NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89)

Swedish Orphan Biovitrum AB

submission of evidence to NICE

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Abbreviations

ACI	autologous chondrocyte implantation
ACL	anterior cruciate ligament
AE	adverse event
ATMP	advanced therapy medicinal product
BMI	body mass index
BSC	best supportive care
CCI	characterised chondrocyte implantation
CGI-E	Clinical Global Impression scale of efficacy
CGI-I	Clinical Global Impression scale of improvement
CUP	compassionate use programme
EDS	efficacy data set
FAS	full analysis set
GP	General Practitioner
HCHS	Hospital and Community Health Services
HCP	healthcare professional
HR	hazard ratio
HRQL	Health-related quality of life
ICER	incremental cost-effectiveness ratio
ICRS	International Cartilage Repair Society
KOOS	Knee Injury and Osteoarthritis Outcome Score
MACI	matrix-applied autologous chondrocyte implantation
MFx	microfracture
MOCART	magnetic resonance observation of cartilage repair tissue
MP	mosaicplasty
MRI	magnetic resonance imaging
MTA	Multiple Technology Appraisal
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
NMB	net monetary benefit
NSAIDs	non-steroidal anti-inflammatory drugs
OA	osteoarthritis
OTC	over the counter
PSS(RU)	Personal and Social Services Research Unit
QALY	quality-adjusted life-year
ROM	range of movement
SAE	serious adverse event
SD	standard deviation
SF-36	36-Item Short-Form Health Survey
SF-6D	Short-Form 6 dimension
SmPC	summary of product characteristics
TKR	total knee replacement
TTF	time to treatment failure
UK	United Kingdom
USA	United States of America
VAS	visual analogue scale

1 Executive summary

Cartilage damage can be debilitating for patients, causing pain, deterioration of function and greatly limiting normal activities. Ultimately, unless treated, the knee will continue to degenerate, eventually resulting in the need for total knee replacement (TKR).

ChondroCelect® is an innovative method for regeneration of hyaline cartilage, which constitutes a superior and longer lasting repair of cartilage damage than currently available treatment options, fully compliant with the SANCO directives on cell and tissue.[1-3] The efficacy of ChondroCelect was demonstrated in a head-to-head trial compared to microfracture (MFx), the current standard of care in the National Health Service (NHS). In this pivotal study of 118 patients (57 ChondroCelect vs 61 MFx), TIG/ACT/01, ChondroCelect showed numerically superior efficacy to MFx at all timepoints; the difference was statistically significant in patients with recent (<3 years) lesions. Further supportive evidence was provided by the compassionate use programme of ChondroCelect (n=370) and a non-interventional study (TGX001-2001 [n=153]), in which outcomes were consistent. The duration of evidence shows sustained efficacy for up to 60 months and similar safety profile to MFx (with identical numbers of procedure related adverse events).

A risk-sharing scheme, where a partial refund is given for patient who fail in the first 3 years after treatment, has been submitted to the Department of Health (Section 3.9). In Belgium a similar scheme is in place for patients with a recent lesion (<3 years from the onset of symptoms, a pre-specified subgroup in TIG/ACT/01). The experience from this scheme is that only four rebates were required from 254 patients over 3 years, with no patients failing in the 3rd year. This scheme demonstrates better results than those seen in the clinical studies, but also that SOBi are prepared to share the risk of implementing ChondroCelect.

Whilst the incidence of cartilage damage requiring treatment in the UK population is estimated at 10,000 per year, ChondroCelect is not the appropriate treatment for the majority of patients. The optimal patient group for treatment with ChondroCelect are those aged 18-50 years (the population of TIG/ACT/01), with the onset of symptoms less than three years before the procedure is performed. Only patients where debridement has failed, who have a lesion between 1 to 5cm^2 are suitable, with the procedure performed by knee specialists. We expect approximately 293 procedures in year 1, increasing to 632 in year 5.

To demonstrate the value of ChondroCelect, a Markov model was constructed in Microsoft® Excel. Using NHS reference costs, clinical efficacy data from TIG/ACT/01, published utility values, and the ChondroCelect list price of £16,000, the incremental cost-effectiveness ratio (ICER) was £6,812 per quality-adjusted life year (QALY) compared to MFx. The model was most sensitive to its time horizon and extrapolation of efficacy after the trial duration. The ICER remained under £20,000 in 98.8% of probabilistic simulations. Over the 75 year time horizon (when all patients are assumed to have died), we predict a 53% reduction in TKRs/TKR revisions required (607 for ChondroCelect vs 1,286 for MFx).

ChondroCelect is a first in class product, which is safe and durable, successfully restoring damaged cartilage, attaining results superior to standard of care in the UK. This is backed by a risk-sharing scheme. As first line treatment for a select group of patients it provides exceptional value for money to the NHS and better outcomes for patients.

2 Product description and licensing

ChondroCelect (10,000 cells/µL implantation suspension) is a product consisting of characterised viable autologous cartilage cells expanded *ex vivo* expressing specific marker proteins. Each vial of product contains 4 million cells in 0.4 mL cell suspension, corresponding to a concentration of 10,000 cells/µL.[4]

ChondroCelect is indicated for the repair of single symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage Repair Society [ICRS] Grade III or IV; 2cm² or greater) in adults. Concomitant asymptomatic cartilage lesions (ICRS Grade I or II) might be present. Demonstration of efficacy is based on a randomised controlled trial evaluating the efficacy of ChondroCelect in patients with lesions between 1 and 5cm^2.[5]

ChondroCelect received the first marketing authorisation for an advanced therapy medicinal product in 2009.[6] Advanced-therapy medicines are different from conventional medicines, which are made from chemicals or proteins. ChondroCelect is classified as a tissue-engineered medicine, based on the four main groups described below[7]:

- **gene-therapy medicines:** these contain genes that lead to a therapeutic effect. They work by inserting 'recombinant' genes into cells, usually to treat a variety of diseases, including genetic disorders, cancer or long-term diseases. A recombinant gene is a stretch of DNA that is created in the laboratory, bringing together DNA from different sources;
- **somatic-cell therapy medicines:** these contain cells or tissues that have been manipulated to change their biological characteristics. They can be used to cure, diagnose or prevent diseases;
- **tissue-engineered medicines:** these contain cells or tissues that have been modified so they can be used to repair, regenerate or replace tissue;
- **combined advanced-therapy medicines:** these are medicines that contain one or more medical devices as an integral part of the medicine. An example of this is cells embedded in a biodegradable matrix or scaffold.

As a result, ChondroCelect meets biopharmaceutical-standard criteria and provides a supportive pharmacovigilance concept, a risk-management plan and SmPC. In addition, quality assurance, reproducibility, standardisation of manufacture and specific potency are regulated resulting in a product which is materially different from those products which are exempt from licensing.

3 Treatment pathway

3.1 Patient numbers

It is estimated that every year in the UK 10,000 people experience cartilage damage which requires treatment. However, not every lesion will require, or be suitable for treatment with characterised chondrocyte implantation (CCI) (Section 3.4).

Patients in Belgium will experience a similar treatment pathway to that experienced by patients in the UK and data from the experience of using ChondroCelect in Belgium acts as

a good basis for estimating the number of likely procedures in the UK. Data from Belgium, where ChondroCelect is fully reimbursed by an established remuneration programme, show that the number of procedures performed using ChondroCelect were 51 (year 1), 93 (year 2) and 110 (year 3). Adjusting for the population difference between Belgium and the UK, it is estimated that ChondroCelect would be used for 293 (year 1), 534 (year 2) and 632 (year 3) procedures. The budget impact of this is further explored in Section 6.4.

3.2 Cartilage structure and defects

Cartilage defects of the knee vary in severity. Small, acute lesions may be diagnosed incidentally using magnetic resonance imaging (MRI) or arthroscopy of the knee. These lesions can be asymptomatic initially, although they may progress. Larger and/or more chronic lesions may cause pain, catching, locking and swelling.

Chondral lesions that are left untreated can progress, resulting in debilitating joint pain, dysfunction and degenerative arthritis. In the medium-term this can result in persistent and increasing limitation of activities and in the longer-term the need for a prosthetic replacement of the knee. These lesions are associated with ongoing costs to the NHS as well as effects on the health, HRQL and daily activities of the patient.

Hyaline-like articular cartilage has a complex structure. This gives it viscoelastic properties and mechanical durability, with the ability to resist shearing forces and adapt to compressive forces. In the knee, articular cartilage assisted by the synovial fluid distributes the load between the femur and tibia to avoid high point stresses on load-bearing areas and to provide a low friction-bearing surface. To fulfil its mechanical function, articular cartilage does not have a blood, nerve or lymphatic supply.

The only cells in articular cartilage, the chondrocytes, are relatively sparse and embedded in the extracellular matrix, which prevents them moving to the site of injury. The inability of cells to reach the site of cartilaginous injury means that, in skeletally-mature adults, articular cartilage does not spontaneously heal or regenerate if damaged. Shallow or partial-thickness cartilage injuries, which do not reach the underlying bone, have the least self-healing capacity due to the inaccessibility of chondrocytes to repair the damage.[8]

However, this process does not usually produce repair tissue the same as the original hyaline-like articular cartilage; it is more likely to form fibrocartilaginous tissue.

The structure of fibrocartilage is different from that of articular cartilage and has a simple linear organisation. The type of collagen also differs; Type I and X collagen predominate in fibrocartilage; while articular cartilage mainly consists of Type II (with some Type IX). Different types of cartilage have different mechanical properties and Types I and X may be associated with calcification, in which cartilage becomes bony. Fibrocartilage is adapted to resist tensile (stretching) forces (for example in tendons and ligaments) rather than compressive forces. Unlike articular cartilage, it does not provide a frictionless gliding surface, and it is much less hard-wearing.

Where repair has been attempted the process does not usually produce tissue the same as the original hyaline-like articular cartilage. It is more likely to form fibrocartilaginous tissue often leading to a temporary improvement in symptoms, but as noted above this tissue does not have the performance characteristics of the original hyaline-like articular cartilage. The

initial improvement following cartilage repair surgery has been shown to deteriorate after about 18 months post-surgery[9-12] with recurrence of symptoms and limitation of activity.

Injuries to articular cartilage are associated with the development of osteoarthritis (OA).[8, 13-20] OA substantially reduces the patient's HRQL and may require total knee replacement and/or long-term drug treatment.

3.1.1 Classification of articular cartilage lesions

Individual articular cartilage lesions are usually classified using the ICRS classification scheme (Table 1).

Table 1: ICRS classification of articular cartilage lesions

ICRS grade	Description
0	Intact cartilage
I	Superficial (soft indentation or superficial fissures and cracks)
II	Lesion less than half the thickness of articular cartilage
III	Lesion greater than half the thickness of articular cartilage
IV	Lesion extending to subchondral bone
Key: ICRS, International Cartilage Repair Society. **Source:** Brittberg 2003[21]	

3.3 Treatment options

Patients with cartilage injury can be treated in a variety of ways; initial treatment may consist of lavage, debridement and pain relief. This initial treatment is designed to alleviate the symptoms rather than affect a repair of the cartilage; many factors influence treatment choice for cartilage repair (Section 3.6).

Interventions available to re-establish the cartilage surface by trying to repair the tissue, include:

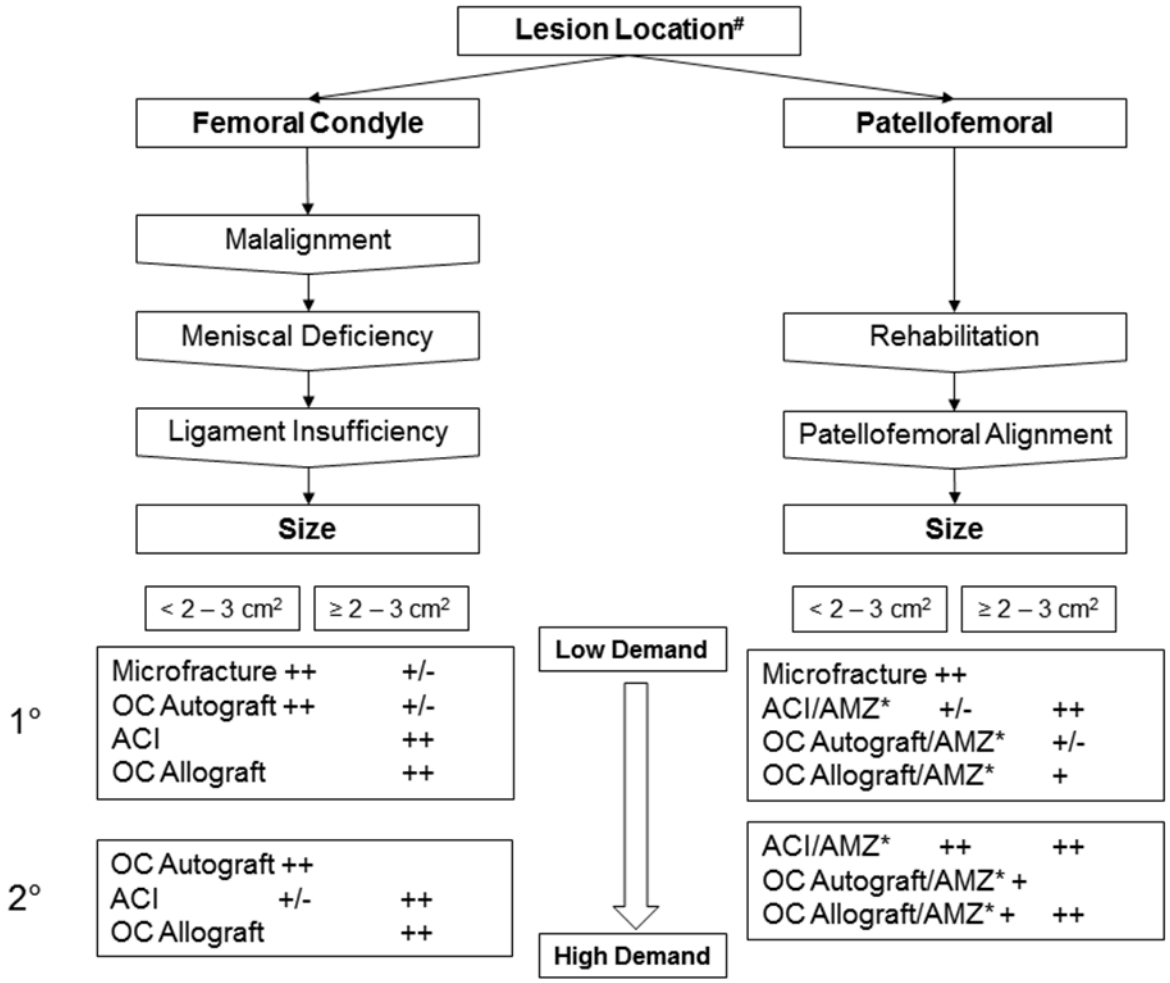
- Marrow stimulation techniques
  - The most commonly practiced type of this technique is MFx, whereby small holes are drilled into the bone in order to allow vascular bone cells to move to the bone surface and stimulate tissue repair. This type of procedure is most likely to produce fibrocartilage.
  - Mosaicplasty is a technique that involves harvesting and transplanting many small cylindrical osteochondral plugs from the less weight-bearing area of the knee and inserting them into drilled tunnels in the defective section of cartilage. It should be noted that mosaicplasty is unsuitable for lesions of the patella.
- Regenerative procedures
  - Autologous chondrocyte implantation (ACI) comprises a series of procedures. First, chondrocytes are harvested from the knee joint. The cells are then

cultured for a few weeks to expand the cell population. In a second surgical procedure, the cultured chondrocytes are implanted into the damaged area. Each damaged area is carefully debrided and covered with a periosteal tissue flap or a porcine collagen membrane, beneath which the autologous cells are injected.

- Matrix-applied ACI (MACI) is a modification of the ACI treatment, where autologous chondrocytes are cultured before being shipped in a collagen matrix, which is then implanted. This product has been acquired by Aastrom (May 2014), and, whilst licensed in Europe (EU) and listed as part of this MTA, sales of MACI throughout the EU have been suspended.[22]
- CCI is also a modification of ACI whereby the cells grown and implanted are selected to keep the chondroctye phenotype which results in a greater likelihood that, on re-implantation, the chondrocytes will form hyaline-like cartilage. This is the technique used for ChondroCelect.

Of the procedures considered as part of this MTA, both location and size inform the treatment option selected (Figure 1).

Figure 1: Treatment choice depending on location and size of lesion

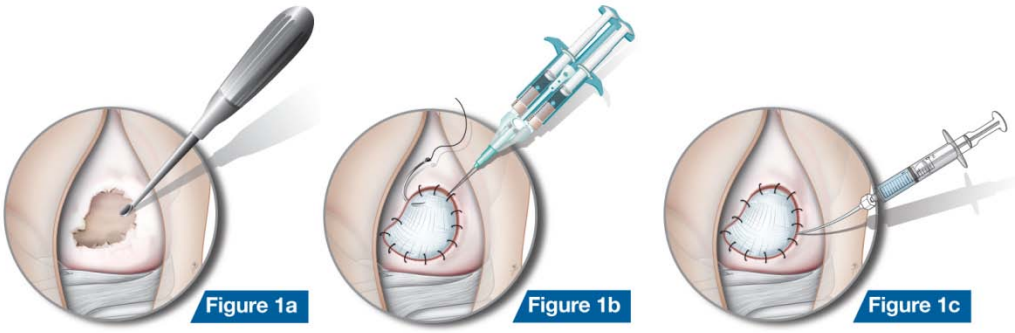


3.4 Description of technology: CCI using ChondroCelect

CCI using ChondroCelect consists of three steps (see also Figure 2):

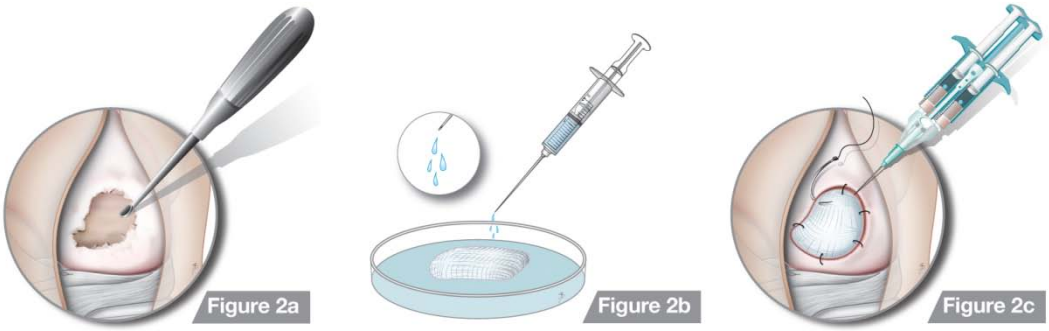
1. An arthroscopy is performed to assess the cartilage defect and to take a small biopsy of cartilage from a low-weight-bearing area of the knee.
2. The chondrocytes contained in the biopsy are freed from the extracellular matrix by enzymatic treatment in a laboratory and expanded in cell culture. ChondroCelect is manufactured using a process in which a gene marker profile is used to determine *in vivo* cartilage-forming potential. This is based on the Ectopic Cartilage Formation Assay.[23]
3. Following expansion, a second procedure is performed, during which ChondroCelect is implanted. There are two methods for performing this part of the procedure: the 'Brittberg' technique (Figure 2) and the 'cell-seeding' technique (Figure 3). In the former a biological membrane (periosteum or collagen) is sutured over the defect and the cell suspension injected underneath; for the latter a bioresorbable membrane is seeded with ChondroCelect cells and sutured cell side down to the cartilage defect and the edges sealed with fibrin glue. TIG/ACT/01 used the Brittberg technique with a periosteal flap while the compassionate use programme used a collagen membrane. The cell-seeding technique is now predominantly used.

Figure 2: An illustration of CCI using the Brittberg technique



Key: CCI, characterised chondrocyte implantation.

Figure 3: An illustration of CCI using the cell-seeding technique



Key: CCI, characterised chondrocyte implantation.

Rehabilitation is very important after CCI, as it is after any cartilage repair procedure. The manufacturer provides a support service for post-operative rehabilitation. Physiotherapists can access a website (www.mycartilagerehab.org) to download a patient specific rehabilitation programme based on the location and size of the repair among other factors. A rehabilitation protocol has been developed by the manufacturer in conjunction with orthopaedic surgeons in The Netherlands. This aims to maximise the repair process noting the phases of chondrocyte development as outlined in Table 2.

Table 2: Comparison of the rehabilitation phases according to Hambly *et al*, Gillogly *et al* and Reinhold *et al*

Hambly *et al*	**Reinhold *et al* and Gillogly *et al***
1. Repair and protection (0 – 4 weeks) Suture of cells, inflammation and proliferation	1. Proliferation phase (0 – 4/6 weeks) Protection of the operated region
2. Inauguration (4 – 8 weeks) Cell differentiation and start of maturation phase	2. Transition phase (4 – 12 weeks) Acquisition of force in repaired tissue
3. Maturation (8 – 12 weeks) Cell differentiation and maturation phase	
4. Integration (12 – 26 weeks) Maturation and integration of cells	3. Remodelling phase (3 – 6 months) Continued remodelling of the tissue into a more organised structure
5. Functional adaptation (26 – 52+ weeks) Maturation and integration of cells	4. Maturation phase (as from 4 – 6 months) Tissue reaches complete development
6. Return to sports (26 – 78+ weeks) Maturation and integration of cells	
Source: Hambly *et al* 2006[24], Gillogly *et al* 2006[25] Reinhold *et al* 2006[26]	

The general aims of rehabilitation with timings post-surgery are provided in Table 3. This shows that it is expected that full range of movement can be achieved approximately 7–8 weeks, reaching complete load bearing capacity around Week 9–10.

Table 3: Rehabilitation guideline summary

Time post-surgery	ROM	Load	Force and function
Preoperative	No limit	No limit	Prevent atrophy
Day 2 - 5	Total CPM 3h/day Extension of CPM 5 – 10°/day	No load	RICE Full slides Isometric exercises Myofeedback
Week 2			Closed and open chain exercises Hydrotherapy
Week 3	0 – 90º active flexion	10 – 15 kg with crutches	Cardiotraining in arms
Week 4	0 – 110º active flexion	Increase by 10 kg, tempo depending on defect	Bicycle and/or rowing ergometry up to 1 h/day
Week 5			Bilateral closed chain exercises
Week 6	0 – 130º active flexion	Reduce the use of crutches depending on defect	Unilateral closed chain exercises depending on defect
Week 7	**FULL ROM**		Increase of knee load during functional activities
Week 8			Proprioceptive training
Week 9		**COMPLETE LOAD**	Improve muscle control, force and endurance
Week 10			
Week 11			
Week 12			
3 – 6 months			Steps within ROM Biking/rowing with mild resistance Bipedal landing on mini-trampoline Build up specific force within safe zone (e.g. triplings)
6 – 9 months			Increase resistance Increase loop training High load isometric control in loaded zone Eccentric training full ROM low impact, safe zone high impact
9 – 12 months			Sport-specific exercises for low impact sport allowed (no pivoting sports and open skills) High impact sports not allowed
> 12 months			Sport-specific exercises for high impact sports Low impact sport exercises

Key: CPM, ROM, range of movement.

3.5 Innovation of ChondroCelect

ChondroCelect is manufactured using a process in which a gene marker profile is used to determine *in vivo* cartilage-forming potential. Unlike previous cell-therapy products implanted in ACI procedures, ChondroCelect has regulatory approval for its controlled and consistent manufacturing process, based on optimised parameters that include enzymatic release, cell culture media, seeding density, time, harvesting procedures and shipping conditions.[23, 27, 28]

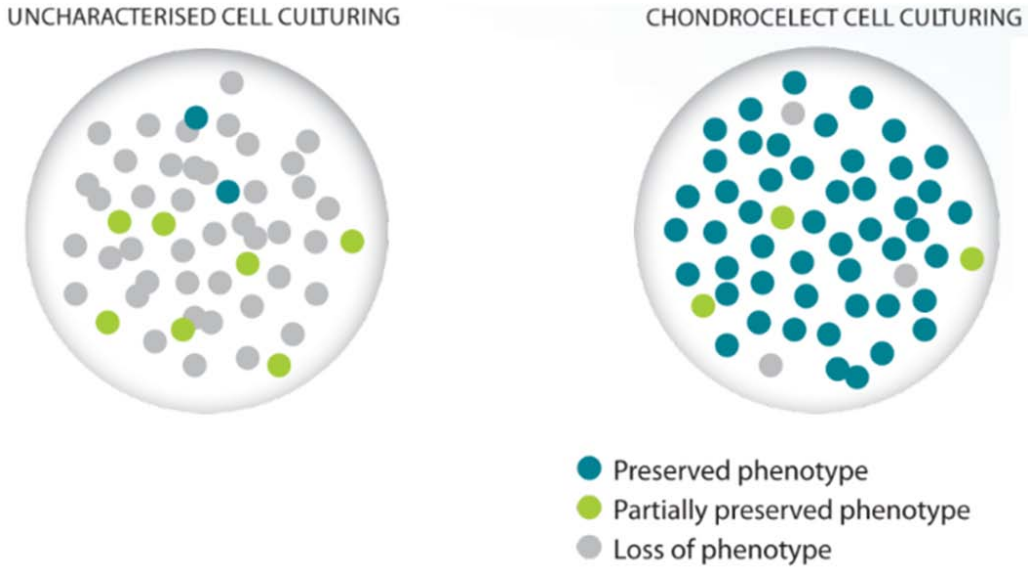
Following growth and harvest of the chondrocytes, the characterisation of cells (see Figure 3) is based on:

- histological assessment (stable *in vivo* tissue formation) at the tissue level;
- three-dimensional cultural assays (proteins and proteoglycans associated with cartilage matrix formation) at the cellular level;
- marker analysis (marker genes important for cartilage biology) at the molecular level.

Figure 3: Comparison of cell populations that pass and fail proprietary *in vivo* assay on gene expression profiles

Previous cell-based products for ACI used chondrocytes which had not been chosen based on a predicted capacity to form stable hyaline-like cartilage *in vivo*.[23] These products were expansions of all the chondrocytes sampled, which included those chondrocytes that would not reliably regenerate hyaline-like cartilage. The CCI expansion process yields highly chondrogenic cells by minimising chondrocyte dedifferentiation and thereby preserving the phenotype (that is, the behaviour and appearance) of articular cartilage cells. This is illustrated in Figure 4.

Figure 4: Diagrammatic comparison of uncharacterised and characterised cell culturing



Adult human articular chondrocytes have a finite capacity to form stable articular cartilage *in vivo*. This capacity is lost during *in vitro* expansion of cells, resulting in the loss of phenotypic stability that can lead to poor quality cartilage repair.[23, 29-31] Building on the work of Dell'Accio *et al*[28], manufacturing methods and protocols have been developed that enhance the capacity of expanded cells to form stable hyaline-like cartilage when implanted in patients. This is important for clinical outcomes because better quality of repair tissue is predictive of improved long-term durability.[32] The process is designed to:

- maintain the differentiation potential and phenotypical stability of the cells, increasing their ability to produce hyaline cartilage;[23]
- preserve the integrity and function of the cells, particularly their ability to produce hyaline cartilage;[5]
- produce autologous cartilage cells, expanded *ex vivo* through a highly controlled and consistent manufacturing process.

ChondroCelect has been developed to enhance the results of cell-based therapy for cartilage lesions so that repair tissue resembles the original articular cartilage rather than fibrocartilage. It offers the prospect of producing fully functional and durable repair tissue, which restores the anatomy as close as possible to its original state. This is intended to improve or cure symptoms, improve HRQL and reduce the risk of developing OA in the affected knee.

3.6 Key advantages of characterised chondrocyte implantation

Some key advantages of CCI that offer the possibility of better results compared with marrow stimulation techniques (MFx and mosaicplasty) for cartilage repair are summarised in Table 4.

Table 4: Summary of advantages of CCI compared with MFx and grafting

Cell-based therapy vs	Advantage of CCI
MFx	CCI with ChondroCelect produces cartilage more closely resembling the original hyaline cartilage rather than fibrocartilage.[31]
MFx	The ChondroCelect implant does not form a clot and therefore is not associated with clot retraction.
MFx Mosaicplasty	CCI results in less damage to the anatomy of the knee in the area of the cartilage damage, minimising further damage to the surface of the cartilage and reducing the chances of inducing or accelerating the development of OA. • In the case of MFx, the tidemark and subchondral bone plate are breached and may lead to bone-forming cells accessing the area of the defect; this is thought to contribute to the deterioration of symptoms and the development of OA.[33] • In the case of mosaicplasty, the anatomy is altered at both the donor site (in autografting) and the implantation site (in both autografting and allografting) making it difficult to ensure congruence between the opposing surfaces.
Mosaicplasty	The ChondroCelect implant is fluid which allows it to adopt a shape that fits the surface required by the position of the lesion and the contours of the opposing surface.
Mosaicplasty	CCI does not involve creating injury in the donor site.
Key: CCI, characterised chondrocyte implantation; MFx, microfracture; OA, osteoarthritis.	

3.7 Current recommendations for treatment

There are no internationally accepted treatment guidelines on how and when to treat cartilage lesions, or which treatments to choose for particular sizes or characteristics of defects. A recent survey of 242 European orthopaedic surgeons revealed that there is consensus that debridement and/or MFx is first-choice treatment for full-thickness cartilage lesions up to 3cm^2.[34] A variety of treatments were preferred for lesions exceeding 3 cm^2: in this survey, MACI was preferred by 33.5% of the experts, followed by MFx (19.0%), debridement (15%), mosaicplasty (9.5%), and several other techniques such as abrasion.[34]

As can be seen, there is no firm consensus as to the 'best' treatment of cartilage defects, even for well-defined subgroups. A range of factors influences the choice of treatment of cartilage injuries, including:

- the demands the patient's normal lifestyle places on the knee;
- the patient's age;
- the length of time since the injury was sustained;
- the location, size, number and depth of cartilage defects;
- other injuries to, or disorders of, the knee, including damaged ligaments, torn menisci and malalignment of the knee.

3.7.1 NICE guidance

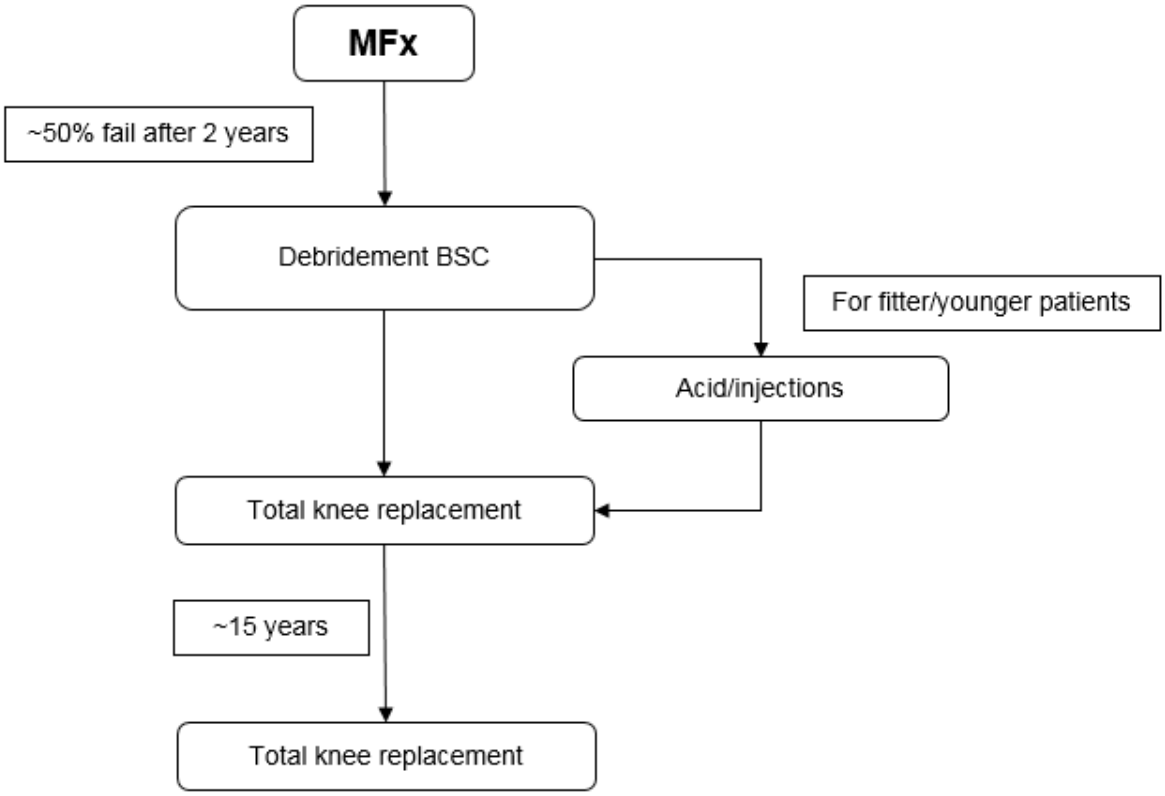
In 2005, NICE published guidance based on a Technology Appraisal of ACI.[35] This did not recommended ACI for the treatment of articular cartilage defects of the knee joint except in

the context of ongoing or new clinical studies designed to generate robust and relevant outcome data, including the measurement of HRQL and long-term follow-up.

As a result, in the UK MFx is the most common procedure performed to repair cartilage injuries of the knee (see Figure 5). However, this tends to require follow-up procedures due to failure.

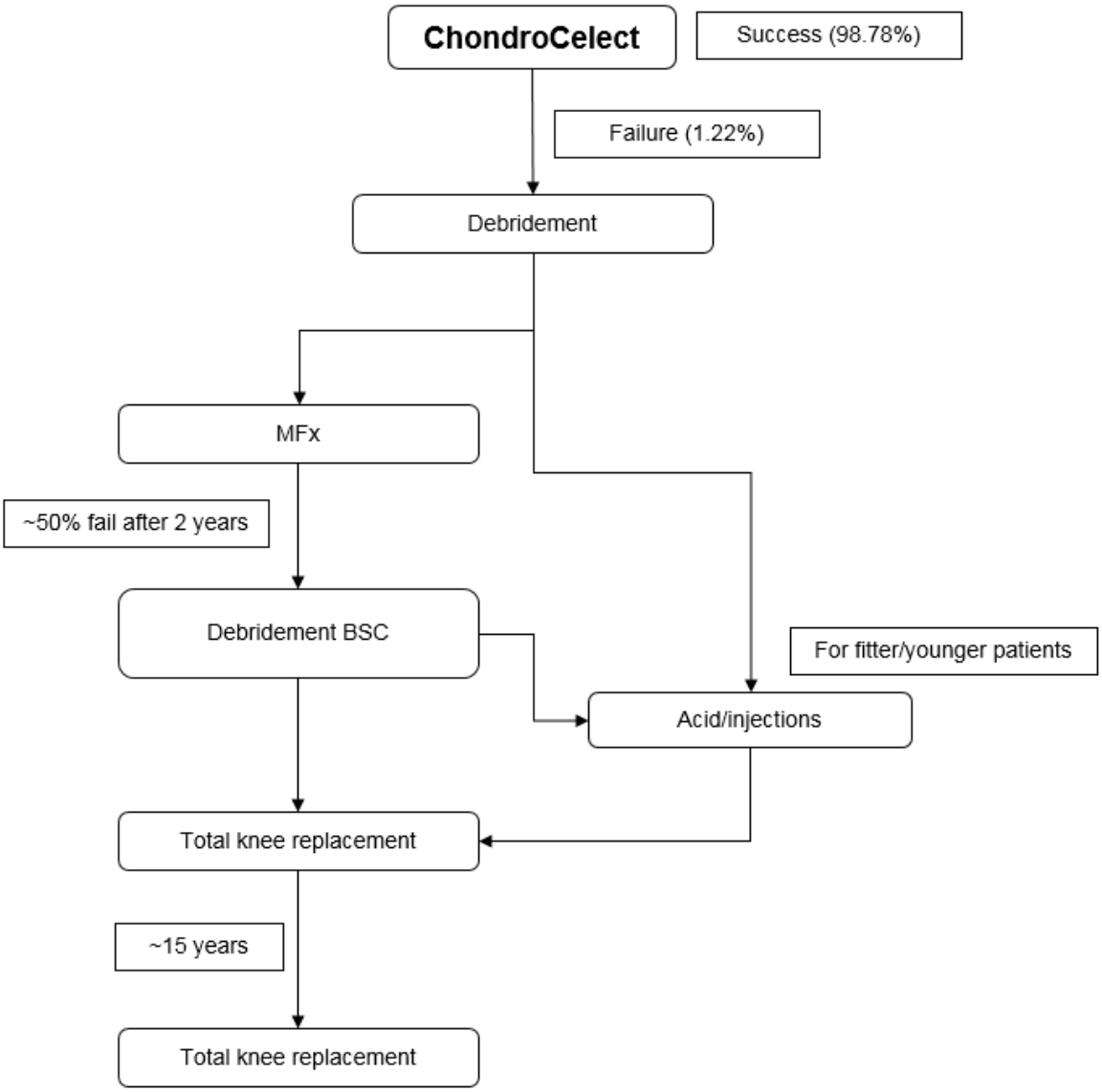
However, as previously noted, ACI using ChondroCelect is more likely to form hyaline-like cartilage than MFx and when this is successful it is likely that patients will not require further procedures (see Figure 6).

Figure 5: Current treatment pathway



Key: BSC, best supportive care; MFx, microfracture.

Figure 6: Treatment pathway with ChondroCelect



Key: BSC, best supportive care; MFx, microfracture.

3.8 Training and support

CCI using ChondroCelect is a technique that should only be performed by specialist knee surgeons. The manufacturer of ChondroCelect supports the use of its product by providing a fully funded, comprehensive training package. Part I of the package consists of a scientific-medical-surgical component, while Part II covers the logistical-administrative part. Prior to being able to receive a biopsy kit for healthcare professionals (HCPs) ChondroCelect, both parts of the training must be provided to those HCPs who will be performing the procedure. In addition, full training in the handling and administration of ChondroCelect is also provided to the hospital pharmacists. Once training has been fully completed by all nominated HCPs within a hospital, training certificates are issued by the manufacturer, which are provided to the HCP and kept on file by the manufacturer.
Training logs will be kept by the hospitals and Sobi.

At yearly intervals the hospital is contacted by the manufacturer to ascertain whether any additional HCPs require training. If this is the case it will be scheduled and performed in a timely manner.

If a trained HCP performs ≤2 CCI procedures per year, the HCP should receive refresher training.

3.9 ChondroCelect risk-sharing scheme (Commercial in confidence)

[redacted] A scheme to provide a rebate to the NHS on a risk-sharing basis will be submitted to Patient Access Schemes Liaison Unit (PASLU). Under the scheme, the manufacturer will [redacted]

Failure has been defined as:

The need for a re-intervention affecting more than 20% of the surface of the index lesion, prompted by the persistence or recurrence of symptoms related to the index knee

4 Clinical efficacy of ChondroCelect

4.1 TIG/ACT/01

Demonstration of efficacy is based on a randomised controlled trial (TIG/ACT/01) evaluating the efficacy of ChondroCelect in patients with lesions between 1 and 5cm^2. This Phase III trial compared ChondroCelect with MFx and reported results at 1-year[36], 3-year[37] and 5-year follow-up.[38]

4.1.2 Study design and methods

Patients were aged 18 to 50 years (mean 33.93 and 33.92 for CCI and MFx respectively, range 18-50) and had a symptomatic single lesion of the articular cartilage of the femoral condyles, between 1cm^2 and 5cm^2 in size. Patients with significant knee abnormalities, patellar lesions, OA, previous MFx performed less than 1 year earlier or previous mosaicplasty were excluded. Patients were not excluded for prior debridement and lavage or repaired anterior cruciate ligament injuries.

After screening for eligibility, all patients underwent arthroscopy and were then randomly allocated to CCI (n=57) or MFx (n=61). Surgeons performed both the CCI and MFx interventions in a standardised manner. After surgery, both groups of patients were enrolled in an identical rehabilitation programme and followed-up according to the same schedule.

One hundred patients were included in the extension phase of the pivotal study (46 CCI and 54 MFx), and 87 patients were clinically evaluated at 36 months post-procedure (42 CCI and 45 MFx).

<u>Histologic analysis</u>

Twelve months post procedure, cylindrical full-thickness cartilage biopsy specimens of 2mm diameter were obtained arthroscopically from the centre of the repair tissue with a custom-made biopsy needle. The overall histology assessment scores were determined by two blinded independent histopathologists specialising in cartilage histology, who assessed the quality of cartilage repair. The histopathologists also evaluated individual components of cartilage repair related to chondrocyte phenotype, tissue structure and other possible negative features of cartilage repair. Each item was scored using a 100mm visual analogue scale (VAS).

<u>MRI structural outcome</u>

Characteristics of the articular cartilage repair tissue were evaluated by MRI scans performed at baseline and 12, 24 and 36 months after CCI or MFx according to magnetic resonance observation of cartilage repair tissue (MOCART)[39, 40] and 9 additional items. This was scored independently by two musculoskeletal radiologists blinded to treatment allocation. A third reader provided final scoring in the case of discrepancy. Four MOCART subscales were selected *a priori* as the most relevant for evaluating cartilage repair quality: filling of the defect, surface of the repair tissue, subchondral lamina and subchondral bone reaction. Of the 9 additional parameters, level of subchondral bone plate was identified *a priori* to be of particular interest, as elevation of the bone front had been previously reported in MFx procedures.[9, 11, 33]

Assessment of clinical outcome

Clinical outcome was assessed using the self-administered Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire.[41-45] This consists of five subdomains: symptoms/stiffness, pain, activities of daily living, function in sports and recreational activities, and HRQL. Scores for the summed (overall KOOS) and individual subdomains were transformed to a scale of 0 to 100, with 0 representing extreme knee problems and 100 representing no knee problems.

The sports domain was not included in the overall KOOS because too many items were not reported by the patients. According to the pre-specified statistical analysis plan, if more than two items had not been completed, the response was considered invalid and no score calculated for that specific domain of the KOOS.

Safety

Safety was assessed by physical examinations, vital signs, electrocardiograms, clinical laboratory tests and continuous monitoring of adverse events (AEs). All AEs experienced by the patient from the time of Screening Visit 1 (Day 28) until completion of both the initial 12-month and extension studies were recorded in the case report form. Investigators were required to assign a causal relationship to the study procedure (CCI or MFx). All AEs were monitored until there was a return to normal or until the condition became stable or had resolved. The patient continued to be followed after completing the study if any AE had not stabilised or resolved at the end of the study period.

For the initial 12-month study the causal relationship refers to whether an AE was considered to be related to the combination of both surgical procedure and ChondroCelect administration for patients in the CCI group and surgical procedure alone for patients who were assigned to the MFx group.

Treatment failure

Treatment failure was defined as a decision by the surgeon that re-intervention was necessary because of the persistence or recurrence of symptoms.

Health-related quality of life

HRQL was evaluated by administration of the SF-36 questionnaire during the extension phase of the study at 18, 24, 30, 36, 48 and 60 months post procedure.

4.1.2 Results

Baseline demographics

The two treatment groups were well matched regarding patient baseline characteristics (Table 5).

Table 5: Summary of baseline demographics at baseline

Characteristic		Statistic	ChondroCelect (N=57)	Microfracture (N=61)	Total Patients (N=118)
Age (years)		Mean (SD)	33.93 (8.54)	33.92 (8.61)	33.92 (8.54)
		Range	18-50	18-50	18-50
		<40 (N [%])	40 (70%)	43 (70%)	83 (70%)
		≥40 (N [%])	17 (30%)	18 (30%)	35 (30%)
Sex:	Male	N (%)	35 (61%)	41 (67%)	76 (64%)
	Female	N (%)	22 (39%)	20 (33%)	42 (36%)
Height (m)		Mean (SD)	1.765 (0.108)	1.770 (0.085)	1.767 (0.097)
		Range	1.57-1.97	1.58-1.92	1.57-1.97
Body weight (kg)		Mean (SD)	78.29 (13.89)	80.56 (13.29)	79.46 (13.57)
		Range	50.0-103.3	50.7-129.0	50.0-129.0
BMI (kg/m^2)		≤25 (N [%])	28 (49%)	31 (51%)	59 (50%)
		>25 & ≤30 (N [%])	26 (46%)	24 (39%)	50 (42%)
		>30 (N [%])	3 (5.3%)	6 (9.8%)	9 (7.6%)
Race:	Caucasian	N (%)	56 (98%)	58 (95%)	114 (97%)
	Black	N (%)	0 (0.0%)	1 (1.6%)	1 (<1%)
	Asian	N (%)	0 (0.0%)	2 (3.3%)	2 (1.7%)
	Afro-Caribbean	N (%)	1 (1.8%)	0 (0.0%)	1 (<1%)
Country	Belgium	N (%)	33 (58%)	35 (57%)	68 (58%)
	The Netherlands	N (%)	19 (33%)	17 (28%)	36 (31%)
	Croatia	N (%)	4 (7.0%)	5 (8.2%)	9 (7.6%)
	Germany	N (%)	1 (1.8%)	4 (6.6%)	5 (4.2%)

Histological results

Structural repair was assessed at 1 year by histopathologists blinded to the treatment using computerised histomorphometry and the Overall Histology Assessment Score. At 1 year post-procedure, histology of biopsies showed significantly better structural results in the CCI group compared with the MFx group (Figure 7, Figure 8 and Figure 9).[36] These results show that CCI is associated with more chondrocyte-like cells and a higher proteoglycan content of the cellular matrix, which gives the tissue the ability to resist compression – an essential feature of durable articular cartilage. The repair tissue of CCI patients was less fibrous and showed elements indicating true regeneration and reconstitution of native articular cartilage structure. Repair tissue composed of fibrocartilage is more likely to degenerate and become symptomatic than hyaline or hyaline-like repairs.[9, 11, 33, 46-49]

Figure 7: Computer-assisted histomorphometry results at 12 months post-procedure[36]

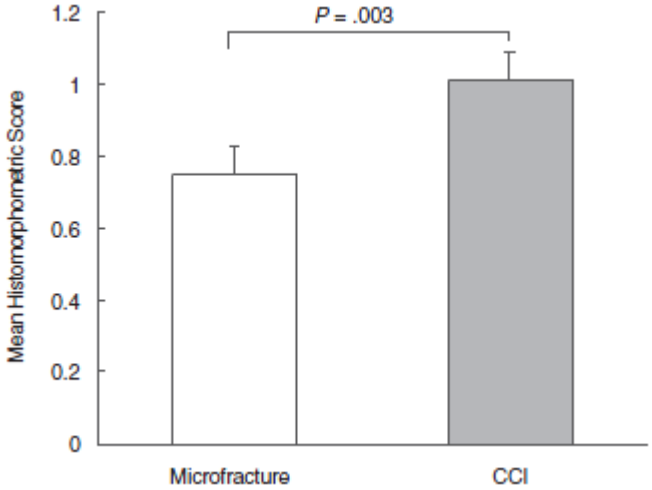
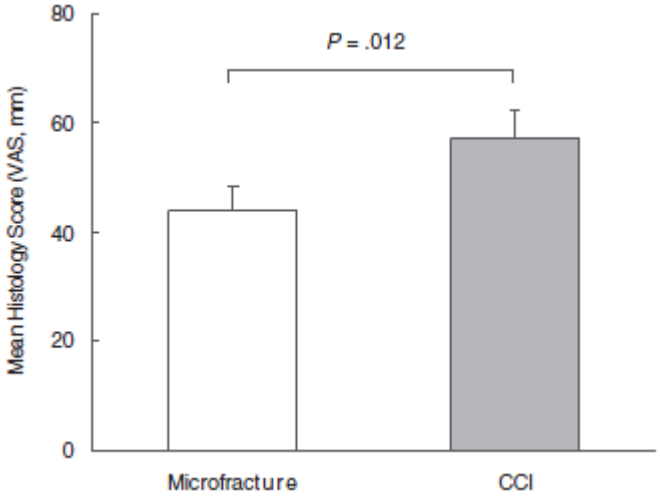
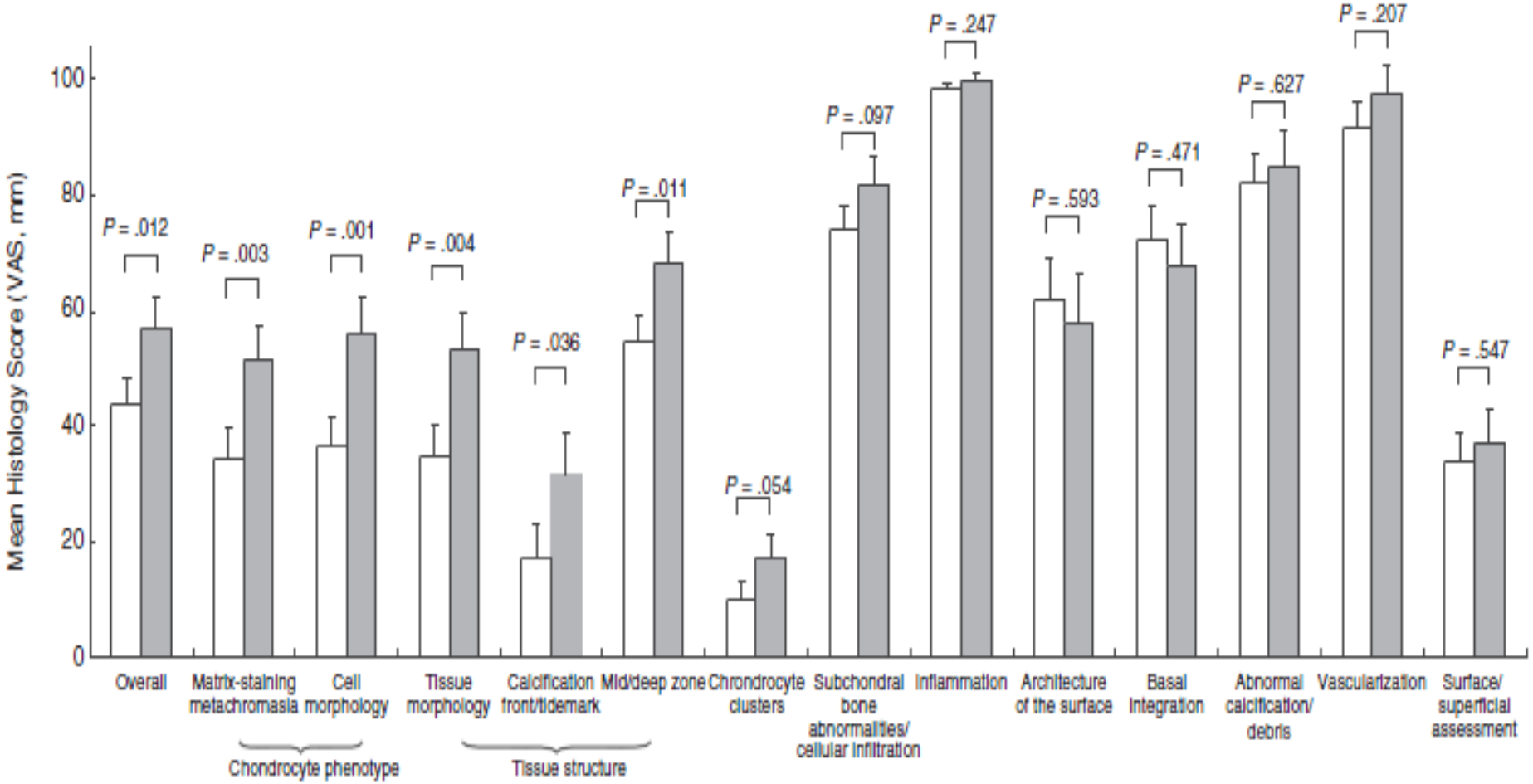


Figure 8: Overall histology assessment by two blinded histopathologists at 12 months post-procedure[36]



Key: VAS, visual analogue scale.

Figure 9: Components of histology assessment by two blinded histopathologists at 12 months post-procedure[36]



Key: VAS, visual analogue scale.

MRI structural results

At 36 months post procedure, no statistically significant between-group differences were observed for the preselected MOCART subscales considered reflective of cartilage repair quality. When considering the mean absolute values, comparable results were noted except for *subchondral bone reaction*, indicating that CCI-treated patients developed less subchondral bone reaction than MFx-treated patients over the 36-month post-operative period (p=0.056). Progressive elevation of the subchondral bone plate compared with baseline was observed at 36 months in both treatment groups but was markedly less pronounced with CCI than MFx (8.3% vs 12.1% at baseline; 25.0% vs 51.5% at 36 months).

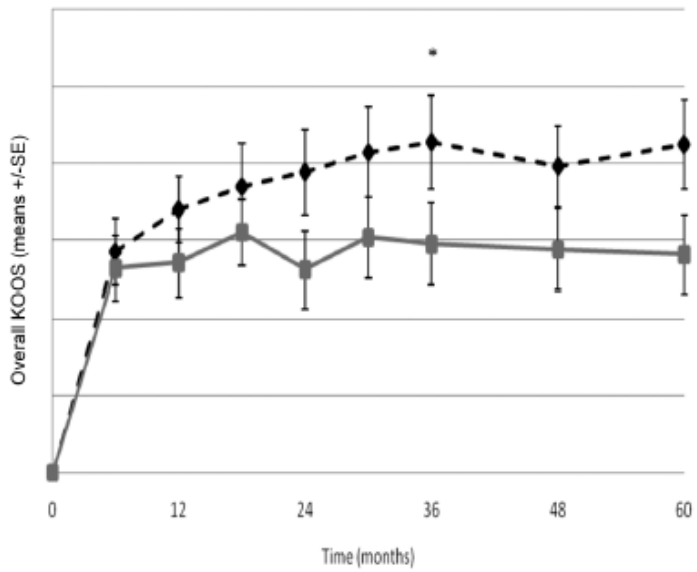
Radiographic results

In 49 patients, radiographic data were available at baseline and 60 months. Four of 49 patients (8%) had a Kellgren Grade 2 score; there was no significant difference in the frequency of radiographic changes between ChondroCelect- and MFx-treated patients at 60 months.

KOOS

The mean change in overall KOOS from baseline in all patients is shown in Figure 10. Both the CCI and MFx groups had statistically significant improvements in overall KOOS, reaching a peak at about 18 months for MFx with a slight fall thereafter compared with a continued improvement to 36 months for CCI patients, which was maintained thereafter.

Figure 10: Mean overall KOOS change from baseline (all patients)

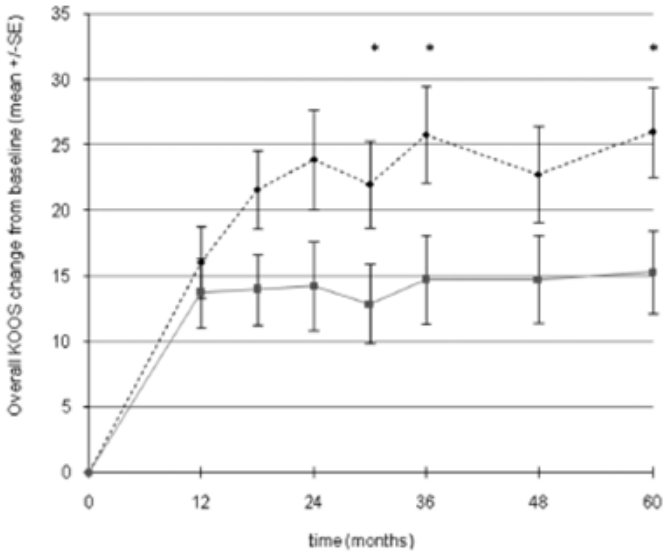


Dashed line = CCI, solid line = MFx
Key: CCI, characterised chondrocyte implantation; KOOS, Knee Injury and Osteoarthritis Outcome Score; MFx, microfracture.
Note: *p<0.05

Sub-set analysis: onset of symptoms <3 years

The same pattern is seen in patients whose onset of symptoms was less than 3 years prior to CCI or MFx (Figure 11). However, in this group there is a statistically significant and clinically relevant difference in improvement in the CCI group compared with the MFx group at 60 months ([mean ± SE] 25.96±3.45 vs 15.28±3.17, respectively; p=0.026). Significant differences between CCI and MFx patients were also observed in the pain and HRQL domains. Finding an improved result from cell-based therapy in patients with more recent onset of symptoms is consistent with earlier literature.[50, 51]

Figure 11: Mean overall KOOS change from baseline (<3 years since onset)



Dashed line = CCI, solid line = MFx
Key: CCI, characterised chondrocyte implantation; KOOS, Knee Injury and Osteoarthritis Outcome Score; MFx, microfracture, SE, standard error.
Note: *p<0.05

Adverse events

AE data were available for 43/51 CCI patients (84.3%) and 45/61 MFx patients (73.7%) for the 60-month study period. The majority of AEs were mild or moderate. Serious AEs leading to prolonged or renewed hospitalisation occurred in 20% of patients in both groups.

In the CCI group, five serious AEs occurred. Two (hypersensitivity and ligament rupture) were considered ‘unlikely’ to be related to the treatment, two were considered ‘possibly’ related (deep vein thrombosis and arthralgia) and one (tendinitis) was considered ‘probably’ related to the procedure.

In the MFx group, five serious AEs (syncope, intervertebral disc disorder, spinal column stenosis and sciatica, and synovial cyst) were considered ‘unlikely’ to be related.

All other serious AEs (10 CCI and 18 MFx) were considered not to be related to the procedure.

The most common treatment-emergent AE reported for patients in the CCI and MFx groups was arthralgia (75% vs 62%, respectively) and after 36 months (14% vs 4%, respectively).

Joint swelling was reported by 22% of CCI patients compared with 7% of MFx patients (p=0.026); beyond 36 months, this event was reported in only one patient (MFx group).

Joint crepitation was significantly more common in the CCI group than in the MFx group 0-18 months after surgery (12% vs 2%, p=0.028), between 18 and 36 months after surgery (11% vs 0%, p=0.011) and from 36 months onward (9.3% vs 0%, p=0.053). Slightly more patients in the CCI group compared with the MFx group reported joint effusion between 36 and 60 months after surgery (12% vs 2%, p=0.106). None of the cases of joint crepitation or effusion were rated as serious or severe.

At 60 months, most of the AEs had resolved (ongoing: effusion, 3/37 CCI [8.1%] and 1/40 MFx [2.5%]; joint crepitation, 1/37 CCI [2.7%] and 1/40 MFx [2.5%]).

Re-intervention and time to failure

Seven out of 51 (13.7%) CCI patients had a re-intervention on the index lesions during the study compared with 10/61 (16.4%) for MFx patients (see Table 6). The failure rate at 5 years in patients with recent onset of symptoms was 9% in the CCI group compared with 18% in the MFx group. Median time to failure in those who failed was 50 months in the CCI group compared with 27 months in the MFx group.

Table 6: Characteristics of failure versus non failure

	Re-intervention		**No re-intervention**	
	CCI (n=7)	**MFx (n=10)**	**CCI (n=44)**	**MFx (n=51)**
Mean age, y (range)	33.7 (29-40)	32.0 (18-45)	33.6 (18-50)	34.3 (19-50)
Patients <35 years, %	57%	50%	57%	47%
Mean height, cm (range)	169 (158-190)	173 (161-183)	178 (157-197)	178 (158-192)
Mean weight, kg (range)	66 (50-87)	72 (51-84)	80 (52-100)	82 (57-129)
BMI, % of patients ≤25 >25 and ≤30 >30	 86% 14% 0%	 60% 30% 10%	 45% 50% 5%	 49% 41% 10%
% of male patients	14%	30%	70%	75%
Mean symptom duration since onset, y (range)	6.81 (0-17)	4.36 (0-18)	2.9 (0-15)	3.1 (0-12)
Mean lesion size, cm^2 (range)	3.5 (2-5)	2.3 (1-5)	2.6 (1-5)	2.5 (1-5)
Acute symptom onset, %	43%	60%	48%	57%
Abnormal opposite knee condition, %	71%	10%	32%	20%
Previous knee surgery, % None 1 ≥2	 14% 43% 43%	 20% 40% 40%	 14% 57% 30%	 24% 59% 18%
Concomitant lesions (ACL, menisci, other), %	86%	80%	86%	77%

Key: ACL, anterior cruciate ligament; BMI, body mass index; CCI, characterised chrondrocyte implant; MFx, microfracture.

Health-related quality of life

At 36 months SF-36 scores were similar in both treatment groups and although numerically better for ChondroCelect, there was no significant difference in the HRQL between treatment groups, or the US standardised population.

Table 7: SF-36 summary scores[a] at 36 months

		ChondroCelect (N=57)	Microfracture (N=61)
Physical Functioning	N	21	20
	Mean (SD)	49.2 (10.9)	47.8 (11.2)
Role-Physical	N	21	20
	Mean (SD)	50.7 (9.3)	49.1 (10.1)
Bodily Pain	N	20	20
	Mean (SD)	50.8 (11.9)	49.8 (11.1)
General Health	N	21	20
	Mean (SD)	55.1 (8.8)	49.5 (10.1)
Vitality	N	20	20
	Mean (SD)	57.4 (7.8)	53.7 (9.6)
Social Functioning	N	21	20
	Mean (SD)	51.9 (10.6)	50.6 (11.2)
Role-Emotional	N	21	20
	Mean (SD)	53.5 (6.1)	47.1 (12.5)
Mental Health	N	20	20
	Mean (SD)	53.9 (8.0)	51.8 (10.1)

Key: [a] normalised data to permit comparison with US population (as assessed in 1998)

Data from the SF-36 at 60 month follow up showed similar scores as for 36 months.

4.2 Compassionate use programme

The results of a non-comparative study of 370 patients in a compassionate use programme have been reported.[52] Despite the limitations of the study's design (i.e. there is no comparative evidence), the findings are summarised here as they report effectiveness and safety results consistent or better than those in the TIG/ACT/01 trial, but in clinical practice rather than a research setting.

4.2.1 Study design and methods

Participants were patients treated with ChondroCelect between October 2004 and July 2008. Patients had symptomatic articular cartilage defects of the knee, but there were no predefined eligibility criteria for entry into the study and no prospectively-defined outcome measures. Defect sizes were recorded in order to calculate the dose of ChondroCelect and surgeons were trained in the use of ChondroCelect as part of a routine educational programme.

Patients were excluded for a number of specific reasons:

- if an active infection was identified at the time of biopsy
- cartilage damage was associated with significant OA lesions
- a known history of hypersensitivity to:
  - penicillin G
  - streptomycin sulphate
  - amphotericin B as
  - products of bovine origin.

Patients (n=370) were treated in 43 orthopaedic centres in seven European countries. Safety data were collected from 334/370 (90.3%) patients and effectiveness data from 282/370 (76.2%) patients.

The procedure performed differed slightly from that used during TIG/ACT/01 in that the implantation of ChondroCelect was secured using a biological membrane rather than an autologous periosteal flap (TIG/ACT/01).

Each participating surgeon was requested to provide completed AE collection sheet per patient with all clinically relevant, knee-related AEs, as well as a Clinical Global Impression scale of improvement (CGI-I) and efficacy (CGI-E) for each patient, retrospectively derived. For each AE, the start and stop dates, the outcome, severity and relationship to ChondroCelect and to the study procedure were requested as well as the seriousness and the action taken. All reported serious adverse events (SAEs), both knee related and not knee related, were also collected.

The CGI-I is a 7-point categorical scale with three categories of improvement and three categories of worsening (minimally, much and very much), centred around a category of 'no change'.[53]

The CGI-E is a 4-point scale with the categories 'very good', 'moderate', 'slight' and 'unchanged or worse'.[53]

Both CGI-I and CGI-E are surgeon-rated scales, where CGI-I intends to measure the clinical global impression of the clinician with respect to the improvement (or worsening) of the patient since baseline or pre-surgery; while CGI-E rates the clinician's global impression of the patient's degree of improvement that is considered to be related to the intervention only. The results were assessed also in patients with short-term (0–≤18 months; mean = 9 months; standard deviation [SD] = 4.58 months) and midterm follow-ups (>18 months; mean = 27 months; SD = 6 months).

The full analysis set (FAS) included all patients treated, the safety analysis set (SAS) included all patients for whom a safety assessment was received, and the effectiveness data set (EDS) consisted of patients for whom effectiveness and safety data were received (Table 8).

Table 8: Patient flow from the compassionate use programme

Patient group	n	Reasons for exclusion
Biopsied	399	n/a
FAS	370	Implantation was not performed in 29 patients: no/insufficient cells isolated from biopsy (n=12); cells stopped growing (n=11); patients refused implantation/did not show for surgery (n=4); positive sterility test result (n=1); low cc score (n=1).
SAS	334	For 36 patients no safety data could be received
EDS	282	For 52 patients no CGI data could be received
Key: CGI, Clinical Global Impression; EDS, effectiveness data set; FAS, full analysis set; n/a, not applicable; SAS, safety analysis set. **Source:** Vanlauwe 2011[38]		

4.2.2 Results

Baseline demographics

Baseline demographic and medical data are presented in Table 9.

Table 9: Key clinical outcome results from the compassionate use programme

Demographic	
Age, mean (SD), years	33.7(9.6)
Sex, % male	56.7
Weight, mean (SD), kg	77.1 (14.2)
BMI, mean (SD), kg/m^2	25.0 (3.4)
Cartilage lesion size, mean (range), cm^2	3.51 (0.25–20.0)
Cartilage lesion location, n (%)	
Medial femoral condyle	190 (43.3)
Patella	84 (19.2)
Lateral femoral condyle	66 (15.1)
Trochlea	39 (8.9)
Femoral condyle	32 (7.3)
Tibial plateau	13 (3.0)
Not specified	13 (3.0)

Single lesions	330 (87)
Multiple lesions	49 (13)
Key: BMI, body mass index; SD, standard deviation. **Source:** Vanlauwe 2011[38]	

Clinical outcomes

Key clinical outcome results are summarised in Table 10

Table 10: Key clinical outcome results from the compassionate use programme

Outcome measure	Category	n (%)
CGI-I	very much improved	82 (29.1%)
	much improved	109 (38.7%)
	minimally improved	47 (16.7%)
	no change	20 (7.1%)
	minimally worse	11 (3.9%)
	much worse	4 (1.4%)
	very much worse	2 (0.7%)
	TOTAL	275 (100%)
CGI-E	very good	107 (37.9%)
	moderate	102 (36.2%)
	slight	33 (11.7%)
	unchanged or worse	31 (11%)
	TOTAL	273 (100%)
Key: CGI-E, Clinical Global Impression scale of efficacy; CGI-I, Clinical Global Impression scale of improvement. **Source:** Vanlauwe 2011[38]		

Most subgroups did not show different responses to treatment. Findings were similar in those who had ≤18 months compared with >18 months follow-up, those with a patellar lesion compared with femoral lesions, and those with large lesions compared with small lesions.

However, differences were found in patients with single lesions compared with multiple lesions

- CGI-I: 204/231 (85.7%) improved compared with 10/44 (77.3%), respectively, p=0.056.
- CGI-I: rated ‘much’ or ‘very much’ improved in 162/231 (68.7%) and 29/44 (65.9%), respectively, p=0.36.
- CGI-E: rated ‘moderate’ or ‘very good’ in 179/229 (75.2%) and 30/44 (68.2%) respectively, p=0.17.

Adverse events

A total of 313 clinically relevant, knee-related AEs were reported in 155/334 (46.4%) patients. Those occurring in ≥2% of patients are shown in Table 11.

Table 11: Safety outcomes reported in ≥2% of patients in the compassionate use programme

Adverse event	n (%)
None	179 (53.6)
Knee pain	79 (23.8)
Joint effusion	29 (8.6)
Joint swelling	27 (8.2)
Joint crepitation	20 (6.1)
Muscle atrophy	20 (6.1)
Joint range of motion decreased	19 (5.7)
Tendon disorder	13 (3.9)
Joint lock	11 (3.2)
Therapeutic product ineffective	11 (3.2)
Bone swelling	10 (2.9)
Joint instability	10 (2.9)
Synovitis	10 (2.9)
Arthrofibrosis	8 (2.5)
Cartilage hypertrophy	7 (2.1)
Source: Vanlauwe 2011[38]	

Of the AEs reported, 233/313 (74.4%) were considered unlikely to be related or unrelated to ChondroCelect; 243/313 (77.6%) of the AEs were mild or moderate; 178/287 (62.0%), were considered to be related to surgery. Nine out of 18 (50%) reports of joint crepitation were considered to be related to ChondroCelect.

Twenty-four SAEs were reported to have occurred in 20 (6%) patients. Seven of these concerned arthrofibrosis of the involved knee (five patellar lesions and two medial femoral condyle lesions) and required manipulation under anaesthesia. Three SAEs were reported as possibly related to ChondroCelect and related to the surgery (one joint range of movement decreased and two therapeutic product ineffective). The other SAEs were considered not related to, or unlikely to be related to, ChondroCelect.

The AEs reported in this study are consistent with those expected in patients undergoing knee surgery and chondrocyte implantation; except that the rate of cartilage hypertrophy is much lower (2.1%) than previous reports using other cell-therapy products for ACI which reported re-interventions of up to 50% for this reason.[54]

4.3 Non-interventional study: TXG001-2011

The interim results of a non-interventional study[55] are presented below. Despite these being an interim assessment and early results representative for the short term outcome only (12 - 24 months), the findings are summarised here as they report effectiveness and safety results consistent or better than those in the TIG/ACT/01 trial, but in clinical practice rather than a research setting.

4.3.1 Study design and methods

TGX001-2011[55] is an ongoing non-interventional study that is conducted as an open label, prospective, multi-centre registry in which efficacy and safety data is collected from routine clinical follow-up in a 'real life' setting.

The study was initiated in Belgium and the Netherlands where ChondroCelect treatment is fully reimbursed by an established national/hospital remuneration programme. Data is being collected in Belgian hospitals through site monitoring, whereas data from hospitals in the Netherlands are obtained through an existing data collection programme managed by the Dutch Orthopaedic Society (NOV).

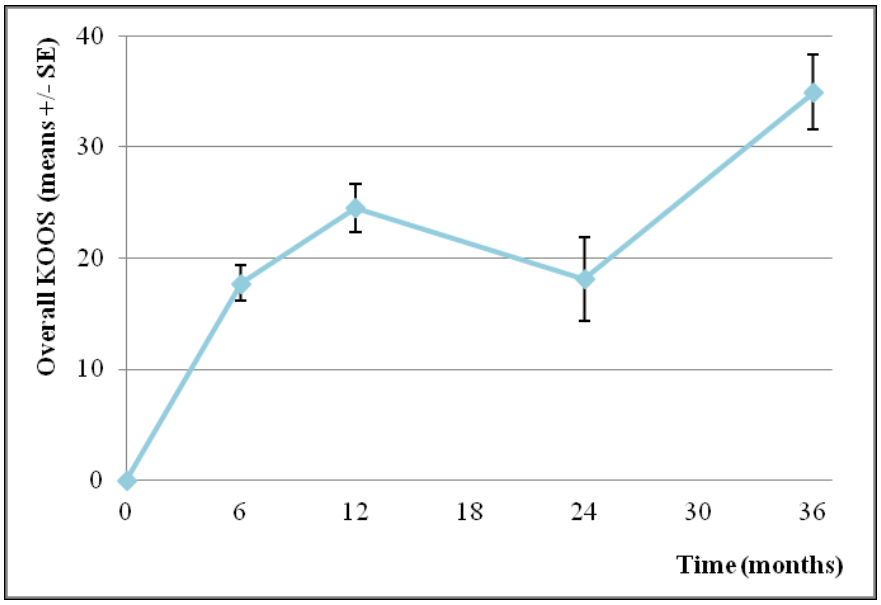
308 patients had been enrolled at the time of the interim report (database lock 7 March 2014) a baseline value has been obtained for 228 patients in total (89 Belgium, 139 The Netherlands). Of these, 153 have already reached the 6-month or a further follow-up time point (statistics dataset). The age at implantation varied from 15 to 50 years with an average (median) age of 32 years.

4.3.1 Results

<u>Clinical outcome</u>

Analysis of the data shows that the clinical benefit as measured by the KOOS is clinically relevant and comparable to the outcome observed in the pivotal TIG/ACT/01 study (Figure 12). Moreover, the size of improvement from baseline is similar to the outcome observed in the early symptom onset subgroup (< 3 years) that showed a statistically significant better outcome over the microfracture comparator group in the TIGACT01 study. This is an expected outcome as patients with a recent symptom onset are actively being targeted in routine practice.

Figure 12: Mean change from baseline in overall KOOS in TXG001-2011 (statistics dataset)



<u>Safety</u>

A total of 133 Adverse Events (AEs) had been reported by data lock point. Table 12 provides a summary of all AEs that were considered to be at least possibly related to ChondroCelect.

Table 12: Summary of all related AEs from TGX001-2011 (MedDRA version 14)

MedDRA SOC term	*MedDRA LLT term*	*Total nr of knees*	*% of 314 knees*
General Disorders and administration site conditions	*Treatment Failure*	*5*	*1.6*
Musculoskeletal and connective tissue disorders	*Knee pain*	*7*	*2.2*
	Joint swelling	*3*	*1.0*
	Joint crepitation	*3*	*1.0*
	Cartilage hypertrophy	*2*	*0.6*
	Knee joint locking	*2*	*0.6*
	Joint effusion	*1*	*0.3*
	Corpus liberum	*1*	*0.3*
	Subchondral bone injury	*1*	*0.3*

Seventeen serious AEs were reported in total, which included 6 treatment failures and 2 cases of deep venous thrombosis. No deaths were reported.

No new safety signals were identified as a result of this interim analysis.

Treatment failure

Treatment failure was defined as the need for a re-intervention affecting more than 20% of the surface of the index lesion, prompted by the persistence or recurrence of symptoms related to the index knee. To date, six treatment failures have been reported in the non-interventional study. Most failures could be attributed to the complexity of the underlying clinical condition.

All cases of treatment failure except 1 were considered to be possibly related to ChondroCelect. One case of treatment failure was associated with cartilage hypertrophy and one case with exostosis. Only one other SAE (a corpus liberum case) was considered to be posibly related to ChondroCelect.

4.4 Belgian reimbursement scheme

Observational data regarding the use of CCI in Belgium provides an additional source of efficacy evidence, having been provided to Belgian authorities as part of the reimbursement process.[56] The data provided includes the number of CCI procedures undertaken over a 3-year period in Belgium from 1st May 2011 to 30th April 2014, and a record of the number of treatment failures during this time.

The observed data shows increasing use of CCI in Belgium, with 51 procedures in year 1, 93 procedures in year 2 and 110 procedures in year 3. From this total number of patients, treatment failed in 2 patients within 1 year after the CCI procedure. A further 2 patients failed within 2 years of the procedure. No further failures were reported within the third year post-procedure among the 51 patients recorded for the full 3-year period.

4.5 Conclusions for clinical efficacy

The clinical data presented from TIG/ACT/01 demonstrate that ChondroCelect has a similar safety profile to MFx, with better efficacy in all measures (though statistical significance is not reached in all cases). The mean lesion size treated in the study (approximately 2.5cm^2) is typically encountered in clinical practice and may be expected to respond well to both ChondroCelect and MFx.[36]

A review by Minas *et al*[57] of 329 patients treated with MFx also demonstrates that defects which had prior treatment affecting the subchondral bone failed at a rate three times that of non-treated defects. These data demonstrate that marrow stimulation techniques have a strong negative effect on subsequent cartilage repair. Care should be exercised when selecting first-line treatment for cartilage defects that are amenable to ACI.

Additional data from the compassionate use programme have been presented that support the most likely uses of ChondroCelect in clinical practice – the results for both safety and efficacy are consistent with the clinical trial programme.

Furthermore, early results from the non-interventional study in patients with an early symptom onset confirm the clinical benefit at a similar level as observed in the TIG/ACT/01 study.

In combination, these results would support use of ChondroCelect as first-line repair treatment for eligible patients, as shown in Figure 6.

5 .Cost-effectiveness analysis

5.1 Introduction

A *de novo* economic model has been developed to assist the Evidence Review Group in estimating the cost-effectiveness of ChondroCelect CCI as part of this MTA. A previous approach to modelling the cost-effectiveness of CCI for the repair of articular cartilage damage was developed by Gerlier *et al*[58] in the Belgian setting. The existing model was, however, constructed some time ago and takes a decision tree structure which fails to account for failure of treatment other than at 3 years. As a new UK-specific Markov model was constructed for the present submission.

5.2 Model details

Details of the overall structure of the cost-effectiveness model, including comparators and the model perspective, are described below.

5.2.1 Treatment pathway and comparator

Various treatment options were considered as potentially relevant comparators in the development of the model, described in Section 3, including:

- MFx
- MACI
- Mosaicplasty
- Debridement
- Best supportive care ([BSC] e.g. pain relief)

Based on the licensed position of ChondroCelect and on clinical input, the MFx procedure was considered to be the only relevant comparator for CCI. MFx is the standard of care that is commonly used to treat knee cartilage defects in the UK, and can be performed in a 1 day clinic. Alternative treatment options were omitted for the reasons detailed in Table 13.

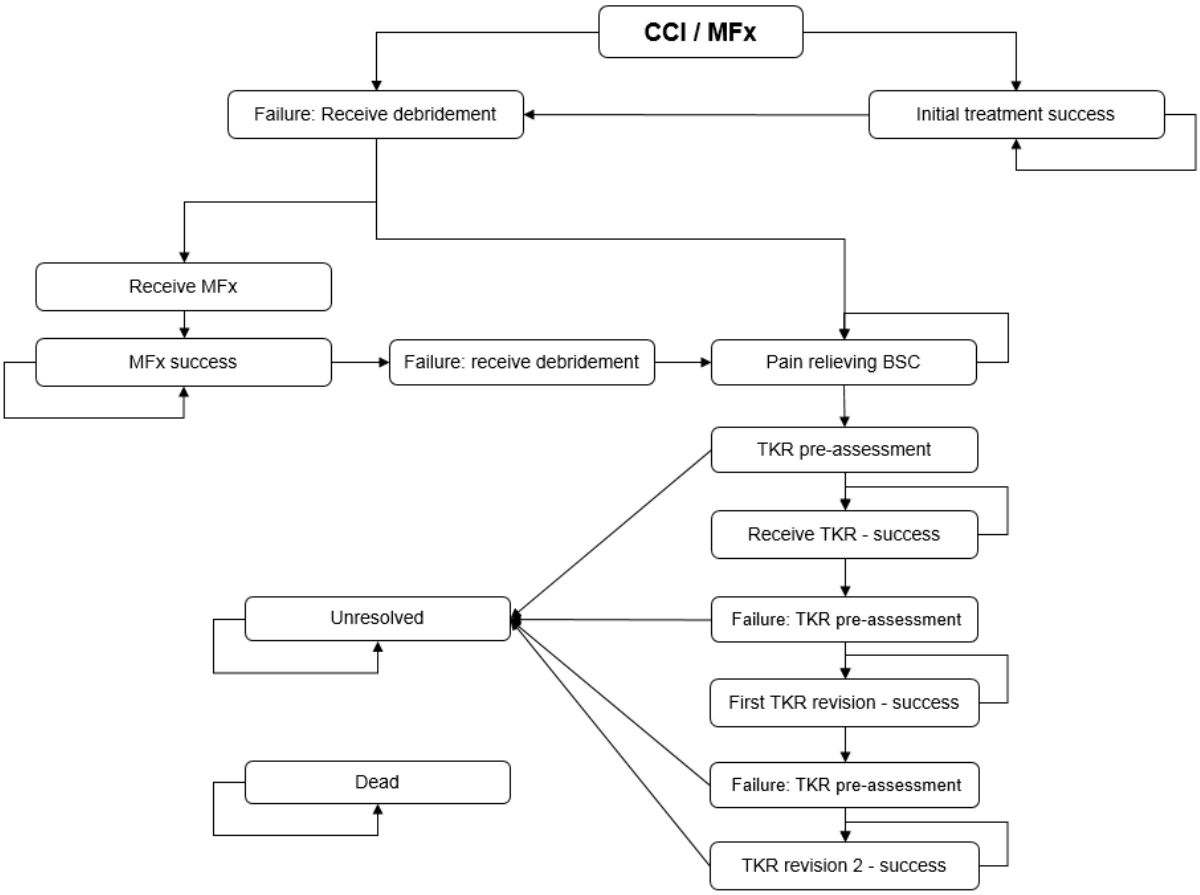
Table 13: Treatment options considered for inclusion in the cost-effectiveness model

Treatment	Reason for model exclusion
MACI	Not currently available in Europe
Mosaicplasty	Rarely used in the UK and not recommended by NICE[59]
Debridement	Included as a subsequent therapy
BSC	Included as a conservative subsequent therapy
Key: BSC, Best supportive care; MACI, matrix-induced autologous chondrocyte implantation; NICE, National Institute for Health and Care Excellence; UK, United Kingdom.	

5.2.2 Model structure

The structure of the Markov model is depicted in Figure 13.

Figure 13: Model structure



Key: BSC, Best supportive care; CCI, characterised chrondrocyte implant; MFx, microfracture; TKR, total knee replacement.

Patients enter the model at the time at which they receive either CCI or MFx. Patients remain in this initial procedure state for 1 cycle (1 month). The treatment may result in a successful resolution of the knee cartilage defect. However, over time the defect can become problematic once again. At this point the initial treatment is deemed to have failed, and patients move on to receive a debridement to remove the damaged tissue, followed by either a second MFx or a first MFx having received ChondroCelect, or alternatively conservative pain relief treatment. Patients who received subsequent treatment with MFx will receive a debridement and pain-relieving BSC if MFx fails.

Over time, patients on BSC will deteriorate to the point at which they are assessed for a TKR. A proportion of these will receive the procedure, while some will be deemed unsuitable and will become unresolved patients, these patients have higher ongoing costs, and a lower quality of life. A TKR can fail over time, at which point patients are assessed for a TKR revision, subsequently either receiving the revision or becoming unresolved patients. Patients are able to receive up to two TKR revisions. If the second TKR revision fails, patients move to the unresolved health state. Unresolved patients continue to receive treatment to relieve pain but undergo no further operative procedures.

Patients can die in any health state due to background all-cause mortality or to a (low) level of risk for patients undergoing TKR.

5.2.3 Model perspective

The present model is applicable to the UK NHS and Personal Social Services (PSS). Costs are reported in UK Pounds Sterling and represent direct costs incurred by the NHS. Accordingly, the NICE Guide to the Methods of Technology Appraisal has been followed where possible.[60]

The model time horizon is 75 years, sufficient to capture the majority of differences in costs and outcomes associated with the treatment of cartilage in patients with a mean age of 33 years. A model cycle length of 1 month is used, however, patient movements are subject to a half-cycle correction (meaning on average transitions occur halfway through the month).

Costs and health outcomes are discounted at a rate of 3.5% per annum to obtain their present value, in accordance with the NICE methods guide.[60]

5.3 Model inputs

Details of inputs used in the model, from sources of efficacy data to costs and HRQL, are presented in the subsections below.

5.3.1 Patient characteristics

The patient population included in the model is the highly targeted patient TIG/ACT/01 trial population, and therefore the patient characteristics relevant to the model have been obtained from the clinical study report[61] as follows:

- Proportion female: 35.6%
- Mean age at baseline: 33.92 years (standard deviation: 8.54)

These characteristics are included in the model because background all-cause mortality is dependent on age and gender. Additionally, the impact of decreasing HRQL with age is determined by a patient's starting age, whilst the younger patients are, the more likely they are to reach the stage of requiring a TKR, and TKR revisions.

5.3.2 Efficacy

The model utilises time to treatment failure (TTF) as a proxy measure of treatment efficacy. This was defined as a necessary reintervention (i.e. new procedure) for the same defect in TIG/ACT/01.[61] In the model, patients reside in the 'Success' health state following CCI or MFx until the point of treatment failure, when they go on to receive subsequent treatment.

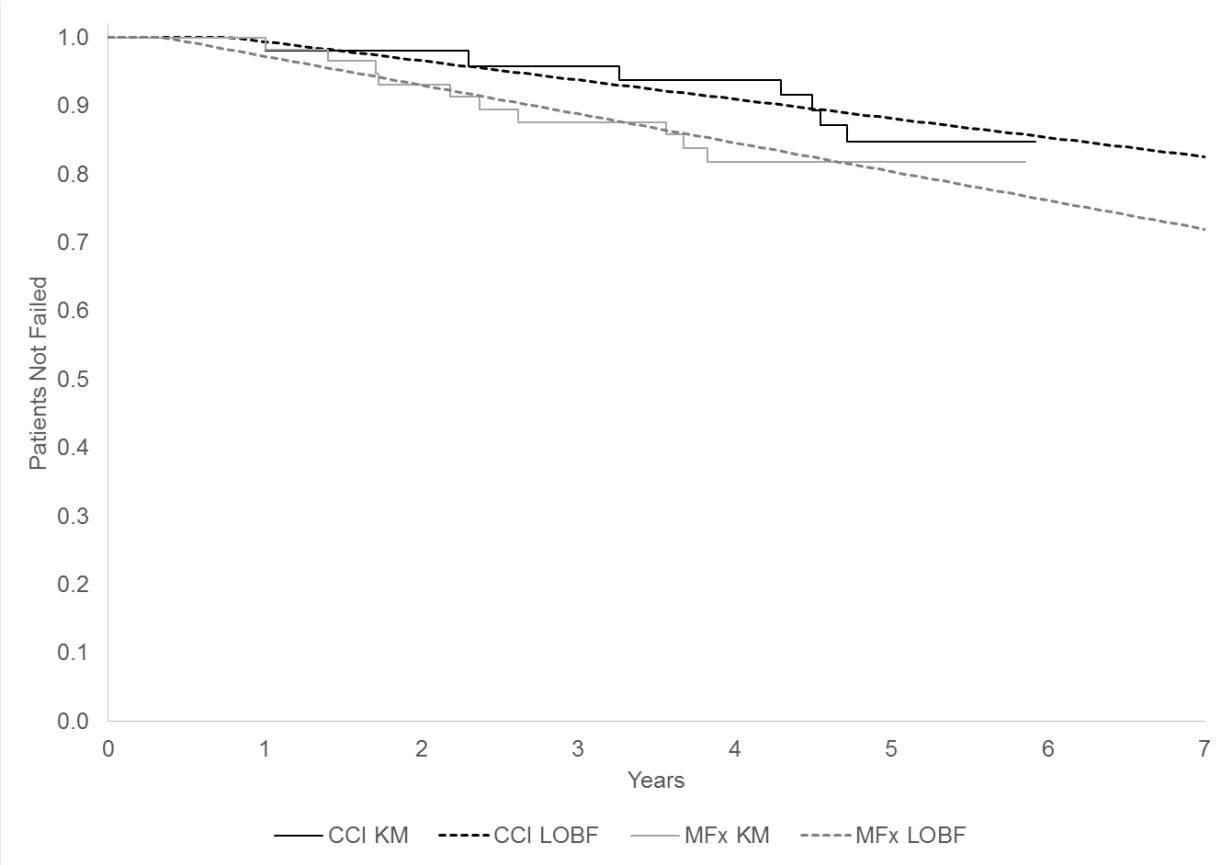
The transition probability of moving from primary treatment success to treatment failure in each 1-month model cycle was informed by the TTF Kaplan–Meier plots reported by Vanlauwe *et al*.[38] These were based upon 5 years of follow-up of the TIG/ACT/01 trial and subsequent compassionate use programme.

A line of best fit was calculated for each Kaplan–Meier plot, shown in Figure 14. The formula for each line of best fit is provided in Table 14. Where the value for 'Not failed' is deemed to be over 1, this was capped at 1.

Table 14: Lines of best fit to TTF Kaplan–Meier data

Dependent variable	Constant term	Coefficient	R^2
CCI failure at month X	1.022034	-0.00234 * (X)	0.8337
MFx failure at month X	1.014648	-0.00351 * (X)	0.8795
Key: CCI, characterised chrondrocyte implant; MFx, microfracture; TTF, time to treatment failure.			

Figure 14: Lines of best fit to TTF Kaplan–Meier data



Key: CCI, characterised chrondrocyte implant; KM, Kaplan–Meier; LOBF, line of best fit; MFx, microfracture; TTF, time to treatment failure.

The TTF profile of CCI is better than that of MFx, meaning patients are resolved for longer before they require a new procedure for the same defect. This translates to benefits in the model by delaying progression along the treatment pathway shown in Figure 13, including TKR and unresolved health states.

<u>Base case TTF setting</u>

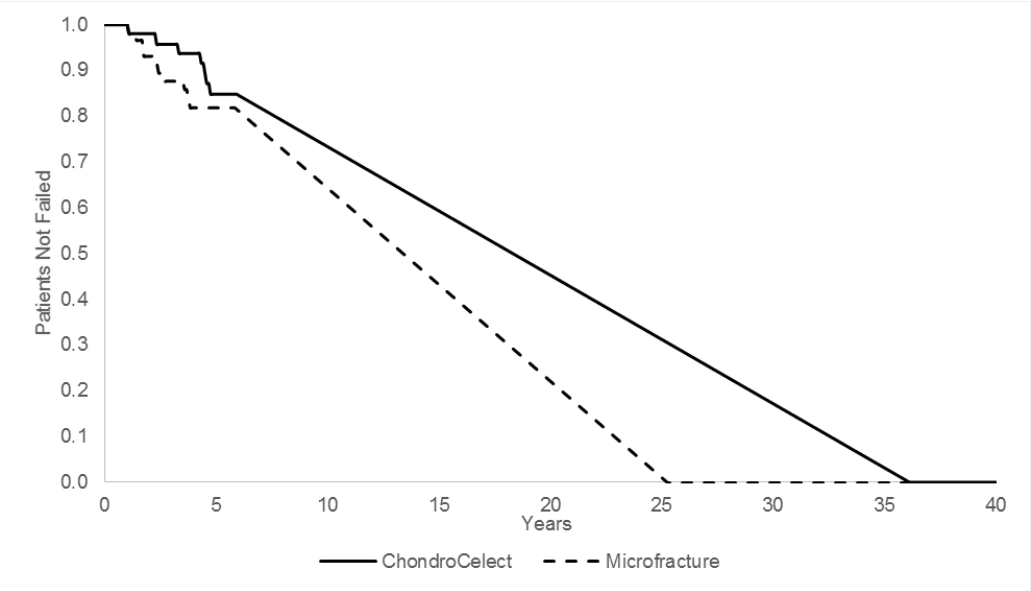
The base case analysis applies a TTF rate per month using the observed Kaplan–Meier data, and beyond this point applies the relevant gradient per month from Table 14 to incur a linear rate of treatment failure each month. The following scenario analyses are also explored in Section 5.5.1:

- Scenario analysis 1: Uses the observed TTF Kaplan–Meier data, followed by the respective linear failure rate. On the CCI arm, the MFx linear failure rate is applied after 20 years (i.e. no CCI benefit after 20 years)

- Scenario analysis 2: Uses the observed TTF Kaplan–Meier data, followed by the respective linear failure rate. On the CCI arm, the MFx linear failure rate is applied after 10 years (i.e. no CCI benefit after 10 years)
- Scenario analysis 3: Uses the observed TTF Kaplan–Meier data, followed immediately by the MFx linear failure rate per month for both model arms (i.e. no CCI benefit beyond the observed data)
- Scenario analysis 4: Uses the lines of best fit for the model duration (i.e. no use of the observed Kaplan–Meier data), restricted at a maximum value of 1.

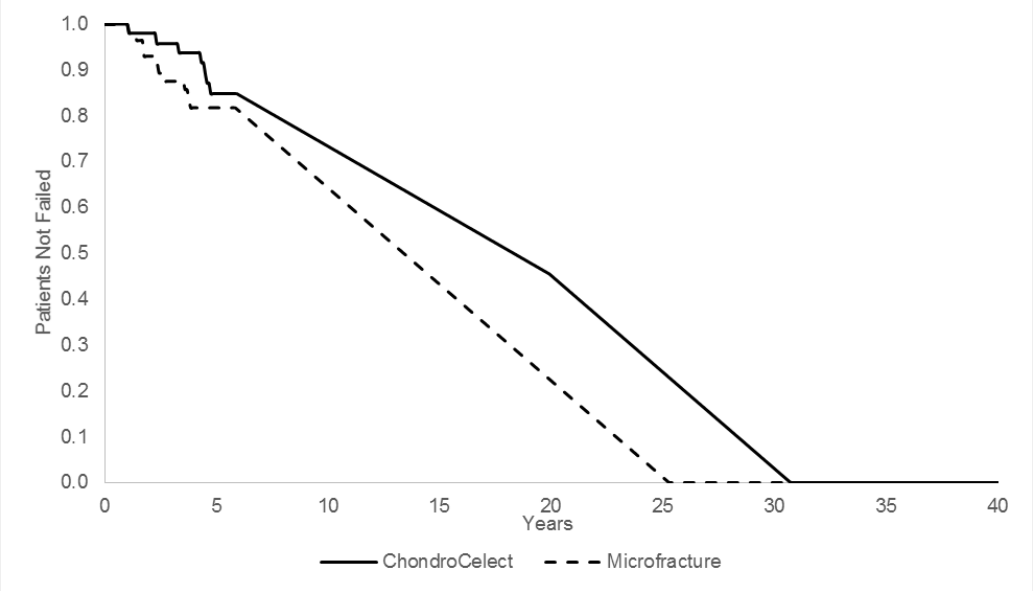
Figures representing the TTF applied in the model in each of these scenarios are provided below.

Figure 15: CCI and MFx failure over time – base case setting (Kaplan-Meier data, then relevant line of best fit)



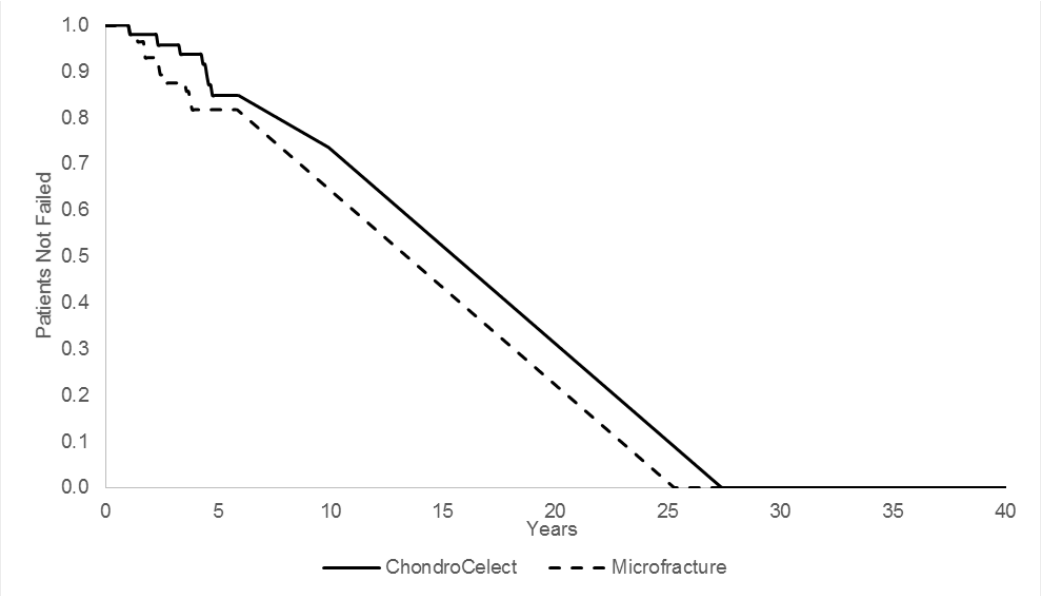
Key: CCI, characterised chrondrocyte implant; MFx, microfracture.

Figure 16: CCI and MFx failure over time – scenario analysis 1 (CCI failure rate maintained until 20 years)



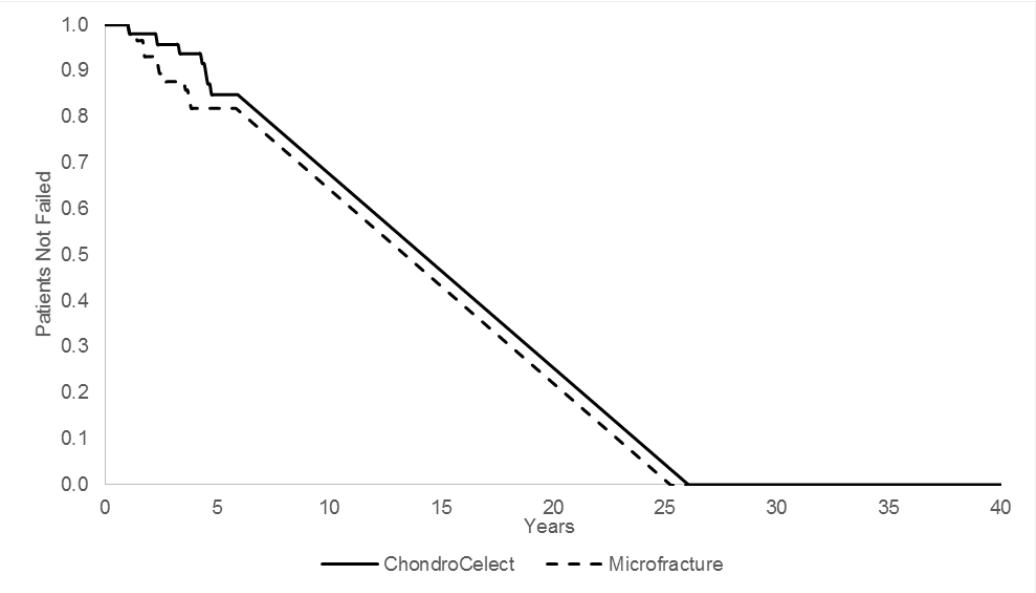
Key: CCI, characterised chrondrocyte implant; MFx, microfracture.

Figure 17: CCI and MFx failure over time – scenario analysis 2 (CCI failure rate maintained until 10 years)



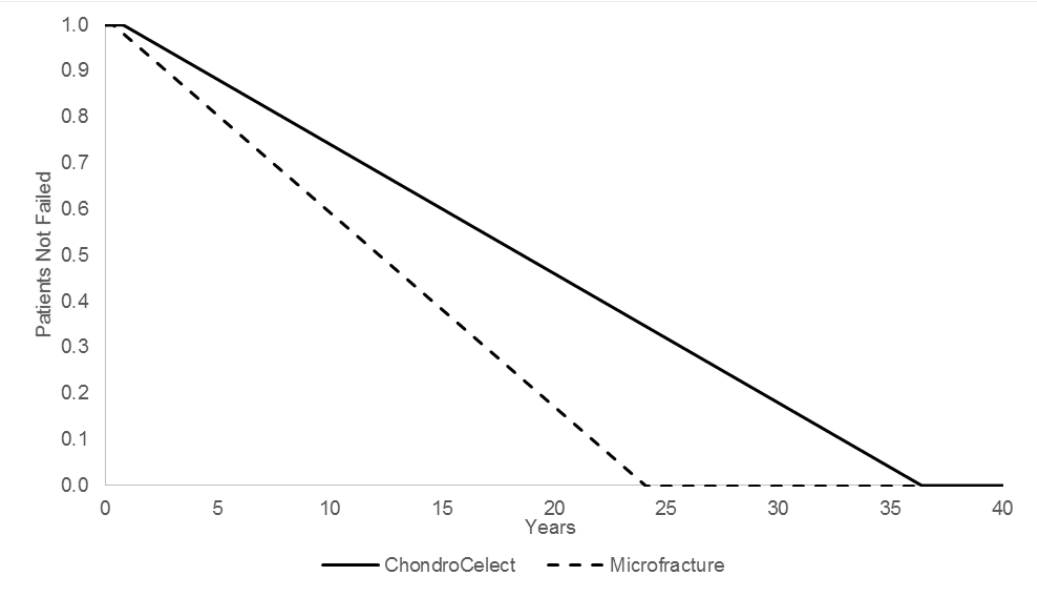
Key: CCI, characterised chrondrocyte implant; MFx, microfracture.

Figure 18: CCI and MFx failure over time – scenario analysis 3 (both arms have the MFx failure rate after the trial period)



Key: CCI, characterised chrondrocyte implant; MFx, microfracture.

Figure 19: CCI and MFx failure over time – scenario analysis 4 (line of best fit used for the entire model duration)



Key: CCI, characterised chrondrocyte implant; MFx, microfracture.

<u>Observational CCI data</u>

A scenario analysis is explored utilising observed CCI data, used to inform the reimbursement process in Belgium (see Section 4.4). These data reflect the treatment failure profile of CCI likely to be observed in a normal clinical setting, rather than a trial setting. The data are applied in the model as failure rates, shown in Table 15.

Table 15: Observed CCI procedures and failures submitted as part of Belgian reimbursement process

Year after CCI	Number of patients' data recorded	Number of failures	Failure rate in year
1	254[a]	2	0.79%
2	144[b]	2	1.39%
3	51	0	0.00%

Key: CCI, characterised chrondrocyte implant.
Note: a, 51+93+110; **b,** 51+93.
Source: Correspondence with National Institute for Health and Disability Insurance[56]

In this scenario analysis, the annual failure rates shown above are applied at the midpoint of the relevant year (i.e. it is assumed that the failures happened halfway through the first, second or third year after CCI). Four alternative methods of extrapolating CCI failure beyond this point are explored in this scenario analysis:

- Analysis 1: Assume the weighted average failure rate from the observed data applies after year 3 – 0.89% per year, converted to a rate of 0.07% per month (i.e. CCI benefit is maintained).
- Analysis 2: Assume the weighted average failure rate holds until year 20, with the MFx linear failure rate applied thereafter (i.e. no CCI benefit after 20 years).
- Analysis 3: Assume the weighted average failure rate holds until year 10, with the MFx linear failure rate applied thereafter (i.e. no CCI benefit after 10 years).
- Analysis 4: Assume the rate of CCI failure equals the MFx failure rate after year 3 (i.e. no CCI benefit beyond the observed data).

5.3.3 Subsequent treatment

As presented in Figure 13, upon failure of the knee cartilage following initial treatment with CCI or MFx patients move through a sequence of subsequent treatments. Patients receive a debridement of the knee, followed by either an MFx procedure or BSC (pain relief). Patients who received an MFx at this stage go on to receive a debridement and BSC upon further failure of the knee. Over time the joint may deteriorate to the point at which the patient is assessed for a TKR; if this procedure is not undertaken, patients remain unresolved. TKR patients may receive up to two revisions.

<u>Debridement</u>

Upon failure of initial treatment with CCI or MFx, all patients receive a debridement of the knee to remove the failed tissue.

<u>Microfracture</u>

The proportion of patients who receive subsequent MFx following initial treatment is assumed to depend upon the initial treatment given. In particular, if a patient initially received an MFx procedure, it was assumed that they are less likely to receive a second MFx compared to patients who initially received CCI.

In the base case analysis, based upon clinical expert advice, it is assumed that 90% of CCI patients who fail will go on to receive a subsequent MFx. This is varied to 50% in sensitivity analysis. Of patients who receive MFx initially, it is assumed that 5% receive a second MFx; a clinical expert advised that this proportion is in fact very low, and even 5% could be a conservative assumption for CCI. This value is increased to 50% in sensitivity analysis to test its importance in determining model results. In both arms, the remaining failed patients receive a debridement followed by pain-relieving BSC.

The failure rate of a subsequent MFx procedure is estimated using an exponential distribution. Rates of MFx failure at specific time points reported in two TIG/ACT/01 studies for MFx patients were used to fit a corresponding distribution.[37, 38] An exponential survival function has a constant failure rate, which was converted to a monthly rate and applied in each model cycle to estimate the number of patients who fail over time following subsequent MFx. Details of the resulting exponential distributions are provided in Table 16.

Table 16: Source of subsequent MFx TTF data applied in scenario analyses

Source	Reported MFx failure rate	Exponential log-scale to achieve reported failure rate	Resulting monthly failure rate
Vanlauwe *et al*[38]	16.4% at 5 years	3.32910	0.30%
Saris *et al*[37]	11.5% at 3 years	3.20098	0.34%
Key: MFx, microfracture; TTF, time to treatment failure.			

In the base case analysis the monthly failure probability is 0.30%, since the Vanlauwe *et al*[38] study reports more recent data than the Saris *et al*[37] paper (5-year follow up versus 3-year follow up). The alternative rate of 0.34% per month is applied in sensitivity analysis (see Section 5.5.1). If the subsequent MFx followed an initial MFx, the efficacy above – based upon TIG/ACT/01 trial publications – is reduced based upon clinical expert advice. Here, it is assumed that the second MFx is half as effective as the first one (i.e. twice the rate of failure).

Upon failure of MFx, patients receive a debridement of the knee prior to commencing BSC.

<u>Best supportive care</u>

Patients who receive BSC, after a debridement following the failure of their initial treatment and potentially subsequent MFx, are subject to a treatment failure rate estimated using an exponential distribution.

Two UK sources of evidence reporting the efficacy of debridement and arthroscopy procedures are used to provide estimates of the monthly failure rate.[62, 63] These are shown in Table 17. No efficacy is directly attributed to the BSC pain relief medication.

Table 17: Source of BSC TTF data applied in the model

Source	Reported debridement failure rate	Exponential log-scale to achieve reported failure rate	Resulting monthly failure rate
Bernard *et al* 2004[62]	18.0% at 5 years	3.22665	0.33%
Forster *et al* 2003[63]	20.0% at 1 year	1.49994	1.84%
Key: BSC, best supportive care; TTF, time to treatment failure.			

In the base case analysis the exponential survival function that satisfies the higher failure rate (20.0% after 1 year) is applied, based upon a clinical expert advising on the low expected efficacy of debridement. The impact on model results of applying the lower failure rate (1.84% per month) is explored in sensitivity analysis (see Section 5.5.1).

Total knee replacement

After failure of BSC, it is assumed that the knee cartilage has deteriorated sufficiently to require a TKR pre-assessment. It is assumed all patients receive at least this pre-assessment, required to evaluate whether the patient is suitable for a TKR.[64] A previous cost-effectiveness model developed by Clar *et al*[65] assumed that 50% or 100% of patients will be deemed suitable for a TKR; a clinical expert advised that this patient group would almost certainly be suitable for TKR, therefore this proportion is 95% in the base case model.

NHS sources suggest that a TKR is expected to resolve knee defects for 10 to 20 years.[66, 67] In the base case analysis therefore, the midpoint duration of 15 years is assumed to be the expected time to TKR failure. This duration was validated by a clinical expert. To translate this into an expected failure rate per cycle, an exponential survival function was calculated with a mean value of 15 years (over a 75-year time horizon). The monthly failure rates associated with a mean TTF of 10 years and 20 years are applied in sensitivity analyses. Monthly failure rates and their corresponding exponential function log-scale parameters are provided in Table 18.

When a TKR fails, the patient is assessed for a TKR revision. In the base case, the same proportion of patients suitable for the first TKR is deemed to be suitable for a revision (95%). A TKR revision is assumed to resolve the knee defect for an expected duration of 10 years, with a higher monthly failure rate than the original TKR; a clinical expert advised that a TKR revision will not be as effective as the original procedure. Patients can receive up to one further TKR revision; where this process is repeated once again. Patients who are unsuitable for a TKR or revision, or who fail following their second revision, become unresolved patients.

Table 18: TKR failure applied in the model based upon a defined expected TTF

Expected TTF	Exponential log-scale to achieve expected TTF	Resulting monthly failure rate
10 years	2.29894	0.83%
15 years (base case)	2.71215	0.55%
20 years	3.01962	0.41%
Key: TKR, total knee replacement; TTF, time to treatment failure.		

Treatment of unresolved cases

Patients with unresolved knee cartilage defects receive BSC (pain relief medication), but receive no further operative treatment. There is no direct efficacy achieved using BSC.

5.3.4 Mortality

Patients can die (transitioning to the death health state) at any time in the model. The mortality rate per month used is UK all-cause mortality, obtained from the National Life

Tables for England & Wales (2010-12).[68] The annual rate varies by age and gender; there is a higher background mortality rate for males, meaning over time females take up a larger proportion of the population. This was accounted for when calculating the average mortality rate, from a mean starting age of 33 years with 64.4% of the population being male.[61] The resulting general population annual probability of death is converted into a mortality rate per month.

All patients are subject to the background UK probability of dying, while patients undergoing a TKR operation are subject to a risk of mortality during the procedure as well as the general mortality risk. In the base case analysis this probability is 1.6%, given that the NHS estimates a 98.4% survival rate nationally.[69] A study by Mahomed *et al*[70] reports a 0.7% and 1.1% probability of death during a TKR and TKR revision respectively (in the US Medicare setting), meaning a TKR revision has a 57.1% greater mortality risk than the initial TKR. This same increase is applied to the base case TKR mortality risk (1.6%), providing a 2.5% probability of death during a TKR revision. The TKR mortality rates reported by Mahomed *et al* are included directly as a scenario analysis.

Finally, a scenario analysis is included in the model (presented in Section 5.5.1) whereby a hazard ratio (HR) is applied to the background UK mortality rate for patients in the unresolved health state. This therefore assumes that patients with continuing knee cartilage defects and no further treatment options will have a higher chance of mortality than the general population. In the base case no difference is assumed (HR=1); scenario analyses increase this HR to 1.2.

5.3.5 Costs

Costs were obtained from UK sources and are relevant to NHS/PSS. Cost items include the cost of each procedure, of rehabilitation post-procedure, of TKR and TKR revisions, and of pain relief medication.

<u>Procedure costs</u>

The cost of ChondroCelect (cell product) includes all costs associated with the CCI product itself; the training of staff, the necessary CCI Kit, transit of cells to and from the laboratory, cell culture.

The costs of other procedures were retrieved from the literature and from the health technology assessment of ACI performed by Clar *et al*.[65] These costs include costs of surgery, days as an inpatient and follow-up physiotherapy. All costs were updated to 2014 using the latest Hospital & Community Health Services (HCHS) index.[71] NHS reference costs were also consulted, however, important cost items such as that of a TKR could not be identified.

All procedure costs are detailed in Table 19.

Table 19: Unit cost of procedures

Treatment	Details	Unit cost	Source
ChondroCelect	Product including two-way courier and development of cell culture	£16,000	UK price of ChondroCelect
	Procedure (1 of 2) – arthroscopy and cell harvest	£722.45	Clar *et al*
	Procedure (2 of 2) – arthrotomy, outpatient setting	£109.65	NHS[72] (Trauma & orthopaedic)
MFx – base case analysis cost	Procedure, inpatient setting, rehabilitation	£2,817,79	Clar *et al* [65] (Aberdeen Royal Infirmary)
MFx – scenario analysis cost	Procedure, day case, rehabilitation	£964.87	Clar *et al* (Southampton General Hospital)
Debridement and arthroscopy	Procedure	£722.45	Clar *et al*
TKR	Procedure, rehabilitation	£6,500.85	Clar *et al*
TKR revision	Procedure, rehabilitation	£12,093.24	Clar *et al*

Key: HCHS, Hospital & Community Health Services; MFx, microfracture; TKR, total knee replacement.
Note: Costs reported by Clar *et al* were uplifted using the HCHS index inflation indices: 2005-06 (240.9) vs. 2012-13 (289.1).

Additionally, a TKR assessment appointment is required when a patient's condition deteriorates sufficiently following a debridement and BSC medication.[64] The unit cost of this assessment is incurred regardless of whether the patient is deemed suitable for TKR or not. An appointment with a general practitioner (GP) is assumed to be followed by referral for a trauma & orthopaedics outpatient appointment for this assessment. The unit cost of a GP appointment, including direct care staff costs but excluding qualification costs, is £37. The unit cost of the outpatient appointment is £109.65, as reported in Table 19. The total unit cost of a TKR assessment is therefore £146.65.

<u>ChondroCelect risk-sharing scheme</u>

ChondroCelect has a risk-sharing scheme (Section 3.9) whereby a rebate on the cost of CCI (£16,000) can be claimed for patients who fail within 3 years of the treatment. The scheme operates as follows:

- Patient fails within 1 year of CCI procedure: 75% rebate to the NHS
- Patient fails within 2 years of CCI procedure: 50% rebate to the NHS
- Patient fails within 3 years of the CCI procedure: 25% rebate to the NHS

This rebate is accounted for in the cost-effectiveness model, with the relevant rebate to the NHS paid every month up to 3 years. Model results are presented both with and without the scheme in place.

Rehabilitation costs

The cost of rehabilitation through physiotherapy is included in the model. The cost is included within the unit costs of MFx and TKR procedures shown in Table 19. Following CCI, physiotherapy has been costed based upon the study TIG/ACT/01 rehabilitation schedule as follows:

- Outpatient visits at Week 8 post-procedure, and follow-up Months 3, 6, 9 and 12.

The unit cost of a rehabilitation admission for joint replacement is incurred at each rehabilitation visit required by the schedule. This cost is £42.47, obtained from NHS Reference Costs (2012-13).[72] This is incurred at every rehabilitation visit required by the rehabilitation schedule. Since the model cycle length is 1 calendar month, the cost of the visit at Week 8 is applied during the model cycle following the procedure.

Pain relief medication costs (best supportive care)

Pain relief medication, given as conservative BSC, is assumed to consist of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs).[73] In the base case analysis the model assumes that 50% of BSC/unresolved patients can manage their pain relief with paracetamol only, while the remaining 50% require NSAIDs. The relative use of paracetamol and NSAIDs was varied in sensitivity analysis (see Section 5.5.1).

Paracetamol in the UK is primarily received over the counter (OTC) as this is a relatively young and active population (and therefore unlikely to receive 'free' prescriptions), and therefore is assumed to incur no cost to the NHS. NSAIDs included in the model were informed by the NHS Choices information on osteoarthritis (a related condition). Their unit costs were obtained from the British National Formulary (BNF)[74] and the Electronic Market Information Tool (eMIT)[75] tool was consulted to find the relative usage of each pack size listed by the BNF. This information is shown in Table 20.

Table 20: Cost of NSAIDs included in the model

NSAID[73]	Dosage[74]	Pack[74]	Pack Cost[74]	Total prescriptions[75]	Share of prescriptions[75]
Celecoxib	200mg daily	60 x 100mg 30 x 200mg	£21.55 £21.55	Not required (same price)	Not required (same price)
Diclofenac sodium	75-150mg daily	84 x 25mg 84 x 50mg	£1.25 £1.10	64,622 1,513,610	4% 96%
Etoricoxib	30mg daily	28 x 30mg 28 x 60mg	£13.99 £20.11	41,682 135,315	23% 77%
Ibuprofen	900-1200mg daily	84 x 200mg 84 x 400mg 84 x 600mg	£3.08 £3.15 £6.93	447,358 2,576,430 263,609	14% 78% 8%
Naproxen	1250mg daily	56 x 250mg 56 x 375mg 56 x 500mg	£2.71 £6.42 £50.2	443,839 34,924 684,047	38% 3% 59%

Key: NSAID, non-steroidal anti-inflammatory drugs.

The above data were used to estimate a weighted average NSAID unit cost per month of £9.79. As only 50% of BSC patients use NSAIDs, with the remaining 50% receive OTC paracetamol, the prevailing cost of pain relief medication to the NHS is £4.90 per month.

Management of unresolved patients

The model includes a cost associated with the ongoing management of unresolved patients. This is informed by a prospective RCT in UK patients with lower limb osteoarthritis, which reported the extent and cost of medical resource use required in typical OA management.[76] Data on healthcare resources used by 159 patients receiving typical OA care were collected in a questionnaire, during interviews at 1 year and through reviews of patient notes. Resources included GP visits, treatment visits, medications, outpatient visits, physiotherapist, prescribed aid, complementary therapy and other therapies.

Unit costs came from the NHS tariffs, BNF and PSSRU, with a mean total direct cost of £320.34 (2002) per patient per year reported. When adjusted for inflation using the HCHS index[71], this is £384.43 per year, or £32.04 per calendar month on average. This cost is applied in the month each month for patients with unresolved defects.

5.3.6 Health-related quality of life

There is a lack of literature reporting utility scores in patients with a knee cartilage defect. A pre-surgery utility score of 0.41 was obtained from the EQ-5D questionnaire filled in by 22 patients on a waiting list for knee surgery by Derrett *et al*.[77] The gain in utility score observed after ACI was 0.23, compared to 0.06 after a mosaicplasty.

The health technology assessment report by Clar *et al*[65] assumed successful knee surgery was associated with a utility gain of 0.1. However, no utility scores were reported for different health states. Utility scores utilised in the present model, derived from study TIG/ACT/01, were consistent with this assumption, and are based on the UK norms developed for the SF-6D questionnaire.[1]

Trial utility data

Utility values included in the present analyses are based upon an analysis of the SF-36 questionnaires collected during the TIG/ACT/01 for up to 60 months. These were analysed as follows, reported by Gerlier *et al*.[58] in a previous cost-effectiveness analysis of CCI:

- Utility scores were derived from the answers to the SF-36 questionnaire at each visit using the algorithm from Brazier and Roberts[78]
- Utility scores were calculated by response status to KOOS in order to characterise the gap between symptomatic and asymptomatic patients, regardless of the surgical treatment received
- Correlations were calculated between the utility scores and the KOOS overall scores

[1] The SF-6D is a scoring algorithm from a subset of questions in the SF-36. Eleven questions are used from the SF-36. These questions were used to construct health scenarios that were evaluated using the standard gamble technique in a representative sample of the UK population. The algorithm assigns a utility score to each health state.

- Given the good linear correlation observed between these scores, a linear functional relationship was estimated in order to predict utility scores at earlier visits (between baseline and Year 2)

The resulting utility scores, and how they have been assigned to the main health states of the present model, are detailed in Table 21. Additionally, a low utility value for patients with severe osteoarthritis prior to receiving a TKR was assumed to apply for patients undergoing a TKR.[79]

The utility experienced with osteoarthritis, used to inform the utility of unresolved patients shown in Table 21, was obtained from a study by Ruchlin *et al*[80], cited in the Gerlier *et al*[58] analysis. In the base case the SF-6D value is used (0.52), however a lower EQ-5D value is used in a scenario analysis (0.44). The difference in utility between 'no clinical success after surgery' and 'pre-surgery' is added to this value to give the utility of unresolved patients (0.557 in the base case model, 0.477 in the scenario analysis).

A scenario analysis is also included which applies a higher utility value for patients who undergo a successful TKR or TKR revision, with the alternative value of 0.730 obtained from the collection of patient reported outcomes among all NHS patients undergoing a TKR.[81]

Additionally, decreasing utility over time is included in the model using the age-related UK population EQ-5D weights reported by Kind *et al*.[82] The age-related weight at the mean patient age of 33 years is 0.93. In the model, this is used as the base weight (i.e. set equal to 1). The Kind *et al* values decrease over time, and these age-related decreases are applied in the model relative to the base weight used. For example, Kind *et al* estimate that a 50 year old will have an age-related utility weight of 0.85. Relative to the weight at the mean starting age of 33, this value is equivalent to a weight of 0.9140, or an 8.6% utility decrease.

Table 21: Utility scores associated with the main health states of the model

Health state	Value	Source/method	Applicable health states
Initial score (pre-surgery)	0.6540	Predicted baseline utility score (linear functional regression: KOOS/utility)	During initial CCI or MFx procedure
Clinical success after surgery	0.8170	Average utility of KOOS responders[a]	Successful CCI or MFx (including subsequent MFx)
No clinical success after surgery	0.6910	Average utility score of KOOS non-responders[a]	Receiving BSC
Undergoing a TKR	0.5177	Batty & Birrell, 2011[79]	During TKR or TKR revision procedure
Following successful TKR and/or revision	0.6830	Utility with osteoarthritis plus the difference between the utility of successful surgery and pre-surgery	Following successful TKR and/or revision
Unresolved (unsuitable for TKR or failed TKR/revision)	0.5570	Utility with osteoarthritis plus the difference between no clinical success after surgery and pre-surgery	Unresolved cases

Key: BSC, best supportive care; CCI, characterised chondrocyte implantation; EQ-5D, EuroQoL five dimensions; KOOS, Knee injury and Osteoarthritis Outcome Score; MFx, microfracture; SF-6D, Short form six dimensions; TKR, total knee replacement.

Note: [a] Utility estimated by KOOS response used as a proxy for patients having successfully resolved defects.

5.3.7 Adverse events

The cost of adverse events were not included in the model as there were no key differences in between treatment arms in TIG/ACT/01 (see Section 4.2.2), therefore they are not likely to be important drivers of cost-effectiveness results. The only adverse reaction included is mortality as a result of TKR and TKR revision procedures.

5.3.8 Time horizon

As noted within the scope, the NICE methods guide[60] stipulates that the model time horizon should sufficiently reflect differences in costs and outcomes between the treatments being compared. The base case time horizon is 75 years, selected because at this time point effectively all patients (>99.9%) have progressed to the death health state. A short model time horizon would not capture the long term benefits of CCI, which maintains knee cartilage for longer and, in doing so, puts off the need for TKR procedures, and deterioration to having an unresolved problem, for longer. The majority of CCI costs are incurred upfront, and therefore a short time horizon would unjustly fail to allow its benefits to be accrued to offset the early cost. Scenario analyses are provided around the time horizon, including a short term 5-year horizon and a medium-term 40-year horizon, however these are insufficient for the base case analysis, with 99.6% and 76.1% of patients still alive at these time points respectively.

5.4 Base case results

5.4.1 Comparison of model and trial outcomes

Outcomes predicted by the model were compared with the 5-year TIG/ACT/01 follow-up outcomes reported by Vanlauwe *et al*.[38] Given the use of the Kaplan-Meier data for TTF in the base case model, treatment failure in the model at 5 years is highly similar to failure observed in the trial (Table 22). The marginally higher 5-year failure reported in the model is due to the background mortality calculations applied.

Table 22: Comparison of 5-year treatment failure in the model and TIG/ACT/01

Treatment	Model	TIG/ACT/01[38]
Microfracture	18.5%	18.2%
ChondroCelect	15.6%	15.2%
Note: TIG/ACT/01 failure at 5 years obtained from digitised KM plot in the publication.		

5.4.2 Summary results

<u>With ChondroCelect risk-sharing scheme</u>

Discounted base case model results, with the ChondroCelect risk-sharing scheme included, are presented in Table 23.

Table 23: Base case cost-effectiveness results (including risk-sharing scheme)

Model arm	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
MFx	£13,547	22.88	15.40				
ChondroCelect	£22,347	23.11	16.69	£8,801	0.23	1.29	**£6,812**
Key: ChondroCelect, characterised chondrocyte implantation; ICER, incremental cost-effectiveness ratio; LYs, life years; MFs, microfracture; QALYs, quality-adjusted life years.							

ChondroCelect is associated with a small gain in life years compared to MFx, attributed to the reduced number of TKR procedures with their increased risk of mortality. The QALY gain of 1.29 for patients who receive ChondroCelect is much more substantial, achieved by fewer patients deteriorating to the point of receiving BSC only, or deteriorating further to become unresolved cases. Additionally, fewer patients receive a TKR and incur the associated low temporary utility weight. Patients treated with ChondroCelect incur a higher total cost over the 75-year time horizon: £22,347 compared to £13,547. This equates to an incremental cost of £8,801 per patient, which reflects the reduction in total knee replacements and other care and somewhat offsets the additional cost of the procedure.

The resulting incremental ICER for ChondroCelect relative to MFx is £6,812 per incremental QALY gained. At a cost-effectiveness threshold value of £20,000 per incremental QALY gained this ICER equates to a net monetary benefit (NMB) to the NHS of £17,039.

Without ChondroCelect risk-sharing scheme

Discounted base case model results without the ChondroCelect risk-sharing scheme are presented in Table 24.

Table 24: Base case cost-effectiveness results (without risk-sharing scheme)

Model arm	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
MFx	£13,547	22.88	15.40				
ChondroCelect	£22,586	23.11	16.69	£8,801	0.23	1.29	**£6,997**
Key: ChondroCelect, characterised chondrocyte implantation; ICER, incremental cost-effectiveness ratio; LYs, life years; MFs, microfracture; QALYs, quality-adjusted life years.							

Excluding the risk-sharing scheme from the model increases the total cost of ChondroCelect by £239, raising the ICER to £6,997. Given the ICER increase is minimal (£185) the scheme makes negligible difference to the cost-effectiveness case of ChondroCelect. As such, results from this point forward are based upon the model with the scheme included.

5.4.3 Disaggregated cost results

The total discounted costs shown in Table 23 are disaggregated into the various cost components included in the model in Table 25.

Table 25: Base case discounted cost results disaggregated by cost item

Cost item	MFx	ChondroCelect	Increment
Procedure (including rehabilitation)	£2,818	£17,044	£14,227
Failure-related rebate	£0	-£239	-£239
Secondary treatments (MFx, debridement)	£731	£2,032	£1,301
TKR (inc. assessments & revisions)	£9,111	£3,236	-£5,876
Treatment of unresolved patients	£886	£274	-£612
Total costs	**£13,547**	**£22,347**	**£8,801**
Key: ChondroCelect, characterised chondrocyte implantation; MFx, microfracture; TKR, total knee replacement.			

The largest difference is cost is caused by the relative procedure costs (including rehabilitation), where ChondroCelect is associated with an additional cost of £14,227 per patient. This is eroded across other cost items however - savings are achieved through the ChondroCelect risk-sharing rebate (£239), and the reduction in the number of patients requiring a TKR or becoming unresolved cases. The cost of secondary treatment is higher among ChondroCelect patients because a larger proportion go on to receive MFx. On the MFx model arm, more patients progress immediately to BSC with only a small percentage receiving a second MFx.

5.4.4 Disaggregated health outcomes

The total discounted health outcomes shown in Table 23 are disaggregated across model health states in Table 26 and Table 27.

Table 26: Base case discounted life year results disaggregated by health state

Health state	MFx	ChondroCelect	Increment
Patients on initial treatment	0.08	0.08	0.00
Patients responding to initial treatment	10.09	12.66	2.57
Patients responding to subsequent MFx	0.29	6.05	5.76
Patients responding to BSC	2.49	1.01	-1.48
Patients undergoing TKR	0.08	0.03	-0.05
Patients following successful TKR	7.54	2.56	-4.98
Patients unresolved	2.30	0.71	-1.59
Total LYs	**22.88**	**23.11**	**0.23**
Key: BSC, best supportive care; ChondroCelect, characterised chondrocyte implantation; MFx, microfracture; TKR, total knee replacement; LYs, life years.			

Table 27: Base case discounted QALY results disaggregated by health state

Health state	MFx	ChondroCelect	Increment
Patients on initial treatment	0.05	0.05	0.00
Patients responding to initial treatment	7.94	9.84	1.90
Patients responding to subsequent MFx	0.21	4.36	4.15
Patients responding to BSC	1.58	0.61	-0.97
Patients undergoing TKR	0.04	0.01	-0.02
Patients following successful TKR	4.50	1.48	-3.01
Patients unresolved	1.07	0.32	-0.74
Total QALYs	**15.40**	**16.69**	**1.29**

Key: BSC, best supportive care; ChondroCelect, characterised chondrocyte implantation; MFx, microfracture; TKR, total knee replacement; QALYs, quality-adjusted life years.

Model results suggest that a patient can expect to require no reintervention for 12.7 years (discounted) following ChondroCelect, an additional 2.6 years compared to MFx. Further QALYs are gained by ChondroCelect patients receiving a subsequent MFx procedure (whereas initial MFx patients are much less likely to do so, and if they do, the revision fails more quickly). MFx patients are more likely to receive BSC and to deteriorate to the point of requiring TKR or becoming unresolved cases.

5.4.5 Patient distribution over time

The total life years shown in Table 26 are depicted graphically in Figure 20 and Figure 21 below. These Markov traces show the evolution of life years over the 75-year model horizon, by displaying the proportion of patients in each health state over time. ChondroCelect patients spend visibly less time having received a TKR/TKR revision and in the unresolved health state.

Figure 20: Markov trace for ChondroCelect patients

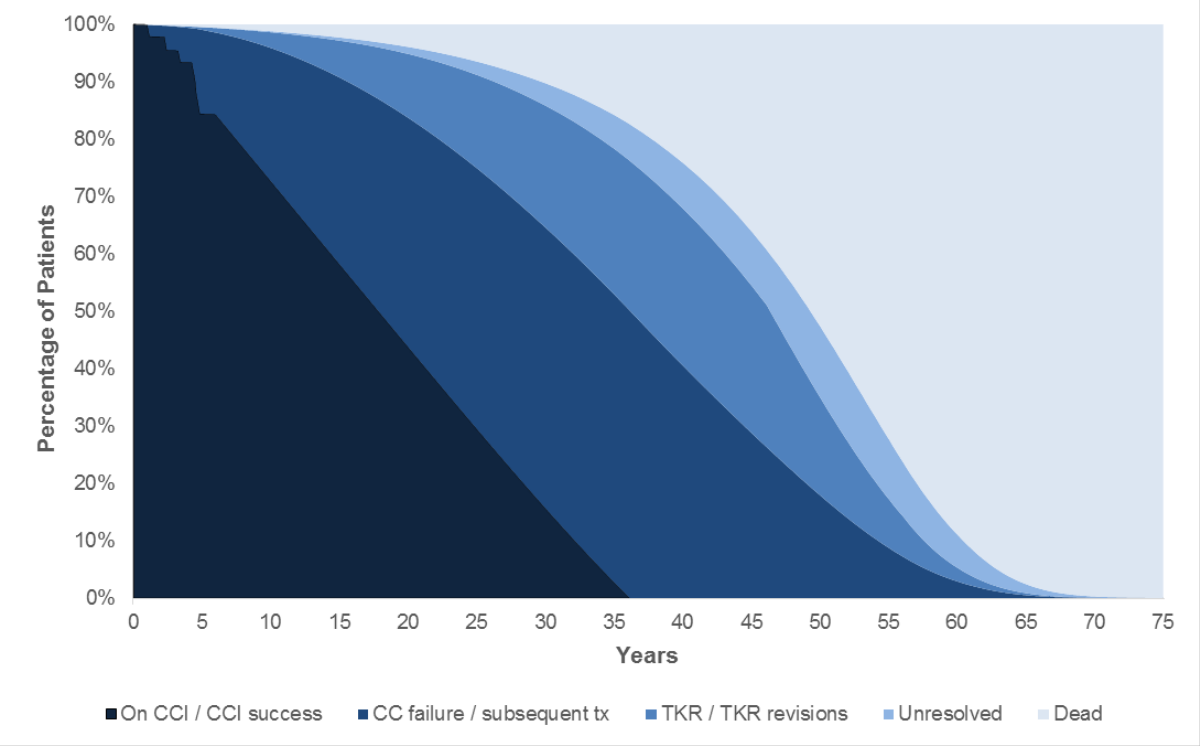
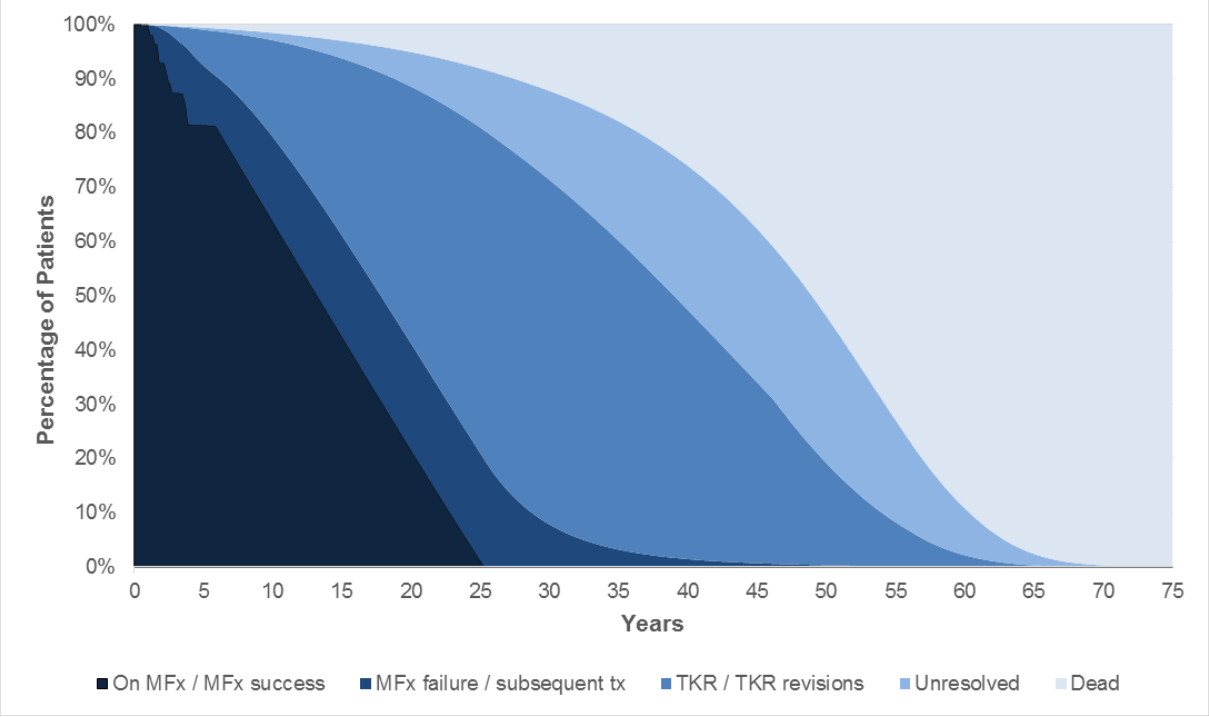


Figure 21: Markov trace for MFx patients

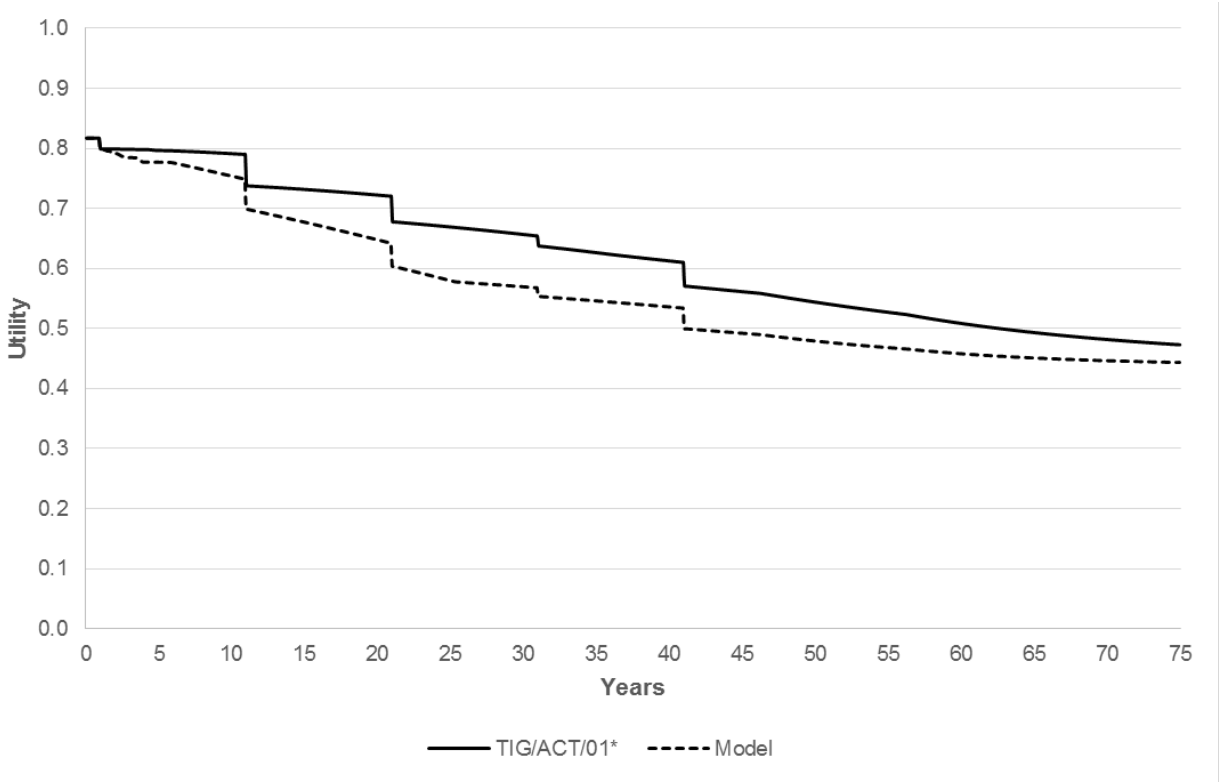


5.4.6 Utility over time

The change in the mean utility value, which combined with life years determines QALYs over time, is presented in Figure 22. This shows a decreasing utility over time following initial response to therapy, as patients gradually progress to treatment with BSC, receive a TKR or

become unresolved cases. The ‘steps’ where mean utility falls are caused by a reduction in age-related utility weights at that time.

Figure 22: Modelled mean utility over time



5.5 Sensitivity analyses

Sensitivity analyses were performed to identify the structural assumptions to which the model is most sensitivity, and to determine the uncertainty around the base case ICER. The former was explored using scenario analyses, where a key model assumption was varied and the change in model results assessed. Uncertainty around the base case ICER was evaluated through probabilistic sensitivity analysis (PSA).

5.5.1 Scenario analysis

<u>Efficacy scenarios</u>

- Use of the observed TTF Kaplan–Meier data, followed by the respective linear failure rate. On the CCI arm, the MFx linear failure rate is applied after 20 years (i.e. no CCI benefit after 20 years)
- Use of the observed TTF Kaplan–Meier data, followed by the respective linear failure rate. On the CCI arm, the MFx linear failure rate is applied after 10 years (i.e. no CCI benefit after 10 years)
- Use of the observed TTF Kaplan–Meier data, followed immediately by the MFx linear failure rate per month for both model arms (i.e. no CCI benefit beyond the observed data)
- Use of the lines of best fit for the model duration (i.e. no use of the observed Kaplan–Meier data), restricted at a maximum value of 1.

- Observed data from Belgium for ChondroCelect: Assume the weighted average failure rate from the observed data applies after year 3 – 0.89% per year, converted to a rate of 0.07% per month (i.e. CCI benefit is maintained).
- Observed data from Belgium for ChondroCelect: Assume the weighted average failure rate holds until year 20, with the MFx linear failure rate applied thereafter (i.e. no CCI benefit after 20 years).
- Observed data from Belgium for ChondroCelect: Assume the weighted average failure rate holds until year 10, with the MFx linear failure rate applied thereafter (i.e. no CCI benefit after 10 years).
- Observed data from Belgium for ChondroCelect: Assume the rate of CCI failure equals the MFx failure rate after year 3 (i.e. no CCI benefit beyond the observed data).

Table 28: Results of scenario analyses around efficacy assumptions

Input	Base case assumption	Scenario analysis	Incremental Costs	Incremental QALYs	ICER
Base case model	-	-	£8,801	1.29	**£6,812**
Treatment failure	Informed by KM then relevant LOBF	KM then LOBF. CCI benefit for 20 years	£9,027	1.27	**£7,125**
Treatment failure	Informed by KM then relevant LOBF	KM then LOBF. CCI benefit for 10 years	£9,516	1.20	**£7,908**
Treatment failure	Informed by KM then relevant LOBF	Informed by KM then MFx LOBF	£9,824	1.16	**£8,472**
Treatment failure	Informed by KM then relevant LOBF	Informed by relevant LOBF only	£8,182	1.39	**£5,871**
ChondroCelect efficacy data	TIG/ACT/01 data used	Observed Belgian data (extrapolated using mean failure rate)	£4,979	1.73	**£2,873**
ChondroCelect efficacy data	TIG/ACT/01 data used	Observed data, CCI benefit for 20 years	£7,917	1.45	**£5,473**
ChondroCelect efficacy data	TIG/ACT/01 data used	Observed data, CCI benefit for 10 years	£8,995	1.29	**£6,948**
ChondroCelect efficacy data	TIG/ACT/01 data used	Observed data followed by MFx failure rate	£9,704	1.19	**£8,176**

These results show the ICER to be reasonably consistent to most structural assumptions related to the efficacy of ChondroCelect and MFx (Table 28). If the ChondroCelect failure rate is equal to MFx following the 5-year trial TTF data, the ICER increases to £8,472, which is still within the range typically considered to be cost-effective (£20,000 per QALY). This is a conservative scenario as it means patients are equally likely to fail ChondroCelect and MFx beyond the observed TIG/ACIT/01 data. All other ICERs are lower than this scenario.

The ICER falls to just £2,873 if the observed ChondroCelect usage and failure data in Belgium is used to inform the ChondroCelect failure rate. This reflects the reduction in failures observed in clinical practice relative to the study TIG/ACT/01. A clinical expert consulted by SOBi confirmed that data from ChondroCelect use in Belgium will accurately estimate usage and failure in the UK.

<u>Subsequent treatment efficacy scenarios</u>

- The failure rate of subsequent MFx set to 11.5% failure at 3 years
- The failure rate of second MFx (i.e. for subsequent MFx on the MFx arm only) is equally as effective as initial MFx (informed by Vanlauwe *et al.*)[38]
- The failure rate of debridement and BSC set to a highly optimistic 18.0% failure at 5 years
- Expected TTF for TKR and TKR revisions reduced to 10 years
- Expected TTF for TKR and TKR revisions increased to 20 years

Table 29: Results of scenario analyses around the efficacy of subsequent treatments

Input	Base case assumption	Scenario analysis	Incremental Costs	Incremental QALYs	ICER
Base case model	-	-	£8,801	1.29	**£6,812**
Subsequent MFx failure	16.4% at 5 years[38]	11.5% at 3 years[37]	£9,038	1.25	**£7,218**
Second MFx failure	Half as effective	Equally as effective as TIG/ACT/01 MFx	£8,902	1.27	**£6,985**
Subsequent debridement failure	20.0% at 1 year[63]	18.0% at 5 years[62]	£11,639	1.10	**£10,567**
TKR failure	Expected after 15 years (after revision = 10 years)	Both expected after 10 years (low efficacy)	£8,039	1.34	**£6,004**
TKR failure	Expected after 15 years (after revision = 10 years)	Both expected after 20 years (high efficacy)	£9,973	1.20	**£8,322**

The base case ICER is reasonably insensitive to structural assumptions around the efficacy of subsequent treatments. If a TKR is expected to fail sooner, the ICER falls as each TKR is less effective, and ChondroCelect delays the need for TKR by maintaining a successfully resolved cartilage defect for longer. The biggest difference is observed when the efficacy of debridement is increased such that failure at 5 years would be 18.0%, relative to the base case of 20.0% after 1 year; however, a clinical expert advised that poor efficacy is expected when treating with debridement.

<u>Subsequent treatment usage scenarios</u>

- Equal subsequent use of MFx (50% after both ChondroCelect and MFx)
- All BSC patients receive NSAIDs (cost met by NHS)
- All patients assessed for first TKR are suitable for TKR (50% for revisions)
- All patients are suitable for TKR and subsequent revisions

Table 30: Results of scenario analyses around subsequent treatment

Input	Base case assumption	Scenario analysis	Incremental Costs	Incremental QALYs	ICER
Base case model	-	-	£8,801	1.29	**£6,812**
Use of subsequent MFx	90% following ChondroCelect 5% following MFx	50% after both ChondroCelect and MFx	£11,308	0.46	**£24,490**
Composition of pain-relieving BSC	50% of patients receive NSAIDs	100% of patients receive NSAIDs	£8,714	1.29	**£6,745**
Suitability for TKR	95% of patients are suitable for first TKR	100% of patients are suitable for first TKR	£9,922	1.39	**£7,138**
Suitability for TKR	95% of patients are suitable for any TKR or revision	100% of patients are suitable for any TKR or revision	£8,371	1.26	**£6,663**

Of the assumptions made regarding subsequent treatments given, the ICER is only sensitive to the proportion of patients given a subsequent MFx procedure (Table 30). If this is equal across model arms, with a 50% likelihood of the second intervention being an MFx procedure, the ICER increases to £24,490. However, this assumption would mean that half of all patients whose first MFx procedure has failed will receive another one; clinical expert advice sought by SOBi confirmed that only a very small proportion of patients will receive a second MFx procedure. The ICER is insensitive to the remaining assumptions listed above.

Time horizon scenarios

The model time horizon was varied from 5 years to 70 years to evaluate the impact on model results (Table 31).

Table 31: Results of time horizon scenario analyses

Scenario analysis time horizon	Incremental Costs	Incremental QALYs	ICER
5 years	£13,839	0.05	£291,867
10 years	£13,177	0.16	£83,159
20 years	£11,177	0.51	£21,910
30 years	£9,427	0.89	£10,543
40 years	£8,940	1.14	£7,842
50 years	£8,832	1.26	£7,029
60 years	£8,804	1.29	£6,828
70 years	£8,801	1.29	£6,812

The model is invariable sensitive to the time horizon, given that the majority of costs on the ChondroCelect arm are incurred early in the model while its benefits, including a reduction in TKR procedures required and delaying progression to the unresolved health state, are experienced in the longer term. After just 5 years the ICER is very high, falling to a value within the range typically considered cost-effective after 20 years (£21,910). By 30 years the ICE is well within the cost-effective range at £10,543. The base case time horizon is 75 years, selected because at this time point effectively all patients (>99.9%) have progressed to the death health state. This is therefore appropriate, given that the NICE methods guide[60]

stipulates that a cost-effectiveness analysis should have a time horizon sufficient to reflect all important differences in costs or outcomes between technologies.

Other scenarios

- Utility: lower quality of life associated with unresolved health states
- Mortality: further increased mortality for unresolved patients (HR = 1.2)
- Mortality: lower risk of death during TKR (informed by Mahomed et al[70].)
- Discounting: no discounting of costs or outcomes
- Time horizon: time horizon varied in 10-year increments

Table 32: Results of other scenario analyses

Input	Base case assumption	Scenario analysis	Incremental Costs	Incremental QALYs	ICER
Base case model	-	-	£8,801	1.29	£6,812
Utility of unresolved cases	0.557	0.477	£8,801	1.75	£5,024
Higher quality of life associated with successful TKR	0.683	0.730	£8,801	1.08	£8,113
Mortality	No difference between resolved and unresolved mortality rate	Mortality of unresolved patients is higher (HR=1.2)	£8,825	1.32	£6,684
TKR Mortality	TKR risk = 1.6%[69] TKR revision risk = 2.5%[69]	TKR risk = 0.7%[70] TKR revision risk = 1.1 %[70]	£8,728	1.22	£7,151
Discounting	Costs and outcomes discounted at 3.5% per year	No discounting	£3,440	3.22	£1,070
Discounting	Costs and outcomes discounted at 3.5% per year	Costs and outcomes discounted at 1.5% per year	£6,339	2.12	£2,995

The base case ICER is robust to changes in the majority of other scenario analysis tested (Table 32). Reducing the utility value associated with having an unresolved cartilage defect improves the cost-effectiveness of ChondroCelect, with a resulting ICER of £5,024, as ChondroCelect delays deterioration to the unresolved health state. The ICER increases when the utility associated with a successful TKR increases, since this makes TKR a better treatment option, and ChondroCelect delays the need for TKR.

The model is reasonably sensitive to the discount rate applied; no discounting of future costs or health outcomes reduces the ICER of £1,070, while discounting uniformly at 1.5% provides an ICER of £2,995. This is highly cost-effective, with the long-term benefits of ChondroCelect no longer eroded by an annual discount rate meaning incremental QALYs increase to 2.12 per patient. Incremental costs also fall, since future costs are higher on the MFx arm as more patient deteriorate to receive a TKR and TKR revisions, and these are no longer eroded by discounting. The uniform discount rate of 3.5% used in the base case analysis corresponds with the NICE Methods Guide.[60] However, it should be noted that the Methods Guide stipulates that the lower discount rate of 1.5% may be considered suitable where health outcomes are improved over a very long period (Section 6.2.19).[60] This may be therefore be relevant for consideration in the case of ChondroCelect.

5.5.2 Probabilistic sensitivity analysis

PSA was performed to estimate the uncertainty around the base case ICER. This involved using distribution information for model inputs, or estimating a reasonable distribution in the absence of alternative information, and sampling values from each distribution simultaneously. Model results were recorded using each set of sampled input values a total of 1,000 times to provide an estimate of the mean PSA results and a dispersion of results, reflecting uncertainty around them.

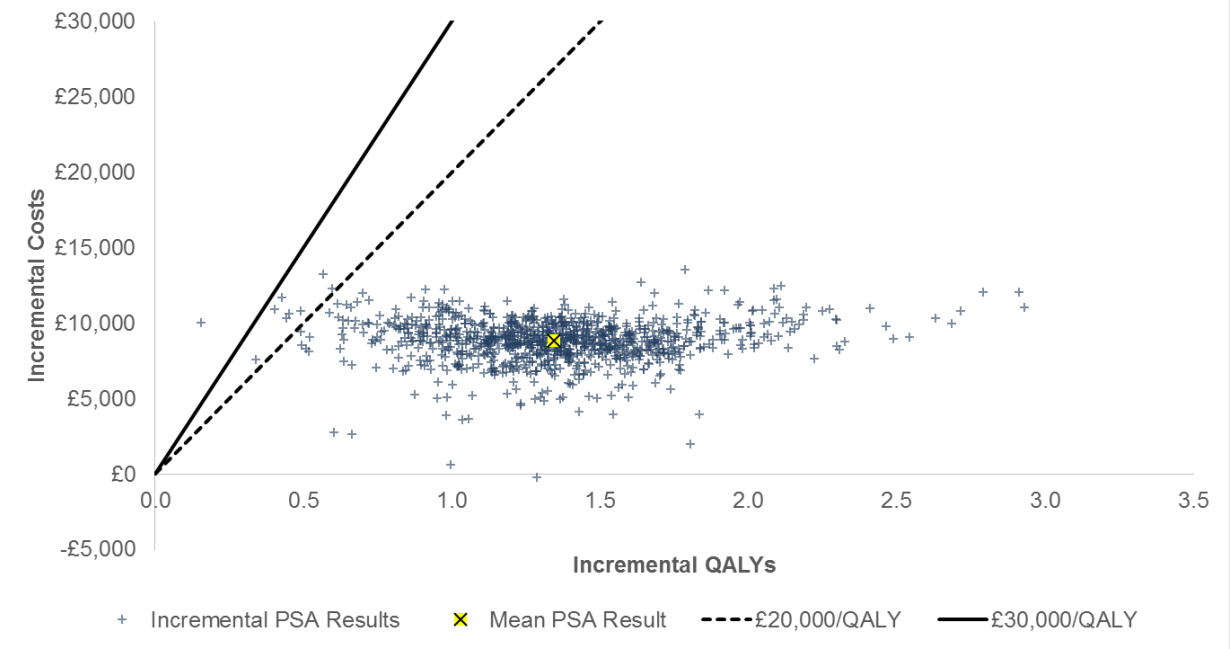
Mean results from the 1,000 PSA runs show the base case ICER to be consistent, with little parameter uncertainty; the PSA ICER of £6,565 is very close to the base case value (Table 33). This relative certainty is reflected in the cost-effectiveness plane showing each individual PSA result; incremental costs are well clustered between £5,000 and £10,000, whereas incremental QALYs are more dispersed, ranging from around 1.0 to 1.7 QALYs gained (Figure 23). This dispersion shows that there is relatively greater uncertainty in the incremental QALY gain than the incremental costs.

Table 33: Mean results of 1,000 PSA simulations (standard deviation in parentheses)

Model arm	Mean Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
MFx	£13,630 (1,930)	23.25 (0.60)	15.78 (2.08)				
ChondroCelect	£22,461 (1,026)	23.55 (0.17)	17,12 (1.86)	£8,831	0.31	1.35	**£6,565**

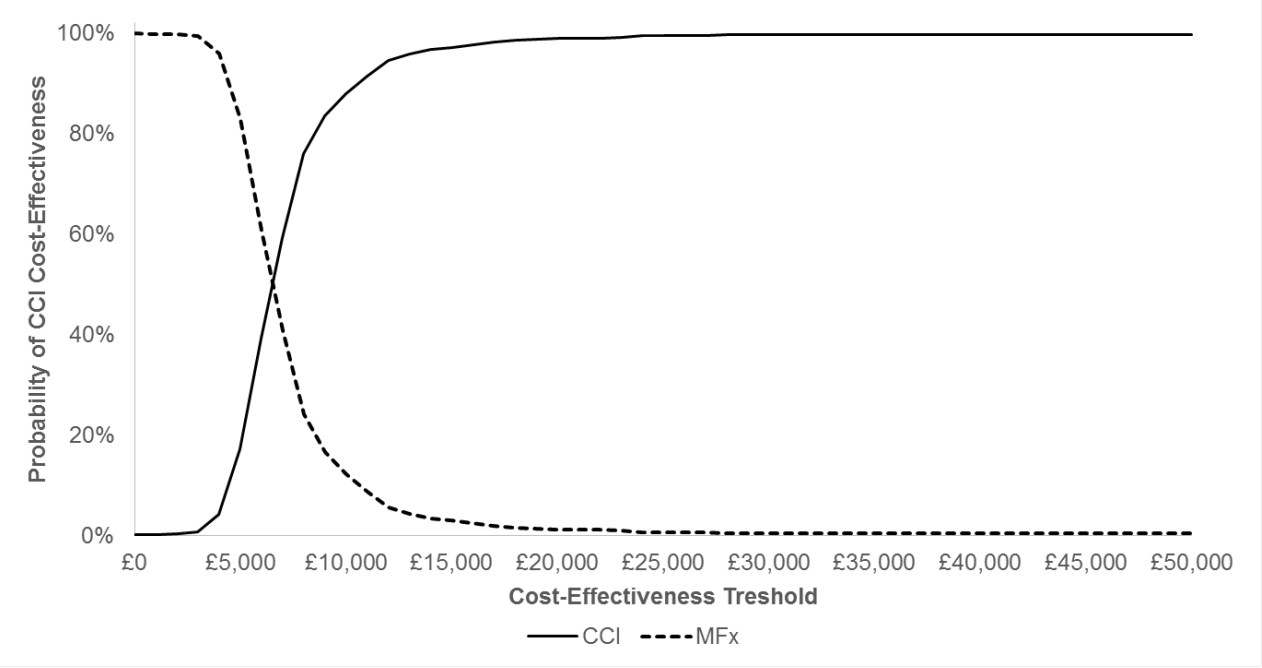
Key ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.

Figure 23: Results of 1,000 PSA simulations



Almost all simulations lie to the south-east of the £20,000 ICER line, meaning at a cost-effectiveness threshold of £20,000 per incremental QALY gained the model predicts ChondroCelect to have a 98.8% chance of being cost-effective. At a threshold value of £30,000, there is a 99.6% likelihood that ChondroCelect is a cost-effective use of NHS resources. These are reflected in the cost-effectiveness acceptability curve (CEAC) shown in Figure 24 below, where MFx is cost-effective at very low threshold values. ChondroCelect becomes the probable cost-effective option at a threshold value between £6,000 and £7,000.

Figure 24: CEAC estimated based upon 1,000 PSA simulations



5.6 Conclusions for cost-effectiveness

A *de novo* economic model has been developed to estimate the cost-effectiveness of ChondroCelect versus MFx. The model utilises data from publications on the pivotal trial, TIG/ACT/01, which included MFx as its active comparator arm. Time to treatment failure has been used as a proxy for treatment efficacy, with patients deemed to be successfully resolved to the point at which they require a subsequent reintervention. Patients can receive up to 2 surgical interventions, followed by pain relieving measures and then a TKR and TKR revisions.

The present analysis predicts ChondroCelect to be a highly cost-effective use of NHS resources, with a base case ICER well below the threshold range typically considered cost-effective by NICE. Results are robust to structural assumptions and parameter uncertainty. There is some sensitivity present around the proportion of patients who receive an MFx reintervention – likely to be lower following initial MFx compared to ChondroCelect – and model time horizon. However this is to be expected, as ChondroCelect accrues long term benefits to the NHS by staving off the need for treatment with only pain relief measures, the need for TKR and the progression to patients living with unresolved cartilage defects. A shorter time horizon would ignore these important future benefits to the NHS, in terms of resources saved and procedures avoided, and more importantly to the quality of life of the patient.

6 Resource implications

6.3 Resource use outcomes

The total number of different procedures was extracted from the cost-effectiveness model, to inform the likely impact on NHS resources. A reduction in required procedures caused by the introduction of ChondroCelect will free up hospitals and health care professionals to provide other care.

If 632 patients were to be treated with ChondroCelect, 86 would have received a secondary MFx by 5 years, compared to just 6 patients who initially received MFx. However more MFx patients would already have progressed to the point of requiring a TKR, with 41 TKRs predicted compared to just 3 among ChondroCelect patients.

Over a 75-year time horizon, again more patients on the ChondroCelect arm will receive a secondary MFx (546 compared to 31), as this procedure is less likely in patients who received an initial MFx procedure. The key resource benefit of ChondroCelect is its reduction in the need for TKRs. It is estimated that 571 patients out of 632 initially treated with MFx will require a TKR at 75 years, compared to just 321 ChondroCelect patients. An estimated 716 TKR revisions will be performed on MFx patients; 287 on ChondroCelect patients. In total, this means 679 fewer TKR/TKR revision procedures will be performed over a 75 year period, if 632 patients received ChondroCelect instead of MFx; a reduction of 52.8%.

6.4 Budget impact

The budget impact to the NHS of introducing ChondroCelect has been estimated based upon the patient numbers presented in Section 3.1. For the purpose of this analysis, the

number of patients in year 3 (632 patients) was assumed to remain stable for years 4 and 5. Undiscounted cost results at years 1 to 5 were extracted used within the model and applied to the relevant number of patients for each year.

The cost-effectiveness model results account for the impact of mortality, cost offsets, reintervention and all other costs detailed in Section 5 of this document. These factors are therefore accounted for in the budget impact estimates. The budget impact has been estimated for ChondroCelect and MFx, with the difference in each year representing the net impact of ChondroCelect in that year. These results, reflect the all differences in costs and therefore the budget impact of treating these patients as a whole, are provided in Table 34.

The introduction of ChondroCelect would lead to an estimated net budget impact of £4,155,954 in year 1, rising to £8,715,612 in year 5 as more patients receive the procedure.

Table 34: Estimated NHS budget impact of ChondroCelect

Year	Number of patients	Budget impact in year		Net Budget Impact (ChondroCelect – MFx)
		MFx	ChondroCelect	
1	293	£825,614	£4,981,568	£4,155,954
2	534	£1,532,734	£9,064,809	£7,532,075
3	632	£1,880,912	£10,716,119	£8,835,207
4	632	£1,992,764	£10,730,824	£8,738,061
5	632	£2,122,940	£10,838,552	£8,715,612

Key: ChondroCelect, characterised chondrocyte implantation; MFx, microfracture; TKR, total knee replacement.

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8 Appendices

8.1 Exploratory cost-effectiveness analysis: MFx vs No MFx

To consider whether MFx is itself a cost-effective treatment options in the first place, the model was used to undertake an exploratory analysis and obtain the ICER relative to BSC. For this analysis, the model was manipulated such that all patients on the MFx arm failed after 1 cycle. These patients all went on to receive BSC, and possible future TKRs. No MFx costs were therefore incurred, and no MFx-related efficacy was experienced. This results in a total discounted cost of £18,354, and 13.55 total QALYs, per patient (Table 35).

These results were compared to the base case MFx model arm results to compute an ICER. The use of MFx is associated with a lower total cost, as without MFx patients progress more rapidly to receive TKR and TKR revisions. Without MFx patients receive the utility associated with BSC management straight away, and more quickly reach the unresolved health state, leading to lower total QALYs. MFx therefore dominates no MFx, with cost savings (£4,807) and a QALY gain (1.85).

Table 35: Exploratory model results of MFx vs no MFx

Input	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Microfracture	£13,547	15.40			
No use of MFx	£18,354	13.55	-£4,807	1.85	**Dominated**
Key: ICER, incremental cost-effectiveness ratio; MFx, microfracture.					

8.2 Exploratory cost-effectiveness analysis: TKR vs No TKR

To evaluate TKR compared to no TKR, the model was manipulated similarly. For this analysis, the starting age of patients was increased from 33 years to 50 years, as a clinical expert advised that younger patients are less likely to be considered for TKR. All patients on the MFx arm failed after 1 cycle, and went on to BSC. In one model they were allowed to receive TKRs and revisions as normal, while in another model TKRs were not allowed. In this model, there was no assessment for TKR; patients who would otherwise have been assessed for TKR moved to the unresolved health state.

These exploratory results are provided in Table 36. When TKR is permissible, incremental costs are £9,408, reflecting the costs associated with the assessment and procedure. The possibility of receiving a successful TKR operation leads to a QALY gain of 1.10. While this analysis therefore does not show TKR to dominate no TKR, the resulting ICER of £8,587 is well within the range typically considered to reflect a cost-effective treatment.

Table 36: Exploratory model results of TKR vs no TKR

Input	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
TKR not allowed	£6,750	10.50			
TKR allowed	£16,157	11.60	£9,408	1.10	**£8,587**
Key: ICER, incremental cost-effectiveness ratio; MFx, microfracture.					