery was in excess of 12 months in some centres. Consented patients and randomised participants were notified by the site staff that the study had closed. Randomised participants were told that their research follow-up visits would no longer continue but reassured that their normal clinical follow-up would continue.

The REC was informed of the decision to cease follow-up, and no objection was communicated. In December 2022, a substantial amendment was submitted to seek approval of a letter to be sent to participants informing them of the study closure and the next steps for their care. This amendment was approved in February 2023.

Sites that were in the process of setting up SISMIC were instructed to cease all set-up activities with immediate effect.

### *Participant withdrawals*

In the period from when the study opened to the notification of closure, one consented patient withdrew from the study because they decided not to have surgery. No randomised participant withdrew.

### *Major protocol deviations*

There were no major protocol deviations. The 10 participants received their allocated intervention; there were no crossovers. There were no requests for unblinding.

### *Participant characteristics*

Participant characteristics are summarised in *Table 4*. The median age was 38 years, and four participants were female. Most participants (eight) were in full-time work. Eight out of 10 knees were the left; most participants (seven) had damage to the lateral femoral condyle, and six had a medial and/or lateral meniscal tear.

### *Surgical procedure and rehabilitation*

Surgical details and post-surgery physiotherapy are summarised in *Table 5*. Eight procedures were performed as elective procedures and two as urgent. In the AMIC, arm surgery took on average 10 minutes longer than microfracture alone. The range of movement (flexion and extension) was well balanced across the groups; three participants in each group underwent meniscal surgery. All participants in the microfracture plus scaffold (AMIC) group received a single Chondro-Gide scaffold secured with glue, and no layering of the scaffold occurred. All participants were referred for post-surgery physiotherapy and braced in line with the study protocol.

### *Primary and secondary outcomes*

Primary and secondary outcome data are summarised in *Table 6*. The data are too few to draw any meaningful comparisons. As expected, the median scores for each domain of the KOOS improved over time. A similar pattern was seen in the other scores.

### *Adverse events*

No instances of postoperative bleeding, infection, DVT or pulmonary embolism were reported. Two AEs (pain and swelling), that were in the list of anticipated events after knee surgery, were reported in one participant.

This synopsis should be referenced as follows:
Whitehouse MR, Howells N, Dabner L, Thirard R, Culliford L, Marques E, *et al*. Microfracture with or without collagen scaffold insertion for adults with chondral or osteochondral defects of the knee: the SISMIC RCT and its challenges during and after the COVID-19 pandemic [published online ahead of print October 29 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/BRTS2415

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DOI: 10.3310/BRTS2415



**TABLE 4** Participant characteristics

| | | Microfracture alone, *n* = 5 | Microfracture plus scaffold (AMIC), *n* = 5 | Overall, *n* = 10 |
|---|---|---|---|---|
| ***Demography*** | | | | |
| Age at screening (years) | Median (IQR) | 34 (34–37) | 40 (39–40) | 38 (34–40) |
| Female | | 3/5 (60%) | 1/5 (20%) | 4/10 (40%) |
| Body mass index | | 33 (30–33) | 29 (26–29) | 29 (26–33) |
| Smoking | Quit more than 6 months ago | 0/5 (0%) | 1/5 (20%) | 1/10 (10%) |
| | Never smoked | 5/5 (100%) | 4/5 (80%) | 9/10 (90%) |
| E-cigarette user | Never smoked | 5/5 (100%) | 5/5 (100%) | 10/10 (100%) |
| Ethnicity | White | 3/5 (60%) | 4/5 (80%) | 7/10 (70%) |
| | Mixed/multiple ethnic groups | 1/5 (20%) | 0/5 (0%) | 1/10 (10%) |
| | Asian/Asian British | 1/5 (20%) | 1/5 (20%) | 2/10 (20%) |
| Occupation | Full-time | 3/5 (60%) | 5/5 (100%) | 8/10 (80%) |
| | Part-time | 1/5 (20%) | 0/5 (0%) | 1/10 (10%) |
| | Looking after home/family | 1/5 (20%) | 0/5 (0%) | 1/10 (10%) |
| ***Baseline knee evaluation*** | | | | |
| Lesion location | Right knee | 0/5 (0%) | 2/5 (40%) | 2/10 (20%) |
| | Left knee | 5/5 (100%) | 3/5 (60%) | 8/10 (80%) |
| Medial femoral condyle | | 1/5 (20%) | 1/5 (20%) | 2/10 (20%) |
| Lateral femoral condyle | | 4/5 (80%) | 3/5 (60%) | 7/10 (70%) |
| Patella | | 1/5 (20%) | 2/5 (40%) | 3/10 (30%) |
| Anterior cruciate ligament injury | Grade III | 1/5 (20%) | 0/5 (0%) | 1/10 (10%) |
| Medial meniscal tear | | 2/5 (40%) | 1/5 (20%) | 3/10 (30%) |
| Lateral meniscal tear | | 1/5 (20%) | 2/5 (40%) | 3/10 (30%) |
| Previous medial meniscal repair | | 1/5 (20%) | 0/5 (0%) | 1/10 (10%) |
| Previous chondroplasty | | 1/5 (20%) | 0/5 (0%) | 1/10 (10%) |

**TABLE 5** Surgical details and physiotherapy

| | | Microfracture alone, *n* = 5 | Microfracture plus scaffold (AMIC), *n* = 5 | Overall, *n* = 10 |
|---|---|---|---|---|
| ***Basic operative details*** | | | | |
| Admission type | Urgent | 1/5 (20%) | 1/5 (20%) | 2/10 (20%) |
| | Elective | 4/5 (80%) | 4/5 (80%) | 8/10 (80%) |
| Operative duration (minutes) | Median (IQR) | 95 (85–100) | 105 (71–112) | 98 (71–112) |
| Passive flexion (degrees) | Median (IQR) | 130 (120–130) | 120 (120–125) | 123 (120–130) |
| Active flexion (degrees) | Median (IQR) | 130 (120–130) | 120 (110–120) | 120 (110–130) |
| Passive extension (degrees) | Median (IQR) | 0 (0–5) | 10 (0–10) | 3 (0–10) |
| Active extension (degrees) | Median (IQR) | 0 (0–0) | 10 (0–10) | 0 (0–10) |
| Pre-debridement size ($cm^2$) | Median (IQR) | 2 (2–3) | 2 (1–3) | 2 (1–3) |
| Post-debridement size ($cm^2$) | Median (IQR) | 3 (2–3) | 2 (2–3) | 3 (2–3) |
| ***Study lesion*** | | | | |
| Medial femoral condyle | | 4/4 (100%) | 1/1 (100%) | 5/5 (100%) |
| Lateral femoral condyle | | | 3/3 (100%) | 3/3 (100%) |
| Patella | | 1/5 (20%) | 1/5 (20%) | 2/10 (10%) |
| ***Additional pathology*** | | | | |
| Additional intra-articular pathology | | 4/5 (80%) | 4/5 (80%) | 8/10 (80%) |
| Other articular cartilage lesion | | 1/4 (25%) | 2/4 (50%) | 3/8 (38%) |
| Lateral tibial lesion | | | 1/2 (50%) | 1/2 (50%) |
| Medial tibial lesion | | | 0/2 (0%) | 0/2 (0%) |
| Medial femoral condyle lesion | | | 1/2 (50%) | 1/2 (50%) |
| Lateral femoral condyle lesion | | 1/1 (100%) | | 1/1 (100%) |
| Ligament injury | | 1/4 (25%) | 1/4 (25%) | 2/8 (25%) |
| Ligament injury grade | II | 0/1 (0%) | 1/1 (100%) | 1/2 (50%) |
| | III | 1/1 (100%) | 0/1 (0%) | 1/2 (50%) |
| Meniscal injury | | 3/4 (75%) | 3/4 (75%) | 6/8 (75%) |

continued

This synopsis should be referenced as follows: Whitehouse MR, Howells N, Dabner L, Thirard R, Culliford L, Marques E, *et al.* Microfracture with or without collagen scaffold insertion for adults with chondral or osteochondral defects of the knee: the SISMIC RCT and its challenges during and after the COVID-19 pandemic [published online ahead of print October 29 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/BRTS2415

DOI: 10.3310/BRTS2415



**TABLE 5** Surgical details and physiotherapy (*continued*)

| | | Microfracture alone, *n* = 5 | Microfracture plus scaffold (AMIC), *n* = 5 | Overall, *n* = 10 |
|---|---|---|---|---|
| ***Additional procedures*** | | | | |
| Tourniquet | | 5/5 (100%) | 4/5 (80%) | 9/10 (90%) |
| Meniscal surgery | | 3/5 (60%) | 3/5 (60%) | 6/10 (60%) |
| Meniscectomy | | 1/3 (33%) | 1/3 (33%) | 2/6 (33%) |
| Meniscectomy planned preoperatively | | 1/1 (100%) | 1/1 (100%) | 2/2 (100%) |
| Meniscal repair | | 3/3 (100%) | 1/3 (33%) | 4/6 (67%) |
| Meniscal repair planned preoperatively | | 2/3 (67%) | 1/1 (100%) | 3/4 (75%) |
| Other: root repair | | 0/3 (0%) | 1/3 (33%) | 1/6 (17%) |
| Ligament repair surgery | | 2/5 (40%) | 1/5 (20%) | 3/10 (30%) |
| Anterior cruciate ligament | | 1/2 (50%) | 0/1 (0%) | 1/3 (33%) |
| Medial patellofemoral ligament | | 0/2 (0%) | 1/1 (100%) | 1/3 (33%) |
| Lateral extra-articular tenodesis | | 1/2 (50%) | 0/1 (0%) | 1/3 (33%) |
| Other procedures performed | | 2/5 (40%) | 0/5 (0%) | 2/10 (20%) |
| Anterior cruciate ligament reconstruction | | 1/2 (50%) | | 1/2 (50%) |
| Lateral femoral condyle fixed | | 1/2 (50%) | | 1/2 (50%) |
| Surgical procedure | With arthrotomy | 2/5 (40%) | 5/5 (100%) | 7/10 (70%) |
| | All-arthroscopic | 3/5 (60%) | 0/5 (0%) | 3/10 (30%) |
| All arthroscopically, number of portals (*n*) | Median (IQR) | 2 (2–3) | | 2 (2–3) |
| With arthrotomy incision length (cm) | Median (IQR) | 5 (3–6) | 4 (4–5) | 4 (4–6) |
| Chondro-Gide scaffold | | | 5/5 (100%) | 5/5 (100%) |
| Glue securing | | | 5/5 (100%) | 5/5 (100%) |
| Single scaffold used | | | 5/5 (100%) | 5/5 (100%) |
| Layered scaffold | | | 0/5 (0%) | 0/5 (0%) |

**TABLE 5** Surgical details and physiotherapy (*continued*)

| | | Microfracture alone, *n* = 5 | Microfracture plus scaffold (AMIC), *n* = 5 | Overall, *n* = 10 |
|---|---|---|---|---|
| ***Postoperative physiotherapy*** | | | | |
| Referred for physiotherapy | | 5/5 (100%) | 5/5 (100%) | 10/10 (100%) |
| Crutches advice | | 5/5 (100%) | 5/5 (100%) | 10/10 (100%) |
| Brace type | Standard | 5/5 (100%) | 4/5 (80%) | 9/10 (90%) |
| | Unloader | 0/5 (0%) | 1/5 (20%) | 1/10 (10%) |
| Lesion protected with unloader | | | 1/1 (100%) | 1/1 (100%) |
| Limiting range of motion | | 1/1 (100%) | 2/2 (100%) | 3/3 (100%) |

**TABLE 6** Primary and secondary outcomes

| Outcome | Microfracture alone, *n* = 5 | | Microfracture plus scaffold (AMIC), *n* = 5 | | Overall, *n* = 10 | |
|---|---|---|---|---|---|---|
| | *n* | | *n* | | *n* | |
| ***KOOS***[a] | | | | | | |
| Pain | | | | | | |
| Baseline | 5 | 56 (50, 61) | 5 | 53 (39, 53) | 10 | 53 (47, 61) |
| 3 months | 1 | 72 | 3 | 61 (36, 67) | 4 | 64 (49, 69) |
| 6 months | 1 | 81 | 2 | 71 (47, 94) | 3 | 81 (47, 94) |
| ***Symptoms*** | | | | | | |
| Baseline | 5 | 57 (50, 61) | 5 | 46 (36, 64) | 10 | 54 (36, 64) |
| 3 months | 1 | 57 | 3 | 50 (36, 57) | 4 | 54 (43, 57) |
| 6 months | 1 | 57 | 2 | 57 (25, 89) | 3 | 57 (25, 89) |
| ***Function in daily living*** | | | | | | |
| Baseline | 5 | 66 (60, 78) | 5 | 49 (37, 62) | 10 | 61 (49, 66) |
| 3 months | 1 | 78 | 3 | 72 (41, 74) | 4 | 73 (57, 76) |
| 6 months | 1 | 97 | 2 | 71 (44, 99) | 3 | 97 (44, 99) |

continued

This synopsis should be referenced as follows: Whitehouse MR, Howells N, Dabner L, Thirard R, Culliford L, Marques E, *et al.* Microfracture with or without collagen scaffold insertion for adults with chondral or osteochondral defects of the knee: the SISMIC RCT and its challenges during and after the COVID-19 pandemic [published online ahead of print October 29 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/BRTS2415

DOI: 10.3310/BRTS2415



**TABLE 6** Primary and secondary outcomes (*continued*)

| Outcome | | Microfracture alone, *n* = 5 | | Microfracture plus scaffold (AMIC), *n* = 5 | | Overall, *n* = 10 | |
|---|---|---|---|---|---|---|---|
| | | *n* | | *n* | | *n* | |
| ***Function in sports and recreation*** | | | | | | | |
| Baseline | | 5 | 56 (50, 61) | 5 | 53 (39, 53) | 10 | 53 (47, 61) |
| 3 months | | 1 | 72 | 3 | 61 (36, 67) | 4 | 64 (49, 69) |
| 6 months | | 1 | 81 | 2 | 71 (47, 94) | 3 | 81 (47, 94) |
| ***Knee-related quality of life*** | | | | | | | |
| Baseline | | 5 | 31 (19, 31) | 5 | 19 (19, 38) | 10 | 25 (19, 38) |
| 3 months | | 1 | 44 | 3 | 25 (6, 38) | 4 | 31 (16, 41) |
| 6 months | | 1 | 63 | 2 | 44 (13, 75) | 3 | 63 (13, 75) |
| ***IKDC*** | | | | | | | |
| Baseline | | 4 | 39 (34, 41) | 5 | 44 (34, 46) | 9 | 40 (34, 44) |
| 3 months | | 2 | 39 (37, 40) | 3 | 37 (33, 72) | 5 | 37 (37, 40) |
| 6 months | | 1 | 55 | 2 | 41 (37, 46) | 3 | 46 (37, 55) |
| ***Tegner-Lysholm knee scoring scale*** | | | | | | | |
| *Lysholm knee score* | | | | | | | |
| Baseline | | 4 | 61 (55, 69) | 5 | 36 (26, 41) | 9 | 46 (36, 55) |
| 3 months | | 2 | 46 (28, 63) | 3 | 57 (50, 59) | 5 | 57 (50, 59) |
| 6 months | | 1 | 82 | 2 | 69 (52, 86) | 3 | 82 (52, 86) |
| *Tegner knee score* | | | | | | | |
| Baseline | Sick leave or disability because of knees | | 0 | | 1/5 (20%) | | 1/9 (11%) |
| | Competitive or recreational sports | | 2/4 (50%) | | 1/5 (20%) | | 3/9 (33%) |
| | Competitive sports: squash, badminton, athletics (jumping, etc.) and/or downhill skiing | | 2/4 (50%) | | 1/5 (20%) | | 3/9 (33%) |
| | Competitive sports: soccer (lower divisions), ice hockey, wrestling and/or gymnastics | | 0 | | 1/5 (20%) | | 1/9 (11%) |
| | Competitive sports: elite | | 0 | | 1/5 (20%) | | 1/9 (11%) |

**TABLE 6** Primary and secondary outcomes (*continued*)

| Outcome | | Microfracture alone, *n* = 5 | Microfracture plus scaffold (AMIC), *n* = 5 | Overall, *n* = 10 |
|---|---|---|---|---|
| | | *n* | *n* | *n* |
| 3 months | Competitive or recreational sports | 0 | 2/3 (67%) | 2/5 (40%) |
| | Competitive sports: squash, badminton, athletics (jumping, etc.) and/or downhill skiing | 1/2 (50%) | 0 | 1/5 (20%) |
| | Competitive sports: soccer (lower divisions), ice hockey, wrestling and/or gymnastics | 1/2 (50%) | 1/3 (33%) | 2/5 (40%) |
| 6 months | Work: heavy labour or competitive sports at least 2 × per week | 0 | 1/2 (50%) | 1/3 (33%) |
| | Recreational sports at least 5 × per week | 0 | 1/2 (50%) | 1/3 (33%) |
| | Competitive or recreational sports | 1/1 (100%) | 0 | 1/3 (33%) |
| ***EQ-5D*** | | | | |
| *Mobility – problems walking about* | | | | |
| Baseline | No problems | 1/5 (20%) | 0 | 1/10 (10%) |
| | Slight problems | 2/5 (40%) | 3/5 (60%) | 5/10 (50%) |
| | Moderate problems | 2/5 (40%) | 1/5 (20%) | 3/10 (30%) |
| | Severe problems | 0 | 1/5 (20%) | 1/10 (10%) |
| 3 months | Slight problems | 1/1 (100%) | 2/3 (67%) | 3/4 (75%) |
| | Moderate problems | 0 | 1/3 (33%) | 1/4 (25%) |
| 6 months | No problems | 1/1 (100%) | 1/2 (50%) | 2/3 (67%) |
| | Moderate problems | 0 | 1/2 (50%) | 1/3 (33%) |
| *Self-care – problems with washing or dressing* | | | | |
| Baseline | No problems | 5/5 (100%) | 2/5 (40%) | 7/10 (70%) |
| | Slight problems | 0 | 3/5 (60%) | 3/10 (30%) |
| 3 months | No problems | 1/1 (100%) | 2/3 (67%) | 3/4 (75%) |
| | Slight problems | 0 | 1/3 (33%) | 1/4 (25%) |
| 6 months | No problems | 1/1 (100%) | 1/2 (50%) | 2/3 (67%) |
| | Slight problems | 0 | 1/2 (50%) | 1/3 (33%) |

continued

This synopsis should be referenced as follows: Whitehouse MR, Howells N, Dabner L, Thirard R, Culliford L, Marques E, *et al.* Microfracture with or without collagen scaffold insertion for adults with chondral or osteochondral defects of the knee: the SISMIC RCT and its challenges during and after the COVID-19 pandemic [published online ahead of print October 29 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/BRTS2415

DOI: 10.3310/BRTS2415



**TABLE 6** Primary and secondary outcomes (*continued*)

| Outcome | | Microfracture alone, *n* = 5 | Microfracture plus scaffold (AMIC), *n* = 5 | Overall, *n* = 10 |
|---|---|---|---|---|
| | | *n* | *n* | *n* |
| *Self-care – problems doing usual activities* | | | | |
| Baseline | No problems | 1/5 (20%) | 0 | 1/10 (10%) |
| | Slight problems | 1/5 (20%) | 3/5 (60%) | 4/10 (40%) |
| | Moderate problems | 2/5 (40%) | 2/5 (40%) | 4/10 (40%) |
| | Unable to do | 1/5 (20%) | 0 | 1/10 (10%) |
| 3 months | Slight problems | 1/1 (100%) | 2/3 (67%) | 3/4 (75%) |
| | Moderate problems | 0 | 1/3 (33%) | 1/4 (25%) |
| 6 months | No problems | 1/1 (100%) | 1/2 (50%) | 2/3 (67%) |
| | Moderate problems | 0 | 1/2 (50%) | 1/3 (33%) |
| *Pain/discomfort* | | | | |
| Baseline | Slight | 2/5 (40%) | 1/5 (20%) | 3/10 (30%) |
| | Moderate | 3/5 (60%) | 4/5 (80%) | 7/10 (70%) |
| 3 months | Moderate | 1/1 (100%) | 2/3 (67%) | 3/4 (75%) |
| | Severe | 0 | 1/3 (33%) | 1/4 (25%) |
| 6 months | None | 0 | 1/2 (50%) | 1/3 (33%) |
| | Slight | 1/1 (100%) | 0 | 1/3 (33%) |
| | Moderate | 0 | 1/2 (50%) | 1/3 (33%) |
| *Anxiety/depression* | | | | |
| Baseline | None | 2/5 (40%) | 3/5 (60%) | 5/10 (50%) |
| | Slight | 2/5 (40%) | 1/5 (20%) | 3/10 (30%) |
| | Moderate | 1/5 (20%) | 1/5 (20%) | 2/10 (20%) |
| 3 months | None | 1/1 (100%) | 0 | 1/4 (25%) |
| | Slight | 0 | 1/3 (33%) | 1/4 (25%) |
| | Moderate | 0 | 2/3 (67%) | 2/4 (50%) |

**TABLE 6** Primary and secondary outcomes (*continued*)

| Outcome | | Microfracture alone, *n* = 5 | | Microfracture plus scaffold (AMIC), *n* = 5 | | Overall, *n* = 10 | |
|---|---|---|---|---|---|---|---|
| | | *n* | | *n* | | *n* | |
| 6 months | None | | 1/1 (100%) | | 1/2 (50%) | | 2/3 (67%) |
| | Slight | | 0 | | 1/2 (50%) | | 1/3 (33%) |
| *VAS* | | | | | | | |
| Baseline | | 5 | 75 (70, 90) | 5 | 70 (65, 75) | 10 | 73 (65, 75) |
| 3 months | | 1 | 76 | 3 | 68 (67, 70) | 4 | 69 (68, 73) |
| 6 months | | 1 | 95 | 2 | 64 (55, 72) | 3 | 72 (55, 95) |
| ***WPAI questionnaire*** | | | | | | | |
| *Per cent work time missed due to knee problem* | | | | | | | |
| Baseline | | 3 | 0 (0, 0) | 5 | 0 (0, 6) | 8 | 0 (0, 3) |
| 3 months | | 2 | 0 (0, 0) | 3 | 13 (0, 100) | 5 | 0 (0, 13) |
| 6 months | | 1 | 0 | 2 | 3 (0, 5) | 3 | 0 (0, 5) |
| *Per cent impairment while working due to knee problem* | | | | | | | |
| Baseline | | 3 | 20 (10, 30) | 5 | 50 (20, 70) | 8 | 25 (15, 60) |
| 3 months | | 2 | 25 (10, 40) | 2 | 45 (20, 70) | 4 | 30 (15, 55) |
| 6 months | | 1 | 40 | 2 | 35 (10, 60) | 3 | 40 (10, 60) |
| *Per cent overall work impairment due to knee problem* | | | | | | | |
| Baseline | | 3 | 20 (10, 30) | 5 | 57 (20, 72) | 8 | 25 (15, 64) |
| 3 months | | 2 | 25 (10, 40) | 2 | 47 (20, 74) | 4 | 30 (15, 57) |
| 6 months | | 1 | 40 | 2 | 36 (10, 62) | 3 | 40 (10, 62) |
| *Per cent activity impairment due to knee problem* | | | | | | | |
| Baseline | | 4 | 65 (35, 75) | 5 | 50 (30, 60) | 9 | 60 (30, 70) |
| 3 months | | 2 | 50 (30, 70) | 3 | 70 (40, 80) | 5 | 70 (40, 70) |
| 6 months | | 1 | 60 | 2 | 60 (40, 80) | 3 | 60 (40, 80) |

a One participant in the microfracture group was followed up at 3 months but did not complete KOOS.

This synopsis should be referenced as follows: Whitehouse MR, Howells N, Dabner L, Thirard R, Culliford L, Marques E, *et al.* Microfracture with or without collagen scaffold insertion for adults with chondral or osteochondral defects of the knee: the SISMIC RCT and its challenges during and after the COVID-19 pandemic [published online ahead of print October 29 2025]. *Health Technol Assess* 2025. https://doi.org/10.3310/BRTS2415

These were considered serious but not related to the trial intervention. There was one SAE that was not anticipated, a suspected anaphylactic reaction of mild intensity lasting 15 minutes. This was resolved without any sequelae. None of the events resulted in hospital re-admission.

## Patient and public involvement during the trial

The study team first met with the PPI group PEP-R in 2018. The group were pleased that there were commissioned calls that were relevant to them. They felt that the trial interventions, methods, outcome measures and conduct were acceptable to patients. They helped to redraft the plain language summary and input into the design of the study. They also discussed the PPI plans for the study and recommended that the research should be taken to the patient; the team was to attend PEP-R group meetings to offer updates, and the PPI co-ordinator should attend trial management meetings to represent them.

The public TSC member, Sgt Helen Jones, was supported by the PPI co-ordinator either by joint attendance or discussion before and after meetings. Helen was provided with information to aid in their role (NIHR role description for public TSC members) and offered funded online training, which was declined due to work pressures.

The PEP-R met again in 2019 to discuss patient-facing documents. The public TSC member, Helen, also gave feedback on the invitation letter and PIL via 1 : 1 online meetings with the PPI co-ordinator.

The PPI co-ordinator attended TMG meetings on behalf of the PEP-R group.

The study lead (Michael R Whitehouse) attended a PEP-R meeting in April 2022 to update the group on the study progress.

The public TSC member, Helen, was advised of the study closure, and they offered their support for any future studies. The PEP-R group will be updated in an upcoming meeting.

## Discussion

### *Challenges*

Recruitment to the SISMIC study was significantly impacted by the COVID-19 pandemic, with delays to sites opening, and once open, site capacity and limited resources. Initially, sites were unable to progress with the study set-up due to staff redeployment to clinical areas, prioritisation of COVID-19 research and suspension of elective orthopaedic surgery. Once elective services began to resume, our communications with potential sites and sites in set-up indicated that staff continued to face significant challenges with capacity to process and take on new studies. For example, one site that wanted to participate in SISMIC returned a completed site feasibility form in June 2021 but asked us to refrain from sending the Local Information Pack [(LIP), which triggers the formal local capacity and capability assessment] until they had the capacity to process it. It took over a year until the site was ready to receive the LIP and did not manage to open before the study closed. In another example, the LIP was sent to the site and progress to set up made, but after several months, the site withdrew citing that they were no longer able to deliver the study due to PI/research team staff capacity and availability issues. Other sites that expressed an interest also withdrew their interest because of capacity issues before the LIP had been received. Our communications with sites suggested that the NIHR's nationwide communication regarding the portfolio created uncertainty for site staff and a reluctance to proceed with site set-up.

Many sites who expressed interest in SISMIC when the study was being designed and funded were not able to commit, so a greater pool of interested sites was required. We took a three-pronged strategy to find more sites. Firstly, the study team directly contacted potential PIs/sites that had previously expressed an interest when SISMIC was discussed and presented at national meetings, to promote the study and the benefits of taking part. Secondly, we contacted our local Clinical Research Network (CRN) (West of England) to ask for help in identifying new sites who contacted all the CRNs across England to advertise SISMIC. The CRNs then contacted sites to provide information on the study and our contact details. Thirdly, our clinical lead (Nicholas Howells) undertook promotion work at the national British Association for Surgery of the Knee meeting (17–18 May 2022) and at other national meetings in the specialty area. We received a number of verbal expressions of interest from sites through this route.

Once sites were open, capacity and resources remained limited, significantly affecting participant recruitment. Post COVID-19, elective surgery had resumed at most centres across the UK but at considerably reduced rates and with frequent disruption. National waiting times for elective services continue to be severely delayed, with many patients waiting over 12 months for knee surgery prioritised for those with urgent conditions and those

with greatest clinical need (e.g. end-stage osteoarthritis awaiting joint replacement). As a result, the time taken to see potentially eligible patients was much greater than anticipated when the study was conceived. There was also an increased lead time between consent and intraoperative randomisation. These issues considerably affected the study's ability to recruit to time and target given what were reasonable assumptions made during the study's design, which ultimately affected the NIHR's decision to close the study.

The research question addressed by SISMIC was identified as priority research for the NHS via a NIHR HTA commissioned call. Currently, there are no other studies addressing this research question for the UK population, so the question remains unanswered. Patients continue to suffer from this condition with impact on their knee function and quality of life. The rates at which the condition studied in this trial occurs is not felt to have been affected by any change in behaviour or other factors related to the COVID-19 pandemic. However, our ability to recruit at the rates planned was affected by the ability of sites to open to recruitment given the challenges of competition for resources and the profound impact on elective surgical activity, which is now reducing but has not yet returned to normal. The TSC and DSMC agreed that SISMIC remains an important research question and were both supportive of the trial continuing with an extension to the pilot phase, but the funder decided to not pursue this option.

### *Trial conduct*

Despite the trial closing early for the reasons outlined above, of the patients screened for the trial, over three quarters were eligible, and all the patients invited to participate consented, suggesting the trial was acceptable to patients. The fact that the e-consent module was not used could be due to when it was introduced (it was not available from the start), and/or a reluctance on the part of site staff and/or potential participants to engage with a system that was not as familiar as the traditional paper-based approach.

The intraoperative eligibility check was included in the trial design because the size of the lesion could not be determined definitively preoperatively prior to intraoperative debridement of loose cartilage. The fact that three patients were found to be ineligible not because the lesion was over 4 $cm^2$ after debridement but because the lesion had healed was not expected, as it does not follow the typical natural history of the condition but may be a function of the substantially longer waits for surgery than was the case prior to COVID-19.

### *Equality, diversity and inclusion*

At the time of funding, an explicit plan for equality, diversity and inclusion (EDI) was not required. With so few participants recruited, it is difficult to comment on EDI. The study sites had good geographical spread and included both urban and rural locations. It is encouraging that 3 of the 10 randomised participants were not of white ethnicity.

### *Future research*

Discussions with the surgical community and national society for this area (British Association for Surgery of the Knee) during the conduct of the trial has indicated that the treatments being used by knee surgeons for chondral and osteochondral defects of up to 4 $cm^2$ has evolved since the commissioned research was first designed and advertised. Chondroplasty (debridement of loose cartilage without microfracture) has now become a more favoured procedure than microfracture. When chondroplasty is used, this is often in conjunction with the use of a scaffold, such as the bilayer collagen scaffold used in SISMIC, with or without impregnation with bone marrow concentrate. At the time of the original commissioned call, autologous chondrocyte implantation (ACI) was a recognised treatment, but there was not established capacity within the NHS to deliver this for the large number of patients affected by this condition. This has now changed, and there are now 12 specialist centres across the UK commissioned to deliver this service (the first specialist centre was approved by NICE in October 2017). To reflect contemporary practice and test areas of uncertainty for which there is not definitive trial evidence, we would therefore recommend that in the future, once elective services are fully recovered, the preferred study design would be a three-group RCT comparing (1) chondroplasty, (2) chondroplasty with the insertion of microstructural scaffold ± impregnation with bone marrow concentrate and (3) ACI to be delivered in sites commissioned to deliver ACI.

### *Lessons learnt*

The main lesson learnt is to try and avoid setting up a trial that relies on recruiting patients from a predominantly elective surgical pathway during a world-wide pandemic that impacts on health services. While the e-consent module was not used in SISMIC, the trend to fewer in person consultations is likely to continue, and we recommend that methods such as e-consent which facilitate 'remote' participation be included in future trials from the start.

### *Limitations*

The primary limitation is the sample size, with just 10 participants randomised and followed up for a limited

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period we are not able to provide any definitive data to answer the research question.

### *Conclusion*

Due to the impact of COVID-19 on the elective orthopaedic pathway and the resources available to deliver research on this pathway, we were unable to meet a randomisation rate that was satisfactory to the funder during our delayed internal pilot phase despite a range of mitigation measures that we put in place. With only 10 patients randomised and incomplete follow-up data (due to the funder requesting study follow-up visits cease), we are unable to produce meaningful comparative data of the interventions tested in this study, and the research question remains unanswered. Our patient partners, the TSC and surgical community believe this remains an important area of research. Treatments currently being used for these patients have evolved since SISMIC was designed and commissioned, and, therefore, we have made a recommendation for a future study to compare chondroplasty, chondroplasty with the insertion of microstructural scaffold and ACI for the treatment of chondral and osteochondral defects of articular cartilage in the knee.

## Additional information

### *CRediT contribution statement*

**Michael R Whitehouse (https://orcid.org/0000-0003-2436-9024):** Conceptualisation (equal), Funding acquisition (equal), Investigation (equal), Methodology (equal), Supervision (equal), Writing – original draft (equal), Writing – reviewing and editing (equal), Validation (equal).

**Nicholas Howells (https://orcid.org/0000-0002-8514-0322):** Investigation (equal), Supervision (equal).

**Lucy Dabner (https://orcid.org/0000-0001-7269-1945):** Investigation (supporting), Writing – original draft (equal), Writing – reviewing and editing (equal), Validation (equal), Project administration (supporting), Data curation (supporting), Software (supporting).

**Russell Thirard (https://orcid.org/0000-0002-1441-1834):** Writing – original draft (equal), Writing – reviewing and editing (equal), Data curation (supporting), Formal analysis (supporting), Validation (supporting), Software (supporting), Visualisation (lead).

**Lucy Culliford (https://orcid.org/0000-0002-9255-6617):** Conceptualisation (supporting), Funding acquisition (supporting), Investigation (supporting), Methodology (supporting), Supervision (equal), Writing – original draft (equal), Writing – reviewing and editing (equal), Validation (equal), Project administration (lead).

**Elsa Marques (https://orcid.org/0000-0003-1360-5677):** Funding acquisition (supporting), Data curation (supporting).

**Petra Baji (https://orcid.org/0000-0003-2899-8557):** Data curation (supporting).

**Andrew Judge (https://orcid.org/0000-0003-3015-0432):** Funding acquisition (supporting), Investigation (supporting), Supervision (supporting).

**Ashley W Blom (https://orcid.org/0000-0002-9940-1095):** Funding acquisition (supporting), Investigation (supporting), Supervision (supporting).

**Amanda Burston (https://orcid.org/0000-0003-3480-4210):** Methodology (supporting).

**Catherine Jameson (https://orcid.org/0000-0002-0772-7574):** Methodology (supporting).

**Chris A Rogers (https://orcid.org/0000-0002-9624-2615):** Conceptualisation (equal), Funding acquisition (equal), Methodology (equal), Supervision (equal), Writing – original draft (equal), Writing – reviewing and editing (equal), Data curation (lead), Formal analysis (lead), Validation (equal).

**Holly McKeon:** Project administration (supporting).

### *Data-sharing statement*

Anonymised individual patient data (baseline, intervention, outcome data and AEs) 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 with the UK Policy Framework for Health and Social Care Research and MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements and value for money. Please contact btc-mailbox@bristol.ac.uk to discuss any data requests. Data will only be made available after publication of the primary results. Only data from patients who have consented for their data to be shared with other researchers will be provided.

### *Ethics statement*

The trial was given a favourable ethical opinion (reference IRAS 270719) by the UK (Black Country) National Research Ethics Service Committee (REC) on 15 June 2021.

### *Information governance statement*

North Bristol NHS Trust is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679.

Under the Data Protection legislation, North Bristol NHS Trust is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here (www.nbt.nhs.uk/about-us/information-governance/privacy-policy-data-protection).

## Disclosure of interests

***Full disclosure of interests:*** Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/BRTS2415.

***Primary conflicts of interest:*** Michael R Whitehouse undertakes teaching on basic sciences for orthopaedic trainees preparing for the Fellowship of the Royal College of Surgeons; his institution receives market-rate payment for this teaching from Heraeus (Hanau, Germany). He was a co-applicant on a completed grant from Stryker Corporation investigating the outcome of the Triathlon total knee replacement. He is lead for the National Joint Registry Lot 2 Contract (statistical analysis) team and a member of the National Institute for Health and Care Research (NIHR) Bristol Biomedical Research Centre. He is chair of the British Hip Society Research Committee and a member of the British Orthopaedic Association Research Committee.

Nicholas Howells: None declared.

Lucy Dabner is a member of a Clinical Trials Unit that was in, in receipt of funding from the NIHR until 30 September 2023.

Russell Thirard is a member of a Clinical Trials Unit that was in, in receipt of funding from the NIHR until 30 September 2023.

Lucy Culliford is a member of a Clinical Trials Unit that was in, in receipt of funding from the NIHR until 30 September 2023.

Elsa Marques is a steering group member of two NIHR projects and a funding panel member previously of the NIHR RfPB panel and now the NIHR PGfAR panel.

Petra Baji: None declared.

Andrew Judge is a member of the National Joint Registry Lot 2 Contract (statistical analysis) team. He is chair of the Data Monitoring Committee (DMC) for: NIHR HTA Dupuytren's Interventions Surgery versus Collagenase (DISC) trial. University of Leicester (25 April 2017–present). He is chair of the TSC for: NIHR HTA. The Gentle Years Yoga Trial. Newcastle University (25 April 2019–present). He is a steering committee member for: Nuffield Foundation. Multilevel Integrated Data for musculoskeletal health intelligence and Actions (MIDAS). University of Keele (1 December 2020–present). He is a DMC member for: Robotic Arthroplasty: a Clinical and cost Effectiveness Randomised controlled trial (RACER). Warwick CTU (30 July 2020 to present).

Ashley W Blom was lead on a completed grant from Stryker Corporation investigating the outcome of the Triathlon total knee replacement. He is a member of the National Joint Registry Lot 2 Contract (statistical analysis) team. Subpanel member of the NIHR Programme Grants for Applied Research (PGfAR) programme (1 September 2015–31 August 2020) versus Arthritis Health Subcommittee (12 October 2016–30 June 2021), cochair versus Arthritis Research Expert group (September 2022–present) Nuffield Foundation Oliver Bird Fund Expert Panel Member (6 August 2019).

Amanda Burston: None declared.

Catherine Jameson: None declared.

Chris A Rogers reports membership of a Clinical Trials Unit that was funded by the NIHR until 30 September 2023. She also reports membership of the NIHR Health Technology Assessment Funding Committee Policy Group (formally CSG) (2017–21) and the Health Technology Assessment Commissioning Committee (2016–21). She has no other competing interests.

## Department of Health and Social Care disclaimer

This publication presents independent research commissioned by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, MRC, NIHR Coordinating Centre, the Health Technology Assessment programme or the Department of Health and Social Care.

This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

## Trial registration

This trial is registered as ISRCTN90992837.

## Funding

This synopsis presents independent research funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme as award number NIHR127849.

This synopsis should be referenced as follows:
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This synopsis provided an overview of the research award *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*. For other articles from this thread and for more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/NIHR127849).

### About this synopsis

The contractual start date for this research was in September 2019. This synopsis began editorial review in June 2023 and was accepted for publication in April 2025. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The Health Technology Assessment editors and publisher have tried to ensure the accuracy of the authors' synopsis and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this synopsis.

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## List of abbreviations

| | |
|---|---|
| ACI | autologous chondrocyte implantation |
| AE | adverse event |
| AMIC | autologous matrix-induced chondrogenesis |
| CI | Chief Investigator |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | case report form |
| CRN | Clinical Research Network |
| DHSC | Department of Health and Social Care |
| DVT | deep-vein thrombosis |
| EDI | equality, diversity and inclusion |
| EQ-5D-5L | EuroQol-5 Dimensions, five-level version |
| HRQoL | health-related quality of life |
| HTA | Health Technology Assessment |
| IKDC | International Knee Documentation Committee |
| KOOS | Knee Injury and Osteoarthritis Outcome Score |
| LIP | Local Information Pack |
| MCID | minimal clinically important difference |
| MRI | magnetic resonance imaging |
| NICE | National Institute for Health and Care Excellence |
| PEP-R | Patient Experience Partnership in Research |
| PI | principal investigator |
| PIL | participant information leaflet |
| PPI | patient and public involvement |
| QALY | quality-adjusted life-year |
| RCT | randomised controlled trial |
| REC | Research Ethics Committee |
| SAE | serious adverse event |
| SD | standard deviation |
| SISMIC | A randomised controlled trial of Scaffold InSertion and MIcrofracture compared to microfracture alone for the treatment of Chondral or osteochondral defects of the knee |
| TSC | Trial Steering Committee |
| VAS | visual analogue scale |
| WPAI | Work Productivity and Activity Impairment |

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