Single-step scaffold-based cartilage repair in the knee

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

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Content

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List of abbreviations

ACI ..... Autologous chondrocyte implantation
AMIC ..... Autologous Matrix-Induced Chondrogenesis (AMIC)
CE ..... Communauté Européenne
CT ..... Controlled trial (non-randomised)
ICRS ..... International Cartilage Repair Society
LBI-HTA ..... Ludwig Boltzmann Institute for Health Technology Assessment
MACI ..... Matrix-induced autologous chondrocyte implantation
MFx ..... Microfracturing
MP ..... Mosaicplasty
MRI ..... Magnetic resonance imaging
OCD ..... Osteochondritis dissecans
RCT ..... Randomised controlled trial
VAEV ..... Verwaltung von Änderungs- und Ergänzungsvorschlägen zum Leistungskatalog

Summary

Introduction

Description of technology

In the single-step scaffold-based treatment of cartilage defects, a matrix is implanted in the area of the damaged cartilage. The used matrix acts as a temporary structure to allow the cells to be seeded and establish a 3-dimensional structure. The matrix decomposes over time.

einzeitige Knorpelreparatur in Kombination mit Mikrofrakturierung

In this report we analysed whether the single-step scaffold-based cartilage repair in combination with microfracturing is more effective and safe in comparison to microfracturing alone or as effective but safer in comparison to two-step cartilage repair procedures (autologous chondrocyte implantation or matrix-induced autologous chondrocyte implantation; (M)ACI).

Mikrofraktuirierung + (M)ACI als Vergleich

Health problem

This systematic review focuses on the treatment of chondral and osteochondral lesions in the knee.

Fokus Schäden Knie

Articular (chondral) cartilage is a thin layer of connective tissue. It provides a smooth surface for articulation and facilitates the transmission of forces to the underlying subchondral bone.

Knorpel ist Gleitschicht

A damage of the cartilage can occur due to traumatic events or degeneration of the joint or due to osteochondritis dissecans (OCD). The damage can also affect the underlying bone (i.e. osteochondral lesion).

Knorpelschaden durch Trauma oder Abnutzung:

Methods

Answering the research questions regarding efficacy and safety-related outcomes was based on a systematic literature search from different databases and an additional hand search. The study selection, data extraction and assessing the methodological quality of the studies was performed by two review authors, independently from each other.

systematische Literatursuche

Domain effectiveness

The following efficacy-related outcomes were used as evidence to derive a recommendation: mobility/joint functionality, quality of life, pain and necessity of total joint replacement.

entscheidende Endpunkte für Wirksamkeit ...

Domain safety

The following safety-related outcomes were used as evidence to derive a recommendation: procedure-related complications, device-related complications and re-operations rate.

... und Sicherheit

Results

Available evidence

keine Studien im Vergleich zu (M)ACI

We could not identify any controlled trials comparing the single-step scaffold-assisted treatment of (osteo)chondral defects in the knee with (M)ACI.

2 RCTs, 1 non-RCT zu einzeitiger matrix-assistierter Behandlung von Knorpeldefekten im Kniegelenk

The only studies that met our inclusion criteria are two randomised controlled trials (RCTs) and one non-randomised controlled trail with 136 patients of the single-step scaffold-assisted chondral repair in the knee joint (scaffold-groups) in combination with microfracturing (MFx), compared to MFx alone (MFx-groups).

Clinical effectiveness

Verbesserungen der Scores zu Funktion Gelenk, Schmerzen + Lebensqualität; keine signifikanten Unterschiede

The scores measuring the mobility or joint functionality and pain (reported in all three controlled trials) plus quality of life (measured in only one study) improved in the groups that received the single-step scaffold-assisted treatment (+ MFx) as well as in the groups that received MFx alone in a comparable extent. In all studies, the differences of the improvements between the study groups were statistically not significant.

ein künstliches Gelenk in Interventionsgruppe

In one study it was stated that one patient who received a (glued) scaffold, the knee joint had to be replaced.

Safety

eingriffsbezogene Komplikationen: 0-93 % vs. 0-77 %

Procedure-related adverse events occurred in 0-93% of the patients in the scaffold-groups and in 0-77% of the patients in the control groups. Device-related adverse events occurred in 0 to 22% of the patients.

Reoperationen nicht berichtet

In none of the identified studies it was stated, if any re-operations were necessary.

Upcoming evidence

vier laufende Studien

Currently, there are four registered ongoing randomised controlled trials of the single-step scaffold-based cartilage repair.

Reimbursement

Intervention in Österreich derzeit nicht erstattet

At this point in time, the single-step scaffold-based repair of cartilage defects or osteochondritis dissecans (OCD) or (osteo)chondral lesions in the knee joint is not reimbursed by the Austrian health care system.

Discussion

insgesamt geringe Evidenzstärke

Overall, the strength of evidence for efficacy and safety is low. Exceptions are some individual outcomes, like joint functionality and pain, for which the strength of evidence was rated as “moderate”.

Studien suggerieren: Gleichwertigkeit einzeitiger matrix-assistierter Knorpelersatz

Considering the findings of the included studies regarding clinical effectiveness, it seems that the single-step scaffold-assisted cartilage repair in combination with MFx leads to similar short to medium-term (up to five years follow-up) results, compared to MFx alone.

relativ kleine Fallzahlen, relativ kurze Nachbeobachtungszeiträume

A major issue of the identified trials are the low patient numbers and relatively short follow-ups of one year or less. Only one of the studies had a follow-up of at least five years. Therefore, reliable data of long-term efficacy and safety-related outcomes are missing.

For assessing the clinical effectiveness and safety of the single-step matrix-assisted cartilage repair in the knee joint (combined with microfracturing) compared to *(M)ACI*, we could not identify any studies that met our inclusion criteria.

keine Studien mit (M)ACI als Vergleich

Conclusion

The current evidence is not sufficient to conclude that the single-step matrix-assisted cartilage repair (combined with microfracturing) is more effective and safer than microfracturing or as effective, but safer than (matrix-assisted) autologous chondrocyte implantation.

keine ausreichend robuste Evidenz

New study results, especially from studies with larger patient numbers and longer follow-up (e.g. ten years), will potentially influence the effect estimate considerably.

Studien mit mehr PatientInnen + längerer Nachbeobachtung nötig

A re-evaluation is recommended not before 2018, since the technique seems to be promising and there are still ongoing studies. At the moment, it seems too early to include the single-step scaffold-assisted cartilage repair of the knee in the catalogue of benefits.

Re-Evaluierung 2018 empfohlen, Aufnahme in Katalog nicht empfohlen

Zusammenfassung

Einleitung

Beschreibung der Technologie

Fokus auf Knorpelreparatur in Kombination mit Mikrofrakturierung

Es gibt verschiedene Varianten für einen einzeitigen matrix-assistierten Knorpelersatz. In dem vorliegenden Bericht liegt der Fokus auf dem Verfahren, bei dem die Matrix in Kombination mit der Mikrofrakturierung verwendet wird.

Mikrofrakturierung stimuliert Knochenmark

Die Mikrofrakturierung ist eine Knochenmarkstimulationstechnik, bei der der subchondrale Knochen perforiert wird. Das austretende Knochenmark enthält Stammzellen und Wachstumsfaktoren, die zur Chondrogenese beitragen.

Matrix als Unterstützung für Zellansiedlung

Beim einzeitigen Knorpelersatz wird eine Matrix in den Bereich des Knorpeldefekts eingebracht, um den Blutpfropf, der durch die Mikrofrakturierung entsteht, abzudecken. Diese Technik wird auch als Autologe Matrixinduzierte Chondrogenese (AMIC) bezeichnet. Die Matrix soll als Unterstützung für die Zellansiedlung dienen.

acht verschiedene Produkte

Insgesamt konnten acht verschiedene Produkte von acht verschiedenen Herstellern identifiziert werden, die alle ein CE-Zertifikat haben:

- BST-CarGel® (Primal Enterprises Limited, Canada
- CaReS®-1S (Arthro Kinetics AG, Germany),
- Chondro-Gide® (Geistlich Pharma, Switzerland),
- Chondrotissue® (BioTissue Technologies GmbH, Switzerland),
- GelrinC® (Regentis Biomaterials Ltd., Israel),
- Hyalofast® (Anika Therapeutics, Inc., USA),
- Maioregen™ (Fin-Ceramica Faenza S.p.A., Italy),
- MeRG® (Bioteck S.p.A., Italy).

Mikrofakturierung als Hauptvergleich

(M)ACI als zusätzlicher Vergleich

Für kleinere Läsionen gilt die Mikrofraktuierung als chirurgische Interventionen der Wahl, während für größere Läsionen die autologe Chondrozytenimplantation (ACI), die ebenfalls matrix-assistiert sein kann (MACI), verwendet werden kann. Daher wurden sowohl die Mirkofrakturieung als auch die (M)ACI als Vergleichsinterventionen herangezogen. Auf den Vergleich mit anderen möglichen chirurgischen Eingriffen, wie autologe osteochondrale Transplantate, wurde verzichtet.

Forschungsfragen

Der Bericht behandelt die Frage, ob der einzeitige matrix-assistierte Knorpelersatz in Kombination mit der Mikrofrakturierung wirksamer und sicherer ist als die Mikrofrakturierung. Weiters soll die Frage beantwortet werden, ob der einzeitige matrix-assistierte Knorpelersatz in Kombination mit der Mikrofrakturierung genauso wirksam, aber sicherer als die (M)ACI ist.

Indikation und therapeutisches Ziel

Fokus auf Schäden in Kniegelenk

Im Fokus des Berichts steht die Behandlung chondraler bzw. osteochondraler Schäden im Kniegelenk.

mehrere Ursachen: Trauma, Abnutung oder Osteochondrosis dissecans

Der Gelenksknorpel ist eine dünne Gewebsschicht, die eine geschmeidige Oberfläche bildet, um die Beweglichkeit des Gelenks zu gewährleisten und um Stöße abzufangen. Eine Schädigung des Knorpels kann entweder durch ein Trauma (z. B. Sportunfall), durch Abnutzungserscheinungen (speziell bei älteren Menschen) oder durch die Osteochondrosis dissecans (OCD) entstehen.

Schmerzen, Bewegungseinschränkungen, bis hin zu Gelenksersatz

Ein Knorpelschaden kann mit Schmerzen und Bewegungseinschränkungen einhergehen. Bei weiterer Fortschreitung kann der Defekt zu einer degenerativen Osteoarthritis führen – bis hin zur Notwendigkeit eines künstlichen Gelenks.

Diagnose

Zur Diagnose von chondralen oder osteochondralen Defekten sind, neben der klinischen Diagnostik (Inspektion, Palpation, Funktionstests), vor allem bildgebende Verfahren (Röntgen und MRT) notwendig.

Methoden

Quellen aus systematischer Literatursuche

Die Beantwortung der Forschungsfragen bezüglich Wirksamkeit und Sicherheit basierte auf einer systematischen Literatursuche in folgenden Datenbanken:

- The Cochrane Library,
- CRD (DARE, NHS-EED, HTA),
- Embase,
- Medline via Ovid,
- PubMed.

Handsuche, Anfrage Hersteller

Zusätzlich wurde noch eine Handsuche durchgeführt und es gab eine Anfrage nach Studien bei den einzelnen Herstellern.

4-Augenprinzip

Die Studienauswahl erfolgte nach dem 4-Augenprinzip, ebenso die Datenextraktion. Insgesamt wurden vier Publikationen für eine Datensynthese eingeschlossen.

Studienbewertung nach GRADE

Die Daten, der für die Entscheidung herangezogenen Endpunkte, wurden aus den einzelnen Studien zusammengefasst und nach GRADE (Grading of Recommendations Assessment, Development and Evaluation) bewertet.

Bias-Risiko je Endpunkt

Zusätzlich wurde das Bias-Risiko für jeden entscheidungsrelevanten Endpunkt nach einer Checkliste von zwei AutorInnen, unabhängig von einander, bewertet.

Klinische Wirksamkeit

entscheidende Endpunkte für Wirksamkeit

Zur Bewertung der Wirksamkeit wurden die folgenden entscheidenden Endpunkte für eine Empfehlung herangezogen:

- Mobilität/Gelenksfunktion
- Lebensqualität
- Schmerzen
- Notwendigkeit eines Gelenksersatz

Sicherheit

entscheidende Endpunkte für Sicherheit

Zur Bewertung der Sicherheit wurden die folgenden entscheidenden Endpunkte für eine Empfehlung herangezogen:

- Eingriffsbezogene Komplikationen
- Implantatsbezogene Komplikationen
- Reoperationsrate

Ergebnisse

Verfügbare Evidenz

2 RCTs, 1 non-RCT zu einzeitiger matrix-assistierter Behandlung von Knorpeldefekten im Kniegelenk

Insgesamt konnten zwei randomisierte kontrollierte Studien (RCTs) und eine nicht-randomisierte kontrollierte Studie identifiziert werden, die den Einschlusskriterien entsprachen. Alle drei Studien verglichen den einzeitgen matrix-assistierten Knorpelersatz (in Kombination mit der Mikrofrakturierung) mit der Mikrofrakturierung.

136 PatientInnen: Ø 33-38 vs. 37-41 Jahre

Produkte: Chondro-Gide®, BST-CarGel®

In den eingeschlossenen Studien befanden sich 136 PatientInnen, mit einem Durchschnittsalter von 33-38 Jahren in den Interventionsgruppen sowie 37-41 Jahren in den Kontrollgruppen. Die Nachbetrachtungszeit betrug 6, 24 und 60 Monate. In den Studien wurde entweder Chondro-Gide® oder BST-CarGel® eingesetzt. In einer Studie wurde nur erwähnt, dass eine Matrix aus Polyethylenglycol-Diacryl verwendet wurde (ähnlich GelrinC®).

keine Studien im Vergleich zu (M)ACI

Es konnten keine kontrollierten Studien identifiziert werden, die den einzeitigen matrix-assistierten Knorpelersatz (in Kombination mit der Mikrofrakturierung) mit der (M)ACI verglichen.

Klinische Wirksamkeit

Messung Funktion anhand verschiedener Scores; Verbesserung, aber Gruppen-Unterschied nicht signifikant

Die Funktionalität des Kniegelenks wurde in allen eingeschlossenen Studien mit verschiedenen Scores gemessen (z. B. modifizierter Cincinatti Score, WOMAC Score und dem IKDC Score). In allen Studien konnte eine Verbesserung der Scores sowohl in den Interventionsgruppen als auch in den Kontrollgruppen festgestellt werden. Jedoch war der Unterschied der Verbesserungen zwischen den Behandlungsgruppen in keiner Studie statistisch signifikant.

in einem RCT ein künstliches Gelenk in Interventionsgruppe

In einem RCT wurde erwähnt, dass während der zweijährigen Nachbeobachtungszeit bei einem/einer PatientIn, der/die mittels einzeitigen matrix-assistierten Knorpelersatz behandelt wurde, der Einsatz eines künstlichen Kniegelenks notwendig war.

Lebensqualität: kein signifikanter Unterschied zwischen Gruppen bei Veränderung

Weiters wurde in einem RCT die Lebensqualität gemessen: mittels psychischer und physischer Komponente des SF-36. Beide Scores konnten eine Verbesserung der Lebensqualität sowohl in den Interventionsgruppen als auch in den Kontrollgruppen festhalten. Jedoch war der Unterschied der Verbesserungen zwischen den Behandlungsgruppen statistisch nicht signifikant.

Verringerung Schmerzen, kein signifikanter Gruppenunterschied

Schmerzen wurden wieder in allen drei eingeschlossenen Studien mit verschiedenen Scores gemessen (z. B. visuelle Analogskala). Auch die Schmerzen konnten sowohl in den Interventionsgruppen als auch in den Kontrollgruppen reduziert werden, wobei der Unterschied der Verbesserungen zwischen den Behandlungsgruppen statistisch nicht signifikant war.

Sicherheit

Eingriffsbezogene Komplikationen traten bei 0-93 % der PatientInnen die mittels einzeitigen matrix-assistierten Knorpelersatz (in Kombination mit Mikrofrakturierung) und bei 0-77 % der PatientInnen, die nur mit Mikrofrakturierung behandelt wurden, auf.

eingriffsbezogene Komplikationen: 0-93 % vs. 0-77 %

Komplikationen, die mit der Implantation der Matrix in Verbindung gebracht wurden, traten bei 0-22 % der PatientInnen auf.

implantatsbezogene Komplikationen: 0-22 %

In keiner der Studien wurde explizit berichtet, wie viele PatientInnen einer Reoperation unterzogen werden mussten.

Reoperationen nicht berichtet

Laufende Studien

Aktuell sind vier laufende RCTs registriert. Zwei der Studien vergleichen den einzeitigen matrix-assistierten Knorpelersatz mit der Mikrofrakturierung und zwei mit der matrix-assistierten autologen Chondrozytenimplantation (MACI).

vier laufende RCTs

Kostenerstattung

Derzeit werden in Österreich die Kosten für den einzeitigen matrix-assistierten Knorpelersatz nicht separat erstattet.

in Österreich derzeit nicht erstattet

Diskussion

Das Ziel des vorliegenden Berichts war es die Wirksamkeit und Sicherheit des einzeitigen matrix-assistierten Knorpelersatzes (in Kombination mit der Mikrofrakturierung) im Vergleich zur Mikrofrakturierung allein sowie zur (matrix-assistierten) autologen Condrozytenimplantation ((M)ACI) zu bewerten.

Ziel: Bewertung Wirksamkeit + Sicherheit

Insgesamt wurden 3 kontrollierte Studien für die Datensynthese eingeschlossen, die den Einschlusskriterien entsprachen. In allen Studien wurden die PatientInnen in den Kontrollgruppen mittels Mikrofrakturierung behandelt. Die Evidenzstärke der Studien war generell gering.

3 Studien mit Mikrofrakturierung als Vergleich

Keine der Studien konnte eine Überlegenheit des einzeitigen matrix-assistierten Knorpelersatz belegen. Die Studien suggerieren eher eine Gleichwertigkeit, im Vergleich zu alleinigen Mikrofrakturierung.

Gleichwertigkeit einzeitiger matrix-assistierter Knorpelersatz

Kritikpunkte der identifizierten Studien sind vor allem die relativ kurzen Nachbeobachtungszeiträume und die kleinen PatientInnenzahlen in der Mehrzahl der Studien. Ein weiterer Kritikpunkt sind die inkonsistenten Angaben zu Komplikationen, was sich insbesondere in den unterschiedlich hohen Raten widerspiegelt. Außerdem wichen die einzelnen Interventionen in den Studien geringfügig voneinander ab (Art der verwendeten Matrix und Fixierung der Matrix im Defekt, etc.).

einige Kritikpunkte der Studien

Entscheidende Schwächen des vorliegenden Berichts sind insbesondere: der konsequente Ausschluss von Ein-Arm-Studien, die weniger als 50 PatientInnen untersuchten und eine Nachbeobachtungszeit von weniger als zwei Jahren hatten. Außerdem der Ausschluss von Studien, in denen nicht ausschließlich der einzeitige matrix-assistierte Knorpelersatz in Kombination mit der Mikrofrakturierung vorgenommen wurde. Sowie der Ausschluss von Studien die retrospektiv angelegt waren (dazu zählten auch Studien mit einer historischen Kontrollgruppe).

Schwächen des Reviews

Empfehlung

kein Beweis, dass wirksamer und sicherer als Mikrofrakturierung

Die gegenwärtige Studienlage lässt keine Rückschlüsse zu, ob der einzeitige matrix-assistierte Knorpelersatz (in Kombination mit der Mikrofrakturierung) wirksamer und sicherer als die Mikrofrakturierung allein, bzw. mindestens genauso wirksam, aber sicherer im Vergleich zur (M)ACI ist.

weitere Studien nötig

Weitere Studienergebnisse, insbesondere von Studien mit längeren Nachbeobachtungszeiträumen sowie größeren Fallzahlen könnten die Ergebnisse beeinflussen.

Aufnahme in den Leistungskatalog derzeit nicht empfohlen

Die Aufnahme in den Leistungskatalog wird derzeit nicht empfohlen. Eine neuerliche Re-Evaluierung wird für frühestens 2018 vorgeschlagen.

1 Scope

1.1 PICO question

1) Is the single-step scaffold-based cartilage repair in combination with microfracturing more effective and safe in comparison to microfracturing alone in patients with indications for cartilage knee surgery concerning the outcomes listed in Table 1-1?

PIKO-Frage Teil 1

2) Is the single-step scaffold-based cartilage repair in combination with microfracturing as effective, but safer in comparison to two-step cartilage repair procedures (autologous chondrocyte implantation or matrix-induced autologous chondrocyte implantation (M)ACI)) in patients with indications for cartilage knee surgery concerning the outcomes listed in Table 1-1?

PIKO-Frage Teil 2

1.2 Inclusion criteria

Inclusion criteria for relevant studies are summarized in Table 1-1.

Einschlusskriterien für relevante Studien

Table 1-1: Inclusion criteria

Population	❁ Adult patients with indications for surgical cartilage repair in the knee ❁ Grade III to IV (Outerbridge classification) localised cartilage damages/defects/disorders in the knee ❁ Grade III to IV (ICRS classification) (osteo)chondral lesions ❁ Osteochondritis dissecans (OCD) ❁ Contraindications: ❁ Defect size <1 and >8 cm² ❁ Allergies of the used material(s) ❁ Inflammatory cartilage diseases ❁ Malposition of the knee ≥5 degrees ICD-10 codes:M24.1, M94.8, M94.9, M93.2 [1]
Intervention	❁ Single-step cell-free scaffold-based cartilage repair in combination with microfracturing ❁ Alternative terms (selection): ❁ Autologous matrix-induced chondrogenesis (AMIC) ❁ Cell-free matrix-induced chondrogenesis ❁ Cell-free (collagen) matrices/matrix ❁ Product names: ❁ BST-CarGel® ❁ CaReS®-1S ❁ Condro-Gide® ❁ Chondrotissue® ❁ GelrinC® ❁ Hyalofast® ❁ MaioRegen™ ❁ MeRG®

Control	❁ Microfracture surgery/microfracturing alone (main comparator) ❁ Autologous chondrocyte implantation/transplantation (ACI/ACT) ❁ Matrix-induced autologous chondrocyte implantation (MACI)
Outcomes	
Efficacy	❁ Mobility/joint functionality ❁ Pain ❁ Return to daily activities/sports/physical activity ❁ Quality of life ❁ Neccessity of total joint replacement
Safety	❁ Adverse events ❁ Mortality (up to 10 days postoperatively) ❁ Re-operation/additional surgery
Study design	
Efficacy	❁ Randomised controlled trials ❁ Prospective non-randomised controlled trials
Safety	❁ Randomised controlled trials ❁ Prospective non-randomised controlled trials ❁ Prospective uncontrolled trials (n>50 pts., follow-up>24 months)

2 Methods

2.1 Research questions

Description of the technology	
Element ID	**Research question**
B0001	What is the technology and the comparators?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparators?
B0004	Who administers the technology and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology

Health problem and Current Use	
Element ID	**Research question**
A0001	For which health conditions, and for what purposes is the technology used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for the patients with the disease or health condition?
A0006	What are the consequences of the disease or health condition for the society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0011	How much are the technologies utilised?

Clinical Effectiveness	
Element ID	**Research question**
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect progression (or recurrence) of the disease or health condition?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of the technology on disease-specific quality of life?

Safety	
Element ID	**Research question**
C0008	How safe is the technology in comparison to the comparator(s)?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?
C0007	Are the technology and comparator(s) associated with user-dependent harms?

2.2 Sources

Quellen: systematische Suche, Handsuche, aber auch Informationen der Hersteller

To answer the research questions, the results from the systematic literature search (see Section 2.3) and from the hand search were used.

Description of the technology

- Handsearch in the POP database for Health Technology Assessments and in Google (for identifying manufacturers and product information)
- Publications identified in systematic database search: see Section 2.3
- Documentation provided by the manufacturers
- Questionnaire completed by the submitting hospitals

Health problem and Current Use

- Handsearch in the POP databases for Health Technology Assessments and in Google
- Publications identified in systematic database search: see Section 2.3
- Documentation provided by the manufacturers
- Questionnaire completed by the submitting hospitals

2.3 Systematic literature search

systematische Literatursuche in fünf Datenbanken

The systematic literature search was conducted between 13th and 15th of January 2016 in the following databases:

- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)
- Embase
- Medline via Ovid
- PubMed

Systematische Suche: 267 Zitate

The systematic search was limited to articles published in English or German. After deduplication, overall 267 citations were included. The specific search strategy employed can be found in the appendix.

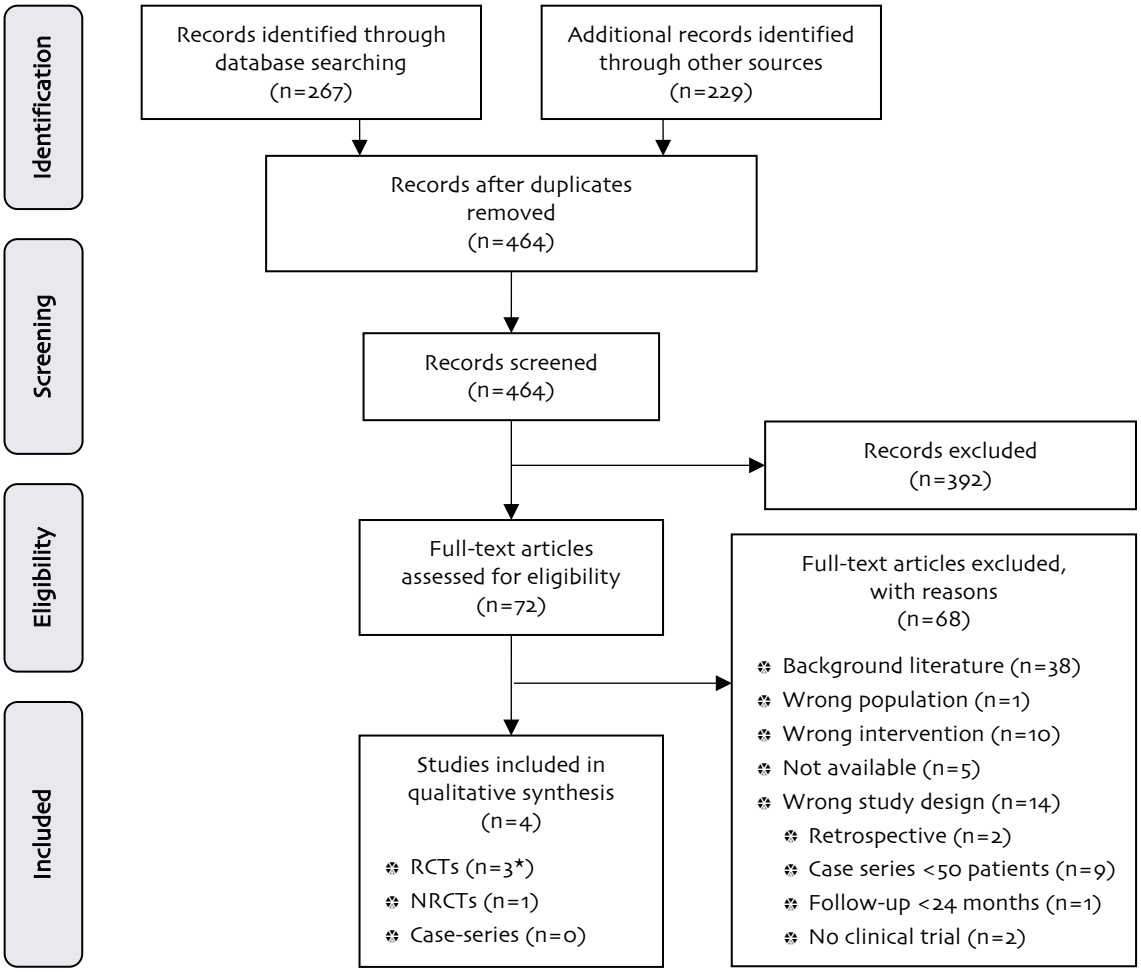
insgesamt 464 Publikationen identifiziert

Manufacturers from the most common products (see Chapter 3, Element ID B0001 – What is the technology and the comparators?) submitted 46 publications of which 14 new citations were identified. By hand-search, additional 183 records were found (164 were found by a Scopus-search, based on four studies), resulting in overall 464 hits.

2.4 Flow chart of study selection

Literaturauswahl

Overall 464 hits were identified. The references were screened by two independent researchers and in case of disagreement a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1. Articles that were excluded due to several reasons but still used as background are categorized under "background literature". Furthermore, we were not able to retrieve the full-texts of five articles. These are categorized under "not available".



**Two publications presented results of one RCT. Therefore, data from both publications are presented together.*

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.5 Analysis

Datenextraktion und Bewertung Bias-Risiko laut Checkliste

The data retrieved from the selected studies (see Chapter 2.4) were systematically extracted into a data-extraction-table (see Appendix). No further data processing (e.g., indirect comparison) was applied. The studies were systematically assessed for quality and risk of bias using the checklists presented in the Appendix.

2.6 Synthesis

Evidenzsynthese mittels GRADE

Based on the data-extraction-tables (see Appendix), data on each selected outcome category were qualitatively synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [2]. The research questions were answered in plain text format with reference to GRADE evidence tables (see Chapter 7).

3 Description and technical characteristics of technology

Features of the technology and comparators

B0001 – What is the technology and the comparators?

Fokus auf ein Verfahren für Knorpelreparatur in Kombination mit Mikrofrakturierung

There are different approaches available for the single-step scaffold-based cartilage repair [3, 4]. However, the procedure is mainly an enhancement of the standard microfracture technique, used to induce reparative marrow-stimulation. Other reparative bone-marrow stimulation techniques, such as drilling, are not considered in this report, as microfracture is the established standard [4, 5]. Thus, we exclusively focus on one approach, where the implantation of the scaffold is combined with microfracture (MFx).

Mikrofrakturierung stimuliert Knochenmark

Microfracture consists in the perforation of the subchondral bone of the articular cartilage defect, leading to the formation of a blood clot and egress of marrow components, including stem cells and growth factors that stimulate chondrogenesis and cartilage repair [6, 7].

Technik auch als AMIC bezeichnet

In the single-step scaffold-based treatment of cartilage defects, a matrix is implanted in the area of the damaged cartilage to cover the blood clot after MFx. This technique is also called autologous matrix-induced chondrogenesis (AMIC) [6-9]. The acronym AMIC is originally a registered trademark of the Ed. Geistlich Söhne AG (Schlieren, Switzerland) [9].

Matrix als Unterstützung für Zellansiedlung

The scaffolds are implanted arthroscopically or by a mini-arthrotomy for "in situ" repair, permitting the ingrowing of mesenchymal stem cells (MSCs) to differentiate into the chondrogenic lineage. The used matrix acts as a temporary structure to allow the cells to be seeded and establish a 3-dimensional structure. The matrices decompose over time [10].

Matrix ist zellfrei

The used matrices are cell-free scaffolds, such as a porcine collagen matrix. However, material and configuration of the scaffolds vary between the individual products [11, 12].

acht verschiedene Produkte

We found eight products from eight manufacturers, which will be further explained below. All products have in common that bone marrow is intended to colonise/seed the matrix.

BST-CarGel®

BST-CarGel® ist Hydrogel

BST-CarGel® (Primal Enterprises Limited, Canada)[1] is a gel that consists of a chitosan solution (a natural polymer) and a buffer. BST-CarGel® must be used in combination with a bone marrow stimulation technique (e.g. microfraturing). During the cartilage repair surgery, the gel is applied to the lesion and mixed with the blood generated from the bone marrow stimulation. BST-CarGel® is only indicated for the repair of cartilage damage in the knee (contra-indications were not identified) [13].

[1] On January 12, 2016 Piramal Enterprises announced the sale of the product BST-CarGel® to Smith and Nephew (UK).

CaReS®-1S

CaReS®-1S ist Kollagen-Matrix

CaReS®-1S (Arthro Kinetics AG, Germany) is a collagen type I matrix for the treatment of chondral lesions. This implant is inserted (by gluing) in the defect zone and is colonised by cells migrating from the surrounding tissue after bone marrow stimulation (e.g. microfracturing). Exemplary contra-indications for the use of CaReS®-1S are: defect sizes >8 cm^2, age younger 18 and older 60, BMI >35 kg/m^2 [14].

Chondro-Gide®

Chondro-Gide® ist Kollagen-Matrix

Chondro-Gide® (Geistlich Pharma, Switzerland) is a bilayer matrix made from porcine collagen type I/III for the treatment of traumatic chondral and osteochondral lesions [15]. Besides AMIC, the product can also be used for MACI (matrix-assisted autologous chondrocyte implantation). Chondro-Gide® is inserted in the damaged area (by gluing or suturing), after microfracturing. The clot formed as a result of haemorrhage is covered and stabilised by the scaffold. Exemplary contra-indications for the use of Chondro-Gide® are: defect sizes >8 cm^2, age older 60, more than two or corresponding cartilage defects, systemic, immune mediated disease or infection of the knee including osteoarthritis, inflammatory joint reactions, instable knee, menisectomy, varus/valgus (concomitant realignement procedure required), hemophilia A/B or allergy to porcine collagen [15].

Chondrotissue®

Chondrotissue® Matrix aus Polyglykolsäure-Filz und Hyaluronsäure

Chondrotissue® (BioTissue Technologies GmbH, Switzerland) is made from polyglycolic acid fleece and freeze-dried sodium hyaluronate for the treatment of chondral lesions. The scaffold is implanted (by gluing, suturing or nailing) into the area of the defective cartilage after bone marrow stimulation procedures (e.g. microfracturing). Exemplary contra-indications for the use of Chondrotissue® are: allergies to one of the constituents, when patients have to undergo chemotherapy and/or radiotherapy up to three weeks after the implant, children or pregnant and lactating women, or patients with inflammatory joint diseases, such as rheumatoid arthritis and Bechterew's disease [16].

GelrinC®

GelrinC® ist Hydrogel

GelrinC® (Regentis Biomaterials Ltd., Israel) is a hydrogel of polyethylene glycol di-acrylate (PEG-DA) and denatured fibrinogen, crosslinked with UVA light in-situ, for the treatment of chondral defects. The gel is applied into the defective cartilage after bone marrow stimulation procedure, typically microfracture [17]. Unfortunately, no information on contra-indications for the use of GelrinC® has been identified.

Hyalofast®

Hyalofast® Matrix aus Hyaluronsäure

Hyalofast® (Anika Therapeutics, Inc., USA) is a biodegradable, hyaluronan based (HYAFF®) scaffold. Hyalofast® is intended for the repair of chondral or osteochondral lesions, acting as a support for mesenchymal stem cells (MSC) from bone marrow aspirate or as a chondroprotective coverage which favours in situ residence of mesenchymal stem cells after their mobilization due to microfracture and/or perforation procedure [18]. Unfortunately, no information on contra-indications for the use of Hyalofast® has been identified.

Maioregen™

Maioregen™ Matrix aus Kollagen und Hydroxylapatit

Maioregen™ (Fin-Ceramica Faenza S.p.A., Italy) is a multi-layer scaffold: the superficial layer consists of deantigenated type I equine collagen and resembles the cartilaginous tissue, while the lower layer consists mostly of mag-

nesium-enriched hydroxyapatite (Mg-HA) and simulates the sub-chondral bone structure. The intermediate layer, composed of Mg-HA and collagen, reproduces the tide-mark [19]. The scaffold is implanted (by gluing) into the area of the defective chondral or osteochondral defect. For the treatment of osteochondral defects, the bone marrow stimulation (e.g. microfracturing) or addition of marrow concentrate is not necessary. MaioregenTM should not be used in patients with advanced osteoarthritic conditions, immune system disorders, neoplastic diseases, infectious diseases, obesity (BMI > 30), or above 60 years of age [19].

MeRG®

MeRG® (Bioteck S.p.A., Italy) is a microfibrillar collagen membrane that is inserted in the chondral lesion after microfracture. The fixation can be done by gluing. The scaffold protects and shields the cells to form new tissue. The only reported contra-indication of MeRG® is a hypersensitivity to collagen [20].

MeRG®
Matrix aus Kollagen

Comparators

For small cartilage lesions, microfracture surgery alone (or microfracturing) is considered the gold standard (information from the submitting hospital). Thus, the main comparator in this review is microfracture surgery alone

Mikrofrakturierung als Hauptvergleich

For larger defects (>2.5 cm^2 according to the submitting hospital), the autologous chondrocyte implantation (ACI) is indicated, which may also be used in combination with a matrix (MACI). Thus, (M)ACI was considered as an additional comparator.

(M)ACI als zusätzlicher Vergleich

The individual interventions are further explained in Chapter 4 (Element ID A0025 – How is the disease or health condition currently managed according to published guidelines and in practice?).

Übersicht Interventionen

A0020 – For which indications has the technology received marketing authorisation or CE marking?

There are different manufacturers providing several products for single-step matrix-assisted cartilage repair, whereas all products have marketing authorisation within Europe (CE mark).

verschiedene Produkte, alle mit CE-Zertifikat

The different products of the individual manufacturers and the year of CE approval are summarised in the following table.

Übersichtstabelle

Table 3-1: Overview of European marketing authorisation of individual products

Product	Manufacturer	CE marking
BST-CarGel®	Primal Enterprises Limited	Yes (2014)
CaReS®-1S	Arthro Kinetics AG	Yes (year unknown)
Chondro-Gide®	Geistlich Pharma	Yes (2010)
Chondrotissue®	BioTissue Technologies GmbH	Yes (year unknown)
GelrinC	Regentis Biomaterials Ltd.	Yes (2013)
Hyalofast®	Anika Therapeutics, Inc.	Yes (2009)
Maioregen™	Fin-Ceramica Faenza S.p.A.	Yes (year unknown)
MeRG®	Bioteck S.p.A.	Yes (2012)

References: individual manufacturers' websites

B0002 – What is the claimed benefit of the technique in relation to the comparators?

Schmerzlinderung, Wiederherstellung Funktion

Single-step treatment by the use of a scaffold is a technique for the repair of chondral or osteochondral defects. The technique is intended to achieve pain relief and to restore the functionality of the affected joint to regain mobility and previous lifestyle – like all interventions for cartilage repair [9, 21].

Verlangsamung Gelenkabnutzung

Furthermore, the technique aims at slowing down joint degeneration with the intent to avoid or delay osteoarthrosis and partial or total joint replacement surgery [8, 11].

Behandlung größerer Defekte

The scaffold-based single-step treatment of cartilage damages is used as an add-on intervention to microfracturing. Thus, the procedure enables the treatment of larger cartilage defects than microfracturing alone. Furthermore, a better microenvironment and structure for cell proliferation has been stipulated for the scaffolds, compared to microfracturing alone [3, 10].

einzeitiger Eingriff

In comparison to (M)ACI, the technique claims the advantage of the single-step procedure, sparing the need for a second intervention (one for biopsy and one for the implant), resulting in fewer complications and lower costs, but at comparable effectiveness with regards to clinical outcomes [22, 23].

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

B0004 – Who administers the technology and the comparators and in what context and level of care are they provided?

Operationen an Gelenksknorpel von Orthopäden auszuführen

The single-step treatment by the use of a scaffold and also microfracturing and (M)ACI should be performed by an orthopaedic surgeon with the support of two persons of the nursing staff. The procedures can be done under general or spinal anaesthesia. Microfracturing, the single-step treatment by the use of a scaffold, and (M)ACI can be done in an outpatient facility [3, 9, 11, 22].

B0008 – What kind of special premises are needed to use the technology and the comparator(s)?

steriler OP notwendig

For all surgical interventions of chondral or osteochondral repair a sterile operation theatre is suggested. Moreover, several instruments are required. Additionally, for the single-step treatment and for MACI, the matrix is needed to allow the cells to be seeded (see also Element ID B0001) [5, 11, 22, 24].

für ACI und MACI: Labor

Furthermore, for (M)ACI, a laboratory is needed for cell culturing and expansion (see also Element ID B0001) [25].

B0009 – What supplies are needed to use AMIC and the comparator(s)?

siehe B0008

See Element ID B0008.

Regulatory & reimbursement status

A0021 – What is the reimbursement status of AMIC?

Intervention in Österreich derzeit nicht erstattet

At this point in time, the single-step scaffold-based repair of cartilage defects or osteochondritis dissecans (OCD) or (osteo)chondral lesions in the knee joint is not included in the Austrian hospital benefit catalogue. Therefore, the intervention itself is not reimbursed by the Austrian health care system. However, the intervention could be billed under another code, like for arthroscopic operations of the knee joint (Code NF020 – Arthroskopische Operationen des Kniegelenks).

4 Health Problem and Current Use

Overview of the disease or health condition

A0001 – For which health conditions, and for what purposes is the technology used?

The scaffolds described in chapter 3 (Element ID B0001 – What is the technology and the comparators?) are intended for the treatment of articular chondral or osteochondral lesions [4, 6, 11].

Behandlung chondraler oder osteochondraler Schäden

A0002 – What is the disease or health condition in the scope of this assessment?

This systematic review will focus on the treatment of chondral and osteochondral lesions in the knee.

Fokus auf Schäden in Kniegelenk

A0003 – What are the known risk factors for the disease or health condition?

Articular (chondral) cartilage is a thin layer of connective tissue. It provides a smooth surface for articulation and facilitates the transmission of forces to the underlying subchondral bone.

Knorpel ist dünne Gewebsschicht

A damage of the cartilage can occur due to traumatic events, degeneration of the joint or due to osteochondritis dissecans (OCD). The damage can also affect the underlying bone (i.e. osteochondral lesion) [3, 4, 25].

mehrere Ursachen:

For instance, traumatic events can be caused by sport injuries (e.g. ski accidents), or incorrect weight-bearing. Altered biomechanics within the joint, due to previous injuries and/or surgical interventions can also play a role. [24, 26].

durch Trauma

Moreover, degenerative cartilage damage of the joint is common in elderly people. Due to the abrasion, particularly in the weight-bearing joints, over the years, structural integrity of the cartilage surface (and eventually also the underlying bone) can be affected [8, 24].

durch Abnutzung

Osteochondritis dissecans – an acquired idiopathic lesion of subchondral bone characterised by osseous resorption, collapse, and sequestrum formation – can possibly involve the damage of articular cartilage [4]. Thus, OCD is also a cause for an osteochondral lesion and defective cartilage.

durch Osteochondritis dissecans

A0004 – What is the natural course of the disease or health condition?

A chondral and osteochondral lesion is a debilitating condition. The damage can occur in nearly every phase of life. However, besides older people (with degenerative cartilage damage), especially young and active people are likely to acquire chondral or osteochondral lesions. Due to the low intrinsic healing capacity of human articular cartilage, spontaneous healing of the damaged tissue cannot be expected. Besides pain and functional impairment, cartilage lesions can lead to the development of osteoarthritis [11, 26].

(Knochen-)Knorpelschaden vor allem bei älteren und jungen, sportlich aktiven Menschen

There are various grading systems for (osteo)chondral defects and OCD, mainly determined by the type of diagnostic examination (e.g. MRI or arthroscopy) [27-29]. The classification systems – mainly used in German speaking countries – are shown in the following four tables.

verschiedene Klassifikations-Systeme

Table 4-1: Classification of chondral defects by ICRS

Grade/stage	Characteristics
0	Normal
1	Nearly normal (soft indentation and/or superficial fissures and cracks)
2	Abnormal (lesions extending down to <50% of cartilage depth
3	Severely abnormal (carilage defects >50% of cartilage depth
4	Severely abnormal (through the subchondral bone)

Reference: [27]

Table 4-2: Classification of chondral defects by Outerbridge

Grade/stage	Characteristics
0	Normal
1	Softening and swelling of cartilage
2	Fragmentation and fissuring, less than 1.5 cm-in diameter
3	Fragmentation and fissuring, greater than 1.5 cm in diameter
4	Erosion of cartilage down to exposed subchondral bone

Reference: [27]

Table 4-3: Classification of OCD/osteochondral defects by Kramer

Grade/stage	Characteristics
1	Bone marrow oedema
2	Demarked bone, possibly altered cartilage
3	Partial osteochondral fissure, partial discontinued cartilage
5	Entire osteochondral fissure, completely discontinued cartilage
6	Dislocated OCD

Reference: [28]

Table 4-4: Classification of OCD/osteochondral defects by Guhl

Grade/stage	Characteristics
1	Normal articular cartilage
2	Fragmentation in situ
3	Partial detachment
4	Complete detachment, loose body present

Reference: [30]

Effects of the disease or health condition on the individual and society

A0005 – What is the burden of disease for patients with the disease or health condition?

Schmerzen, Bewegungseinschränkungen

Patients with chondral and osteochondral defects are suffering from pain and impaired mobility, leading to a lower quality of life [8].

vorzeitige Osteoarthritis, bis zu Gelenksersatz

In addition, the chondral or osteochondral lesion can lead to the development of degenerative osteoarthritis and a further progression can lead to the requirement of a joint replacement [11, 24].

A0006 – What are the consequences of the disease or health condition for the society?

in 2014 fast 80.000 Op's an Kniegelenk in Ö

In 2014 in Austria, nearly 80,000 surgeries of the knee joint were performed [31]. However, no information regarding the prevalence or incidence of cartilage disorders or OCD (especially for Grade 3-4 of the Outerbridge classification) have been identified.

Current clinical management of the disease or health condition

A0024 – How is the disease or health condition currently diagnosed according to published guidelines and in practice?

keine österreichischen, dafür 3 internationale Leitlinien identifiziert

No Austrian guidelines for the diagnosis (and treatment) of (osteo)chondral defects or OCD were identified. We identified two international guidelines for the treatment of OCD and one for articular cartilage lesions [32-34].

zunächst klinische Diagnostik: Inspektion, Palpation, Funktionstest

First of all, there should be a physical examination of the affected joint. This includes an inspection (swelling of the joint, gait, etc.), palpation (pressure pain, extrusion in the joint, etc.) and specific tests for functioning and pain (motion, Wilson's test[2], etc.) [32-34].

danach Einsatz bildgebende Verfahren

As a second step, the affected joint should be examined by diagnostic imaging, i.e. X-rays and/or magnetic resonance imaging (MRI) [32, 33, 35].

Röntgen

X-rays provide detailed pictures of dense structures, like bone. An X-ray of the affected joint is essential to clarify if the underlying bone is also affected [32, 33, 35].

Magnetresonanztomografie

In comparison to X-rays, MRI can create better images of soft tissues like cartilage. An MRI should be performed in addition to X-Ray to evaluate the extent to which the overlying cartilage is affected [32, 33, 35].

weitere bildgebende Verfahren

Alternative diagnostic imaging techniques, like ultrasound, computed tomography, or arthroscopy can also be used [32, 33].

A0025 – How is the disease or health condition currently managed according to published guidelines and in practice?

zahlreiche Behandlungsoptionen

There are numerous treatment options for (osteo)chondral lesions or OCD, starting with conservative treatment and followed by surgical interventions [32-35].

[2] Pain with internally rotating the tibia during extension of the knee between 90° and 30°, then relieving the pain with tibial external rotation.

Beseitung Schaden als primäres Ziel

Generally, the treatment of chondral or osteochondral lesions aims at pain reduction, regaining joint mobility, reactivation of the affected area, preventing/slowing of the progression and prevention of osteoarthritis, and eventually avoiding total joint replacement [32, 34, 35].

konservative Behandlung

Conservative treatment includes physical therapy (e.g. progressive knee motion), partial weight-bearing or activity restrictions and pain management [32-35].

chirurgische Behandlung

A variety of surgical techniques and associated devices have evolved, aiming at resurfacing and repairing the (osteo)chondral lesions. However, none of the identified guidelines recommends one specific surgical intervention. The application of the individual techniques depends on several factors, like defect size (or grade) and localisation, age of the patient, or grade of discomfort [32, 33, 35].

Lavage: Reinigung

Arthroscopic lavage (or debridement) is a "cleaning up" procedure of the (knee) joint. This intervention is a short term solution and is not considered as a chondral repair procedure. Lavage is rather a palliative treatment to reduce pain, mechanical restriction, and inflammation. Lavage focusses on removing degenerative articular cartilage flaps and fibrous tissue [6, 21].

Stimulation Knochenmark

During *bone marrow stimulating techniques (e.g. microfracuring)*, damaged cartilage is drilled or punched until the underlying bone is exposed. Thereby, the subchondral bone is perforated to generate a blood clot within the defect [7].

Mikrofrakturierung ist Technik der Knochenmarkstimulation

Microfracturing (MFx) is a repair surgical technique that works by means of creating tiny fractures (e.g. by drilling) in the subchondral bone. The underlying idea is to promote cartilage regeneration from a so-called "super-clot" (after bleeding from the bone marrow). The surgery is performed by arthroscopy after the joint is cleaned of calcified cartilage. Microfracturing has been declared the first-line treatment for focal cartilage defects by various sources. However, the procedure seems less effective in treating older patients, overweight patients, or cartilage lesions larger than 2.5 cm^2 [7, 24].

Autologe Chondrozyten Implantation: 2 Eingriffe

kann auch matrix-induziert sein

ACI (or ACT) is performed in different steps. In a first step, intact cartilage is sampled arthroscopically from a non-weightbearing area of the affected cartilage. The generated cells are then cultured in vitro until there are enough cells to be re-implanted into the cartilage lesion. These autologous cells should adapt themselves to their new environment by forming new tissue. If chondrocytes are applied onto the damaged area in combination with a membrane (tibial periosteum or biomembrane) or pre-seeded in a scaffold matrix, this technique is called MACI. The intention of (M)ACI is to treat larger defect sizes than MFx [24-26].

autologe osteochondrale Transplantate

Another treatment option is *autologous osteochondral transplantation* (osteoarticular transfer system or mosaicplasty). During mosaicplasty (MP), the unhealthy tissue is removed to leave the healthy bone underneath. The surgeon obtains the healthy tissue, for instance from a non-weight-bearing area, which will be placed into the holes in the joint until it forms a smooth surface. It may require multiple plugs to fill the gaps in the joint surface. This gives the repaired surface the appearance of a mosaic. The intervention can be done arthroscopically. However, MP is intended for the treatment of small sized lesions (up to 2 cm^2) [6, 21]. Since MFx is declared as the first-line treatment of small cartilage damages, we did not consider MP as a comparator.

osteochondrales Transplant von Spender oder künstliches Gelenk

In later stages of (osteo)chondral lesions, especially associated with an extensive bone loss, patients can be treated by osteochondral allografts (coming from a donor) or by a total knee/joint replacement [6].

Target population

A0007 – What is the target population in this assessment?

Zielpopulation

The target population in this assessment are patients with chondral or osteochondral lesions (or OCD).

diverse Einschränkungen seitens Hersteller

However, there are several population restrictions given by the individual manufacturers of the matrices (see Chapter 3). A selection is provided below, representing the most overlapping specifications [14, 15, 19]:

- ICRS or Outerbridge classification Grade 3 and 4
- Defect size 1-8 cm^2
- Age 18+ (some manufacturers have also restrictions regarding a maximum age)
- Patients without two or more corresponding cartilage defects or an allergy to one of the scaffold components.

A0011 – How much is the technology utilised?

geschätzte Erbringung in einreichendem KH: 15 p.a.

Based on the information given on the VAEV, the estimated annual utilisation of the matrix-assisted single-step scaffold-assisted cartilage repair in the submitting hospital is around 15.

keine Angaben zu jährlicher Erbringung in Gesamtösterreich

There is no information provided regarding the estimated annual utilisation in Austria.

5 Clinical effectiveness

5.1 Outcomes

entscheidende Endpunkte für Wirksamkeit

The following outcomes were defined as *crucial* to derive a recommendation:

- Mobility/joint functionality
- Quality of life
- Pain
- Necessity of a total joint replacement

Wahl Endpunkte, die Ziele der Behandlung von (Knochen-)Knorpelschäden am besten repräsentieren

The outcomes chosen represent the aims of a treatment of chondral and osteochondral defects (see Element ID A0005 – What is the burden of disease for patients with the disease or health condition?): pain reduction, regaining joint mobility, reactivation of the affected area, prevention/delay of disease progression, and prevention of osteoarthritis and/or avoiding total knee replacement.

Mobilität/ Funktion Gelenk

Mobility or joint functionality (before and after the intervention) can be measured by different scores [29]:

- Knee Injury and Osteoarthritis Outcome Score (KOOS),
- International Knee Documentation Committee (IKDC) Subjective Knee Form,
- Western Ontario McMaster Universities Osteoarthritis Index (WOMAC),
- Modified Cincinnati Knee Rating System,
- Short Form 36 (SF-36),
- Lysholm scoring scale,
- Modified International Cartilage Repair Society (ICRS) Score.

Lebensqualität

Quality of life can also be measured by several scores, like the EQ-5D and the Short-Form Health Survey (SF-36, SF-12, SF-8).

Schmerzen

Pain was defined as another crucial outcome, since it is considered a main contributor to symptom burden in patients suffering from (osteo)chondral defects. It can be measured with several instruments, e.g. dedicated visual analogue pain scales (VAS).

verwendete Messinstrumente später erklärt

The individual scores to measure joint functionality or mobility, quality of life, and pain will be further explained later in this chapter and in the evidence tables (see Appendix) where applicable.

Notwendigkeit Gelenksersatz als Langzeitoutcome

Since one major aim of the treatment of chondral and osteochondral defects is to avoid progression of the disease and joint replacement, the necessity of a joint replacement was considered as a crucial long-term outcome.

weiterer Endpunkt zur Beantwortung Fragen

A further outcome that was not considered crucial, but was used to answer the effectiveness-related research questions in this chapter is “return to activities” (like sports or daily activities).

5.2 Included studies

kontrollierte Studien für Wirksamkeitsendpunkte

For evaluating efficacy-related outcomes, we exclusively considered RCTs and prospective non-randomised controlled trials (see Chapter 1.2).

keine Studien im Vergleich zu (M)ACI

We could not identify any controlled trials comparing the single-step scaffold-assisted treatment of (osteo)chondral defects in the knee with (M)ACI.

2 RCTs, 1 non-RCT zu einzeitiger matrix-assistierter Behandlung von Knorpeldefekten im Kniegelenk

The only studies that met our inclusion criteria were two randomised controlled trials[3] (RCTs) [36-38] and one non-randomised controlled trial (non-randomised CT) [39] with a total of 136 patients assessing the clinical effectiveness of the single-step scaffold-assisted chondral repair in the knee joint (scaffold-groups) in combination with microfracturing (MFx), compared to MFx alone (MFx-groups) [36-39].

PatientInnen: Ø 33-38 vs. 37-41 Jahre, 15-44 vs. 20-36 % Frauen, Stadium 3-4, Nachbetrachtungszeit 6-60 Monate

The mean age of patients ranged from 33 to 38 years in the treatment groups and from 37 to 41 years in the control groups across trials. Between 15 and 44% of the patients in the scaffold-groups and 20-36% of the patients in the control groups were females across trials. Patients had grade 3 to 4 (Outerbridge Classification) of chondral defects with a mean lesion size of 2.3-3.7 cm^2 in the scaffold-groups and 2-2.9 cm^2 in the control groups. The follow-up of the studies was 6, 24 and up to 60 months (5 years) [36-39].

Produkte: Chondro-Gide®, BST-CarGel®

In one study, it was Chondro-Gide® [37], in another BST-CarGel® [36, 38], and in the third study, a polyethylene glycol diacylate hydrogel (comparable to GelrinC®) that were applied [39].

keine Studien zu anderen Produkten

There were no studies assessing the clinical effectiveness of other products, like CaReS®-1S, Chondrotissue®, Maioregen™ or MeRG® (see Chapter 3) that met our inclusion criteria.

Extraktionstabellen in Anhang

Study characteristics and results of included studies are displayed in Table A-1 and in the evidence profile in Table 7-1.

5.3 Results

Morbidity

D0005 – How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?

Beantwortung Frage anhand Endpunkt „Mobilität/ Gelenksfunktion"

Answering this research question was based on the outcome "mobility/joint functionality".

Single-step scaffold-based treatment + MFx vs. MFx

in drei Studien berichtet

The effect on mobility or joint functionality was measured in all three controlled trials by five different scoring systems, comparing the scaffold-based single-step cartilage repair plus microfracturing with microfracturing alone [36-39].

[3] Data from 2 publications of one study population, presenting results after 1 year and results after 5 years of follow-up, are presented together.

In one RCT with 28 patients and two scaffold groups (one group received a glued, the other group a sutured scaffold), the joint functionality was measured with the Modified Cincinnati Score[4] (scale: 6-100) and with (a modified) ICRS Score[5] [37]. The Modified Cincinnati Score increased in all study groups over time. After 24 months, the score improved by 46 and 37 points in both treatment groups and by 44 points in the control group. The difference of the change between the study groups was statistically not significant. For the change of the ICRS Score, it was only stated that there were no statistically significant differences between the study groups after 12 and 24 months of follow-up, without reporting numerical results [37].

Messung anhand modifizierter Cincinnati Score: kontinuierliche Verbesserung, Unterschied zwischen Gruppen nicht signifikant

In the second RCT, joint functionality was measured with the WOMAC[6] subscale scores for stiffness (scale: 0-20) and for function (scale: 0-170). After 12 months, the score for stiffness improved by nearly 6 points in the treatment group and by ca. 6.6 points in the control group. After 60 months (compared to baseline), the score improved by 5.6 points in the treatment group and by 6.7 points in the control group. The score for function improved in both study groups over time. After 60 months, the score improved by ca. 57 points in the scaffold-group and by ca. 62 points in the MFx-group. The changes of WOMAC sub-scores between the study groups were statistically not significant at any time point [36, 38].

Messung anhand WOMAC Scores für Steifigkeit und Funktion: Verbesserung, aber Gruppen-Unterschied nicht signifikant

In the non-randomised CT, joint functionality was measured with the IKDC Score[7]. However, it was only stated that there were no statistically significant differences of the score changes between the study groups after 3 and 6 months of follow-up [39].

Messung anhand IKDC Score: kein signifikanter Gruppen-Unterschied

Single-step scaffold-based treatment + MFx vs. (M)ACI

There was no evidence available assessing the effect of a single-step scaffold-assisted cartilage repair (combined with MFx) on "mobility or joint functionality", compared to (M)ACI.

keine Evidenz

D0006 – How does the technology affect progression (or recurrence) of the disease or health condition?

To answer this research question, the outcome "necessity of a total joint replacement" was used to measure the progression of the disease. Thus, the higher the rate of the total joint replacement, the less is the effect of the intervention of the disease progression.

Beantwortung Frage anhand Endpunkt „Notwendigkeit eines Gelenksersatz"

[4] The Modified Cincinnati Score consists of three parts: knee function (6-30 points), clinical pathology (0-20 points), highest activity level without pain (0-50 points).

[5] The Modified ICRS (International Cartilage Repair Society) Score consists of ratings by the patient (pain, functional status of knee) and the surgeon (functional status knee, classification + crepitation).

[6] The WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) scoring system includes pain, stiffness, and physical function, measured on a visual analogue scale (VAS).

[7] The IKDC (International Knee Documentation Committee) scoring system includes 10 items investigating symptoms, function, and return to sporting activities.

Single-step scaffold-based treatment + MFx vs. MFx

in einem RCT während 2 Jahren Nachbeobachtung ein künstliches Gelenk in Behandlungsgruppe

The necessity of a total joint replacement was reported in one RCT with 28 patients and 24 months of follow-up. In one patient who received a (glued) scaffold, the knee joint had to be replaced. In none of the patients who underwent MFx alone, the joint had to be replaced (likewise for patients who received a sutured scaffold) [37].

Single-step scaffold-based treatment + MFx vs. (M)ACI

keine Evidenz

There was no evidence available assessing the effect of a single-step scaffold-assisted cartilage repair (combined with MFx) on "necessity of a total joint replacement", compared to (M)ACI.

Function

D0016 – How does the use of the technology affect activities of daily living?

Beantwortung anhand Endpunkt „Wiedererlangung Aktivitäten"

Answering this research question was based on the outcome "return to activities".

Single-step scaffold-based treatment + MFx vs. MFx

keine Evidenz

This outcome was not reported in any of the identified studies comparing the single-step scaffold-based treatment with MFx.

Single-step scaffold-based treatment + MFx vs. (M)ACI

keine Evidenz

There was no evidence available assessing the effect of a single-step scaffold-assisted cartilage repair (combined with MFx) on "return to activities", compared to (M)ACI.

Health-related quality of life

D0012 – What is the effect of the technology on generic health-related quality of life?

Single-step scaffold-based treatment + MFx vs. MFx

Verbesserung bei psychischer Komponente des SF-36, kein signifikanter Unterschied zwischen Gruppen

The generic quality of life was measured in one RCT (with initially 80 patients) using the mental components of the SF-36 (version 2)[8]. After 12 months, the score improved by 13 points in the treatment group and by ca. 14.8 points in the control group. After 60 months (compared to baseline), the score improved by 13.1 points in the treatment group and by 14.5 points in the control group. The differences in changes of the scores between the study groups were statistically not significant at both time points [36, 38].

Single-step scaffold-based treatment + MFx vs. (M)ACI

keine Evidenz

There was no evidence available assessing the effect of a single-step scaffold-assisted cartilage repair (combined with MFx) on generic health-related quality of life, compared to (M)ACI.

[8] The Short-Form Health Survey (SF-36) version 2 is an eight-scale profile of functional health and well-being scores plus summary components of physical and mental health.

D0013 – What is the effect of the technology on disease-specific quality of life?

Single-step scaffold-based treatment vs. MFx

physische Komponente des SF-36, kein signifikanter Unterschied zwischen Gruppen bei Veränderung

The disease-specific quality of life was measured in one RCT (with initially 80 patients) using the physical component of the SF-36 (version 2)[8]. After 12 months, the score increased by 3.5 points in the treatment group and by ca. 0.8 points in the control group. After 60 months (compared to baseline), the score increased by 2.7 points in the treatment group and decreased by nearly 0.2 points in the control group. The difference in changes of the score between the study groups was statistically not significant at either time points [36, 38].

Schmerzen zusätzlich berichtet

Additionally, since (osteo)chondral defects can cause pain, resulting in a low quality of life, the results of the treatments on pain are presented as well. Pain was measured in all of the included studies, however, the methods of measurement differed.

visuelle Analogskala: Verringerung Schmerzen, kein signifikanter Gruppenunterschied

In one RCT, pain was measured on a visual analogue scale (scale: 0-100). The score for pain decreased (improved) over time in both treatment groups. After 12 months, the score improved by 32 points in the treatment and the control group, respectively. After 24 months (compared to baseline), the score improved by 37 points in the treatment group and by 38 points in the control group. The difference in changes of the scores between the study groups was statistically not significant at either time points [37].

WOMAC Score: Verringerung Schmerzen, kein signifikanter Gruppenunterschied nach 5 Jahren

In the other identified RCT, pain was measured with the WOMAC[9] subscale score for pain (scale: 0-50). After 12 months, the score improved by 16.2 points in the treatment group and by ca. 16.9 points in the control group. After 60 months (compared to baseline), the score improved by 15.4 points in the treatment group and by 16.6 points in the control group. The difference in changes of the scores between the study groups was statistically not significant at either time points [36, 38].

in nicht-randomisierter kontrollierter Studie: Stärke und Frequenz der Schmerzen verringert, keine Aussagen zu Signifikanz

In the identified non-randomised CT, the severity and frequency of pain was measured. However, it was not stated on which scale or scoring system the measurement was based on. After six months, the score for the severity of pain improved by 32.1 points in the treatment group and by 15.3 points in the control group. The score for the frequency of pain improved after 6 months of follow-up by 52.9 points in the treatment group and by 41 points in the control group. It was not stated whether the differences between study groups in changes were statistically significant or not [39].

Single-step scaffold-based treatment + MFx vs. (M)ACI

keine Evidenz

There was no evidence available assessing the effect of a single-step scaffold-assisted cartilage repair (combined with MFx) on disease-specific quality of life, compared to (M)ACI.

[9] The WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) scoring system includes pain, stiffness and physical function, measured on a visual analogue scale (VAS).

6 Safety

6.1 Outcomes

The following outcomes were defined as *crucial* to derive a recommendation:

entscheidende Endpunkte für Sicherheit

- Procedure-related complications
- Device-related complications
- Re-operations rate

Procedure-related adverse events are complications that are associated with the surgical intervention. Possible procedure-related complications are events associated with anaesthesia, infections, damages to nerves or blood vessels, bleeding, or the occurrence of blood clots (e.g. thrombosis).

eingriffsbezogene Komplikationen

Device-related complications are adverse event associated with the implantation of the scaffold. Possible complications are, e.g. movement or release of the scaffold or allergic reactions.

implantatbezogene Komplikationen

The re-operation rate shows how often patients had to undergo additional surgeries. It was chosen as an indicator for (major) adverse events.

Reoperationsrate

6.2 Included Studies

For evaluating safety-related outcomes, we considered RCTs, prospective non-randomised controlled trials, and prospective single-arm studies, the latter only in case they included at least 50 patients and had a follow-up of at least 24 months (see Chapter 1.2).

(un)kontrollierte Studien für Sicherheit

We could not identify any clinical trials comparing the single-step scaffold-assisted treatment of chondral defects in the knee with (M)ACI.

keine Studien im Vergleich zu (M)ACI

The only studies that met our inclusion criteria were two RCTs[10] [36-38] and one non-randomised CT [39] with a total of 136 patients, assessing the safety of the single-step scaffold-assisted cartilage repair in the knee. Of the 136 patients, 84 received single-step scaffold-supported intervention and the remaining 52 were in the control groups.

3 Studien mit 136 PatientInnen

The included controlled trials compared the single-step scaffold-assisted chondral repair in the knee joint (scaffold-groups) in combination with microfracturing (MFx) [36-39], compared to MFx alone (MFx-groups) [36-39].

Studien zu chondralen Läsionen im Kniegelenk

The mean age of patients ranged from 33 to 38 years in the treatment groups and from 37 to 41 years in the control groups across trials. Between 15 and 44% of the patients in the scaffold-groups and 20-36% of the patients in the control groups were females across trials. Patients had grade 3 to 4 (Outerbridge Classification) of chondral defects. The follow-up of the studies was 6, 24 and up to 60 months (5 years) [36-39].

PatientInnen: Ø 33-38 vs. 37-41 Jahre, 15-44 vs. 20-36 % Frauen, Stadium 3-4, Nachbetrachtungszeit 6-60 Monate

[10] Data from 2 publications of one study population, presenting results after 1 year and results after 5 years follow-up, are presented together.

Produkte: Chondro-Gide®, BST-CarGel®

In one study, it was Chondro-Gide® [37], in another, BST-CarGel® [36, 38], and in the third study, a polyethylene glycol diacylate hydrogel (comparable to GelrinC®) that were applied [39].

keine Studien zu anderen Produkten

There were no studies assessing the clinical effectiveness of other products, like CaReS®-1S, Chondrotissue®, Maioregen™ or MeRG® (see Chapter 3) that met our inclusion criteria.

Extraktionstabellen in Anhang

Study characteristics and results of included studies are displayed in Table A-1 and in the evidence profile in Table 7-1.

6.3 Results

Patient safety

C0008 – How safe is the technology in comparison to the comparator(s)?

Single-step scaffold-based treatment + MFx vs. MFx

eingriffsbezogene Komplikationen: 0-93 % vs. 0-77 %

Adverse events – that were *related to the surgical procedure*, in comparison to MFx – were reported in two RCTs [36-38] and in one non-randomised CT [39]. The reported rates ranged from 0 to 93% in the scaffold-groups and from 0 to 77% in the MFx-groups [36-39].

implantatsbezogene Komplikationen: 0-22 %

Adverse events – that were *related to the scaffold* – occurred in 0-22% of the patients (reported in two RCTs) [36-38]. Since the control groups did not receive a scaffold, no scaffold-related complications occurred.

keine umfangreichen Details zu Komplikationen

In none of the identified studies it was clearly stated which kind of adverse events occurred. In one study, it was stated that one patient in the treatment group had mild haemarthrosis [39]. In another study, it was stated in general terms that the most frequent adverse were arthralgia, pain, and nausea in the treatment group, and arthralgia and pain in the control group [36, 38].

Reoperationen nicht berichtet

Moreover, in none of the identified studies it was stated if any re-operations were necessary.

Single-step scaffold-based treatment + MFx vs. (M)ACI

keine Evidenz

There was no evidence available assessing the safety of a single-step scaffold-assisted cartilage repair (combined with MFx), compared to (M)ACI.

C0004 – How does the frequency or severity of harms change over time or in different settings?

keine verlässliche Evidenz

Based on the identified evidence, this research question cannot be answered in an appropriate way.

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of the technology?

keine Evidenz

No direct evidence was found to answer this research question.

C0007 – Are the technology and comparator(s) associated with user-dependent harms?

keine Evidenz

No direct evidence was found to answer this research question.

7 Quality of evidence

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme [2] for each endpoint, individually. Each study was rated by two independent researchers. In case of disagreement a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [2].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

GRADE-Tabelle nächste Seite

The ranking according to the GRADE scheme for the research question can be found in Table 7-1.

Gesamtstärke Evidenz gering

Overall, the strength of evidence evaluating the effectiveness and safety of single-step scaffold-based cartilage repair of the knee in combination with microfracturing compared to microfracturing alone is “low”.

Evidenzstärke bei vereinzelten Outcomes moderat

Exceptions are the results from one RCT [36, 38] regarding the measurement of joint functionality and pain (measured with the WOMAC subscale scores for function, stiffness and pain). Even though the patient number of this RCT was small, the standard deviations of these outcomes were low and baseline values between the study groups were similar. Another exception is the outcome “necessity of total joint replacement”, reported in another RCT [37]. The strength of evidence of these outcomes was rated as “moderate”.

keine Evidenz mit (M)ACI als Vergleich

For the comparison to (matrix-assisted) autologous chondrocyte implantation no evidence was available.

Table 7-1: Evidence profile: efficacy and safety of single-step cartilage repair of knee joints with a scaffold in combination with microfracturing in comparison to microfracturing alone (results of controlled trials)

No of studies/ patients	Study Design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Efficacy							
Mobility/joint functionality: change from baseline (IKDC Score: 0-100)							
1/18	CT	3 mo: n/a; p=N.S.	Serious limitations (-1)[11]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Very low
1/18	CT	6 mo: n/a; p=N.S	Serious limitations (-1)[11]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Very low
Mobility/joint functionality: change from baseline (Modified ICRS Score)							
1/30	RCT	12 mo: n/a; p=N.S.	Serious limitations (-1)[13]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Low
1/27	RCT	24 mo: n/a; p=N.S.	Serious limitations (-1)[13]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Low
Mobility/joint functionality: change from baseline (Modified Cincinnati Score: 6-100)							
1/30	RCT	12 mo[14]: +35 (±29)/+19 (±22) vs. +31 (±13); p=N.S.	Serious limitations (-1)[15]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Low
1/27	RCT	24 mo[14]: +46 (±17)/+37 (±14) vs. +44 (±15); p=N.S.	Serious limitations (-1)[15]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Low
Mobility/joint functionality: change from baseline (WOMAC subscale score for stiffeness: 0-20)							
1/78	RCT	12 mo: -5.97 (±0.68) vs. -6.56 (±0.71); p=N.S.	Serious limitations (-1)[16]	n/a (only 1 trial)	Direct	None	Moderate
1/59	RCT	60 mo: -5.63 (±0.72) vs. -6.68 (±0.58); p=N.S.	Serious limitations (-1)[17]	n/a (only 1 trial)	Direct	None	Moderate
Mobility/joint functionality: change from baseline (WOMAC subscale score for function: 0-170)							
1/78	RCT	12 mo: -55.96 (±4.24) vs. -60.59 (±4.41); p=N.S.	Serious limitations (-1)[16]	n/a (only 1 trial)	Direct	None	Moderate
1/59	RCT	60 mo: -56.52 (±4.57) vs. -62.10 (±3.43); p=N.S.	Serious limitations (-1)[17]	n/a (only 1 trial)	Direct	None	Moderate

[11] High risk of bias due to likely confounding (patient's baseline characteristics not comprehensively provided or controlled for), selection of participants (study protocol was switched from "randomised" to "non-randomised", unclear consecutively patients' recruiting) and outcome measurement (subjective measurement, patients + personnel were aware of intervention).

[12] Low incidence/patient numbers.

[13] High risk of bias due to likely selective outcome reporting (unclear approach for assessing Modified ICRS + values not stated, not study protocol), no blinding (patients + personnel were aware of intervention) and other aspects (study is interim analysis, no adherence of possible effects of physiotherapy or pain killers).

[14] Two treatment modalities were used in the scaffold-arm: one group received a sutured and the other group received a glued scaffold.

[15] High risk of bias due to no blinding (patients + personnel were aware of intervention) and other aspects (study is interim analysis, no adherence of possible effects of physiotherapy or pain killers).

[16] High risk of bias due to unclear allocation concealment, no blinding (patients + personnel were aware of intervention) and other aspects (no adherence of possible effects of physiotherapy or pain killers).

[17] High risk of bias due to unclear allocation concealment, no blinding (patients + personnel were aware of intervention) and other aspects (no adherence of possible effects of physiotherapy or pain killers + post-hoc extension).

No of studies/ patients	Study Design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Quality of life: change from baseline (SF-36 physical component)							
1/78	RCT	12 mo: +13.02 (±1.5) vs. +14.76 (±1.52); p=N.S.	Serious limitations (-1)[16]	n/a (only 1 trial)	Direct	Imprecise data (-1)[19]	Low
1/59	RCT	60 mo: +13.12 (±1.63) vs. +14.48 (±1.42); p=N.S.	Serious limitations (-1)[18]	n/a (only 1 trial)	Direct	Imprecise data (-1)[19]	Low
Quality of life: change from baseline (SF-36 mental component)							
1/78	RCT	12 mo: +3.54 (±1.56) vs. +0.84 (±1.58); p=N.S.	Serious limitations (-1)[16]	n/a (only 1 trial)	Direct	Imprecise data (-1)[19]	Low
1/59	RCT	60 mo: +2.72 (±1.3) vs. -0.17 (±1.76); p=N.S.	Serious limitations (-1)[18]	n/a (only 1 trial)	Direct	Imprecise data (-1)[19]	Low
Pain: change from baseline (VAS: 0-100)							
1/30	RCT	12 mo[14]: -32 (±n/a)/-32 (±n/a) vs. -35 (±n/a); p=N.S.	Serious limitations (-1)[20]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Low
1/27	RCT	24 mo[14]: -37 (±n/a)/-38 (±n/a) vs. -49 (±n/a); p=N.S.	Serious limitations (-1)[20]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Low
Pain: change from baseline (WOMAC subscale score for pain: 0-50)							
1/78	RCT	12 mo: -16.16 (±1.16) vs. -16.91 (±1.21); p=N.S.	Serious limitations (-1)[16]	n/a (only 1 trial)	Direct	None	Moderate
1/59	RCT	60 mo: -15.37 (±1.47) vs. -16.56 (±1.19); p=N.S.	Serious limitations (-1)[17]	n/a (only 1 trial)	Direct	None	Moderate
Pain: change from baseline (severity)							
1/18	CT	3 mo:: -29 (±n/a) vs. -34.7 (±n/a); p=n/a	Serious limitations (-1)[21]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Very low
1/18	CT	6 mo:: -32.1 (±n/a) vs. -15.3 (±n/a); p=n/a	Serious limitations (-1)[21]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Very low
Pain: change from baseline (frequency)							
1/18	CT	3 mo:: -41 (±n/a) vs. -62.6 (±n/a); p=n/a	Serious limitations (-1)[21]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Very low
1/18	CT	6 mo:: -52.9 (±n/a) vs. -41 (±n/a); p=n/a	Serious limitations (-1)[21]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Very low
Necessity of total joint replacement (in % of patients)							
1/27	RCT[14]	24 mo: 0/8 vs. 0; p=n/a	No serious limitations[22]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Moderate

[18] High risk of bias due to unclear allocation concealment, no blinding (patients + personnel were aware of intervention) and other aspects (no adherence of possible effects of physiotherapy or pain killers + post-hoc extension). It is not clear how many patients were exactly included in analysis for quality of life.

[19] High margin of deviation, no baseline values stated.

[20] High risk of bias due to no blinding (patients + personnel were aware of intervention) and other aspects (study is interim analysis, no adherence of possible effects of physiotherapy or pain killers). Furthermore, values for dispersion / variability were not stated.

[21] High risk of bias due to likely confounding (patient's baseline characteristics not comprehensively provided or controlled for), selection of participants (study protocol was switched from "randomised" to "non-randomised", unclear consecutively patients' recruiting) and outcome measurement (subjective measurement, patients + personnel were aware of intervention). Furthermore, values for dispersion / variability were not stated and it was not stated if study-group-difference was statistically significant or not.

[22] Potentially, risk of bias due to missing study protocol and the fact that study is interim analysis. However, risk of bias was classified as low.

No of studies/ patients	Study Design	Estimate of effect	Study limitations	Inconsistency	Indirectness	Other modifying factors	Strength of evidence
Safety							
Procedure-related complications (in % of patients)							
1/18	CT	6 mo: 7 vs. 0	Serious limitations (-1)[23]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Very low
1/78	RCT	12 mo: 93 vs. 77; p=n/a	Serious limitations (-1)[24]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Low
1/38	RCT	24 mo: 0 vs. 0	Serious limitations (-1)[25]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Low
1/60	RCT	60 mo: 6 vs. 8; p=n/a	Serious limitations (-1)[26]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Low
Device-related complications (in % of patients)							
1/78	RCT	12 mo: 22 vs. -	No serious limitations[27]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Moderate
1/38	RCT	24 mo: 0 vs. -	Serious limitations (-1)[28]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Low
1/60	RCT	60 mo: 3 vs. -	Serious limitations (-1)[29]	n/a (only 1 trial)	Direct	Imprecise data (-1)[12]	Low
Re-operation rate (in % of patients): no evidence							

Abbreviations: CT = (non-randomised) controlled trial; ICRS = International Cartilage Repair Society; IKDC = International Knee Documentation Committee; mo = month(s); n/a = data not available; N.S. = not statistically significant; RCT = randomised controlled trial; SF-36 = Short-Form Health Survey; S.S. = statistically significant; vs. = versus; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: n/a: not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

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[23] High risk of bias due to likely confounding (patient's baseline characteristics not comprehensively provided or controlled for), selection of participants (study protocol was switched from "randomised" to "non-randomised", unclear consecutively patients' recruiting) and outcome measurement (patients + personnel were aware of intervention). Furthermore, it seems likely that procedure-related complications were not reported comprehensively and the definition of "procedure-related" complications was not stated.

[24] High risk of bias due to no blinding (patients + personnel were aware of intervention). Furthermore, it was not stated if study-group-difference was statistically significant or not. Furthermore, the definition of "procedure-related" complications was not stated.

[25] High risk of bias due to no blinding (patients + personnel were aware of intervention) and other aspects (study is interim analysis). Furthermore, it seems likely that procedure-related complications were not reported comprehensively and the definition of "procedure-related" complications was not stated.

[26] High risk of bias due no blinding (patients + personnel were aware of intervention) and other aspects (study is an extension). Furthermore, the definition of "procedure-related" complications was not stated.

[27] Potentially, risk of bias since the definition of "device-related" complications was not stated. However, risk of bias was classified as low.

[28] High risk of bias due to the fact, that study is interim analysis. Furthermore, it seems likely that device-related complications were not reported comprehensively and the definition of "device-related" complications was not stated.

[29] High risk of bias due to the fact, that study is an extension. Furthermore, the definition of "device-related" complications was not stated.

8 Discussion

Knorpeldefekte schwierig zu behandeln

Chondral or osteochondral lesions are difficult-to-treat entities that often affect young and active persons. Moreover, cartilage has limited intrinsic healing potential due to the fact that it is isolated from the systemic regulation and lacks vessels plus nerve supply, which contributed to the fact that cartilage healing remains challenging.

Schaden am Knorpel bedeutet Schmerzen

Chondral and osteochondral defects severely reduce the quality of life of the affected persons, especially due to the associated pain. Untreated or progressing defects can lead to osteoarthrosis and to the necessity to replace the affected joint in the long run.

Ziel: Bewertung Wirksamkeit + Sicherheit

The aim of this report was to assess the clinical effectiveness and safety of the single-step matrix-assisted cartilage repair in the knee joint (combined with microfracturing), compared to MFx alone or (M)ACI.

3 Studien mit Mikrofrakturierung als Vergleich

For assessing the clinical effectiveness and safety of the single-step matrix-assisted cartilage repair in the knee joint (combined with microfracturing) compared to *MFx alone*, we identified three clinical trials (two randomised trials and one non-randomised study) involving 168 patients that met our inclusion criteria.

in Studien 2 Produkte explizit genannt

All trials used different products of scaffolds: Chondro-Gide® and BST-CarGel®. Furthermore in one trial, a polyethylene glycol diacrylate hydrogel was used. Due to the same components, it is possible that the used product was GelrinC®. All of the identified studies included patients with chondral defects in the knee.

vergleichsweise kleine Defektgrößen

The mean defect sizes were slightly larger in the intervention groups compared to the control groups (2.3-3.7 vs. 2-2-9 cm^2). None of the studies included exclusively patients with defect sizes larger than 2.5 cm^2. However, the comparison to MFx alone would have not been ideal.

keine signifikanten Unterschiede bei Verbesserungen der Scores zu Funktion Gelenk, Schmerzen + Lebensqualität

The scores measuring the mobility or joint functionality and pain (reported in all three controlled trials) plus quality of life (measured in only one study) improved in the groups that received the single-step scaffold-assisted treatment (+ MFx) as well as in the groups that received MFx alone in a comparable extent. The differences of the improvements between the study groups were not significant in any of the studies [36-39].

Komplikationen: 0-93 % versus 0-77 % eingriffsbezogen 0-22 % implantatsbezogen

Complications were reported in all extracted studies. However, the complication rates between the studies differed considerably, keeping in mind that different follow-up periods might have contributed to this observation. Procedure-related adverse events occurred in 0-93% of the patients in the scaffold-groups (0-77% in the control groups) across studies. The rates for device-related complications differed from 0 to 22% across studies [36-39].

Studien suggerieren: Gleichwertigkeit einzeitiger matrix-assistierter Knorpelersatz

The clinical results are consistent in their suggestion that the single-step scaffold-assisted cartilage repair in combination with MFx leads to similar short to medium-term (up to five years follow-up) results, compared to MFx alone.

Evidenzstärke gering bis sehr gering, tw. bedingt durch Studiendesigns

However, the overall strength of evidence for clinical effectiveness and safety was determined as “low”. For the identified non-randomised CT this is due to the study design: the strength of evidence of observational studies generally starts with “low”. The strength of evidence of identified RCTs was mainly downgraded due to the fact that the outcomes were subjective and the patients as well as the assessing personnel were aware of the intervention.

relativ kleine Fallzahlen

A major issue of the identified trials is the low number of patients of each study. One RCT consisted of 80 patients, whereas the smallest controlled trial included only 18 patients. Especially for identifying rare (unanticipated) complications, these patient numbers might be insufficient. Small numbers are furthermore likely to have impacted the trials' ability to detect between-group differences in efficacy outcomes.

relativ kurze Nachbeobachtungszeiträume

Two of the studies had a relatively short follow-up of one year or less. Only one of the studies had a follow-up of at least five years. Therefore, reliable data of long-term efficacy and safety-related outcomes are missing.

Interventionen in Studien wichen teilweise leicht voneinander ab

The applied interventions differed slightly between the individual studies. First of all, in one study, the scaffold was a hydrogel and in the other studies it was a kind of "fleece". Another potential effect on the outcomes could be the fixation-technique of the scaffold (e.g. if it was glued or sutured). Furthermore, the MFx-procedure in the control groups was either performed arthroscopically or by miniarthrotomy.

Notwendigkeit Gelenksersatz in nur einer Studie berichtet

One outcome that was defined as crucial – necessity of a total joint replacement – was exclusively reported in only one trial (whereas one patient in the scaffold-group required a new joint). However, this outcome is important to assess the long-term efficacy of the treatment of chondral or osteochondral defects. It is however acknowledged that for meaningful prospective data to be collected on joint replacement rates, a very long follow-up and/or large samples might be necessary.

inkonsistente Angaben zu Komplikationen

Due to the incomprehensive or inconsistent screening, recording and/or reporting of adverse events across the majority of included studies, aggregated statements on the safety are barely possible. This was deemed an important shortcoming for the majority of included studies. In one RCT, it seems that adverse events were recorded systematically, resulting in a procedure-related complications rate of ca. 93% in the treatment group. In another RCT, the rates of procedure-related complications were only reported as 0%. This discrepancy hints at different approaches to safety. It has to be stated that due to the invasive nature of the interventions compared, an AE rate close to 0% could be questioned. Furthermore, in none of the studies was it clearly stated and sufficiently explained which adverse events occurred.

tw. unklare Angaben zu begleitenden Interventionen

Not all studies conclusively reported additional interventions (e.g. meniscectomies, etc.) during or before the initial surgery. However, it is possible that additional procedures have had an impact on the outcomes.

unklare Angaben zu Medikamentation

Moreover, it was barely reported if patients received additional medication after the surgical procedure or even in the long run, e.g. for symptom control. It is evident that e.g. the intake of painkillers at the time of follow-up could have impacted outcome assessment, like pain and quality of life.

eine Studie ursprünglich RCT, aber Randomisierung abgebrochen

One of the identified studies [39] was initially conducted as an RCT. However, the randomisation was stopped after only three patients were assigned to the control group. This study was treated as non-randomised CT in our report. Alternatively, it could have been considered as a case-series since the change in protocol during the trial had the subsequent patients recruited exclusively to the scaffold arm to enlarge the safety database.

There is no robust evidence that the single-step scaffold-assisted cartilage repair combined with microfracturing leads to better outcomes than MFx alone. From the extracted evidence, it appears that the intervention is not superior compared to MFx, at best equal. Long-term data are lacking. Furthermore, there is a need for safety trials that focus on rare adverse events.

keine Evidenz zu Überlegenheit einzeitiger matrix-assistierter Behandlung von Knorpeldefekten

For assessing the clinical effectiveness and safety of the single-step matrix-assisted cartilage repair in the knee joint (combined with microfracturing) compared to *(M)ACI*, we could not identify any studies that met our inclusion criteria.

keine Studien mit (M)ACI als Vergleich

Nevertheless, several systematic reviews have shown that there is no sufficient evidence to conclude whether ACI or MACI is superior to other treatment strategies for treating cartilage defects (in the knee). It appears that the (M)ACI procedure is relatively safe and that it is not associated with serious adverse events. However, patients need to be aware that as the (M)ACI procedure involves two operations, it may be associated with a higher rate of adverse events than other treatments [40-42].

scheinbar keine Evidenz zu Überlegenheit (matrix-induzierte) autologe Chondrozyten Implantation ...

In the short to medium-term, the effectiveness of (M)ACI in terms of functional, pain, and quality of life outcomes appears to be comparable to microfracturing, mosaicplasty, conservative treatments, or osteochondral allograft [40-42].

... wohl eher Gleichwertigkeit gegenüber anderen Interventionen

In 2009, the Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA) in Germany concluded that MACI (ACI was not in the focus of that assessment) is a promising intervention. However, the evidence was not sufficient to demonstrate a clinical benefit and therefore, the intervention should be re-evaluated (the re-evaluation was planned for 2014, but no results are published yet) [43].

G-BA in 2009: abschließende Bewertung nicht zweckmäßig

Naturally, our systematic review has several weaknesses too:

Schwächen Review:

First of all, we decided to include case-series exclusively for assessing the safety and therefore we just considered larger case series with a longer follow-up. Thus, we excluded case series with less than 50 patients or a follow-up of less than 2 years. Presumably then, there were studies with less than 50 patients with a longer follow-up or studies with more patients and a shorter follow-up. Therefore, it is possible that we excluded studies that reported results of e.g. other products or complications.

Ausschluss Studien <50 PatientInnen, Nachbeobachtungszeit <24 Monate

Moreover, we excluded all studies in which the single-step matrix-assisted cartilage repair was not exclusively performed in combination with microfracturing. Due to this reason, we excluded one non-randomised controlled trial (patients in the control groups received MACI) and two single-arm studies.

Ausschluss Studien, wo einzeitiger Knorpelersatz nicht in Kombination mit Mikrofrakturierung

Furthermore, we excluded retrospective studies – even controlled studies with a retrospective control group – because the sources of error due to confounding and bias are more common in retrospective studies than in prospective ones.

Ausschluss retrospektive Studien

It might be that we did not identify all appropriate studies, although we used different terms in the systematic literature search, asked the manufacturers for studies and supplemented our search by a handsearch and an additional search in Scopus. This is mainly due to the inconsistent wording for the assessed technology of cartilage repair. Thus, we identified a large part of the studies by handsearch. In addition, it is possible that we did not identify all manufacturers asking for studies.

Möglichkeit der Nicht-Identifikation von relevanten Studien

9 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Empfehlungsschema

Table 9-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is ***currently*** **not recommended.**
	The **inclusion in** the catalogue of benefits is **not recommended.**

Reasoning:

The current evidence is not sufficient to conclude that the single-step matrix-assisted cartilage repair (combined with microfracturing) is more effective and safer than microfracturing or as effective, but safer than (matrix-assisted) autologous chondrocyte implantation.

keine ausreichend robuste Evidenz

New study results, especially from studies with larger patient numbers and longer follow-up (e.g. ten years), will potentially influence the effect estimate considerably.

Studien mit mehr PatientInnen + längerer Nachbeobachtung

A re-evaluation is recommended not before 2018, since the technique seems to be promising and there are still ongoing studies (see Appendix). At the moment, it seems too early to include the single-step scaffold-assisted cartilage repair of the knee in the catalogue of benefits.

Re-Evaluierung 2018 empfohlen

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Single-step cartilage repair of knee joints with a scaffold in combination with microfracturing: Results from controlled trials

Author, year	Anders 2013 [37]	Sharma 2013 [39]	Shive 2014 [36] (Stanish 2013 [38])
Country	Germany	Germany, Italy, Netherlands	Canada, Spain, South Korea
Sponsor	n/a[30]	Arthritis Foundation, NIH	BioSyntech Canada Inc., Piramal Life Sciences
Intervention/Product	Arthroscopy+miniarthrotomy, single-step cartilage repair[31] + MFx/Chondro-Gide®	Miniarthrotomy, single-step cartilage repair + MFx/n/a[32]	Arthroscopy+miniarthrotomy, single-step cartilage repair + MFx/BST-CarGel®
Comparator	Arthroscopic MFx alone	Miniarthrotomic MFx alone	Arthroscopic MFx alone
Study design	RCT	CT[33]	RCT[34]
Number of pts.	28 (13/15)[35] vs. 10	15 vs. 3	41 vs. 39
Lesion	Cartilage defect of knee	Medial femoral condyle defect (knee)	Femoral condyle cartilage lesion (knee)
Inclusion criteria	Pts. with isolated cartilage defects (2-10 cm^2) in the knee, Grade 3-4 Outerbridge Classification, aged 21-50 yrs.	Pts. aged 18 - 50 years, standing radiograph showing a Kellgren score of 0–2, diagnostic arthroscopy/MRI identification of a medial femoral condyle defect, stable and asymptomatic contralateral knee	Pts. with a single, focal cartilage lesion in the knee and moderate pain, aged 18-55 yrs.

[30] It is not clear, who sponsored the study. However, it is stated that the authors acknowledge Geistlich Pharma for the support.

[31] Patients in the treatment group were divided, whether the scaffold was sutured or glued into the affected area. Thus, two treatment groups exist.

[32] A polyethylene glycol diacrylate hydrogel was used as scaffold (like GelrinC).

[33] Study was initiated as a RCT, however, randomisation was stopped during the study to increase the size of the hydrogel cohort.

[34] Study results after 1 year were published in Stanish 2013 (assessing 41 vs. 39 pts.) and results after 5 years follow-up were presented in Shive 2014 (assessing 34 vs. 26 pts.). Therefore, data from both publications are presented together. However, the initial study protocol was planned for 12 months follow-up only. 67 of the 80 intial pts. were enrolled in the extension study.

[35] In 13 patients the scaffold was sutured and in 15 patients the scaffold was glued.

Author, year	Anders 2013 [37]	Sharma 2013 [39]	Shive 2014 [36] (Stanish 2013 [38])
Exclusion criteria	Pts. with: >2 defetcs, 2 corresponding defets, defects on both knees, sign of ostoarthrosis, bone lesion >0.7 cm, uncorrected knee instability. Rheumatoid arthritis, (para)infectious diseases, chronic heart, endocrine, metabolic or autoimmune diseases, varus or valgus deformation, previous complete meniscus resection, mosaicplasty, treatment with cartilage specific medication, chondropathia patellae or dysplasia of patella	Alcohol or drug abuse, passive motion deficit of the knee (>5° of extension, >15° of flexion), osteoarthritis, rheumatoid arthritis or gout, pregnant or nursing mothers, active inflammatory disease, such as lupus, history of severe allergy (as defined by a reaction which required treatment such as injection with epinephrine), atopic disease, or known allergy to bovine proteins, evidence of significant haematological disorder (severe preexisting coagulation disorder requiring active coagulation therapy), cardiovascular, liver, or neoplastic disease, bone malignancy, autoimmune disorders, or kidney disease, recent history (less than 4 weeks) of myocardial infarction or concurrent acute injury that might compromise the subject's welfare, diabetes mellitus, life expectancy of less than 5 years, untreated depression, chronic steroid intake, patellofemoral instability, malalignment with >5° valgus or varus compared to normal, prior cartilage surgery of the affected knee (e.g. subchondral drilling, microfracture, abrasion arthroplasty, mosaicplasty, autologous chondrocyte implantation)	Pts. with multiple lesions or kissing lesions, clinically relevant compartment malalignment (> 5 degrees), pts who underwent ligament treatments in the affected knee within 2 years prior to trial, inflammatory arthropathy, such as rheumatoid arthritis, systemic lupus, or active gout, previous surgical cartilage treatments in the affected knee in the last 12 months
Prior surgery, n (%)	8 (62)/8 (53) vs. 5 (50)	None (exclusion criterion)	n/a[36]
Postoperative treatment(s)	Physiotherapy/rehabilitation (all pts.)	Physiotherapy/rehabilitation (all pts.)	Physiotherapy/rehabilitation (all pts.)
Age of patients (yrs.)	Ø 33/38 vs. 41; p=n/a	20-59 vs. 40-49[37]; p=n/a	Ø 35 vs. 37, p=N.S.
Sex (% female)	15/20 vs. 20; p=n/a	n/a	44 vs. 36; p=n/a
BMI (kg/m²)	Ø 27.8/27.7 vs. 24.6; p=n/a	20-30+ vs. 20-30[37]; p=n/a	Ø 27.0 vs. 25.2; p=N.S.
Defect size (cm²)	Ø 3.7/3.5 vs. 2.9; p=n/a	1-3 vs. 2-3[37]; p=n/a	Ø 2.32 vs. 1.95; p=N.S.
Clinical classification (% pts)	Grade 3 (Outerbridge): 54/40 vs. 40; p=n/a Grade 4 (Outerbridge): 46/60 vs. 60; p=n/a	n/a	n/a
Primary endpoint(s)	n/a	n/a	Degree of lesion fill & repair cartilage T2 relaxation time (both via MRI)
Follow-up (months)	24	6	60
Loss to follow-up, n (%)	12 months: 4 (31)/2 (13) vs. 2 (20); p=n/a 24 months: 5 (38)/2 (13) vs. 4 (40); p=n/a	0 vs. 0	12 months: 0 vs. 2 (5); p=n/a 60 months: 8 (20) vs. 13 (33)[38]; p=n/a

[36] There was no prior surgery in the last 12 months before the start of the study.

[37] Values were only given as ranges and not as means or medians (or exact numbers).

[38] Loss to follow-up for assessing joint functionality by WOMAC score.

Author, year	Anders 2013 [37]	Sharma 2013 [39]	Shive 2014 [36] (Stanish 2013 [38])
Effectiveness[39]			
Mobility/joint functionality	*Modified Cincinnati Score (6-100)* [40]*:* Baseline: ø 47 (±20)/47 (±15) vs. 37 (±14)[41]; p=n/a Change after 3; 6 months: n/a Change after 12 months: ø +35 (±29)/+19 (±22) vs. +31 (±13); **p=N.S.** Change after 24 months: ø +46 (±17)/+37 (±14) vs. +44 (±15); **p=N.S**. Change after 36; 48; 60 months: n/a *Modified ICRS Score*[42]*:* Baseline: n/a Change after 3; 6 months: n/a Change after 12 months: n/a; **p=N.S.** Change after 24 months: n/a; **p=N.S.** Change after 36; 48; 60 months: n/a	*IKDC Score (0-100)* [43]: Baseline: n/a, **p=N.S.** Change after 3 months: n/a; **p=N.S.** Change after 6 months: n/a; **p=N.S.** Change after 12; 24; 36; 48; 60 months: n/a	*WOMAC subscale score **stiffness** (0-20)* [44]: Baseline: ø 10.5 (±4.4) vs. 9.4 (±4.9); **p=N.S.** Change after 3; 6 months: n/a Change after 12 months: ø -5.97 (±0.68) vs. -6.56 (±0.71); **p=N.S.** Change after 24; 36, 48 months: n/a Change after 60 months: ø -5.63 (±0.72) vs. -6.68 (±0.58); **p=N.S.** *WOMAC subscale score **function** (0-170)* [44]: Baseline: ø 80.3 (±38.5) vs. 75.9 (±38); **p=N.S.** Change after 3; 6 months: n/a Change after 12 months: ø -55.96 (±4.24) vs. -60.59 (±4.41); **p=N.S.** Change after 24; 36, 48 months: n/a Change after 60 months: ø -56.52 (±4.57) vs. -62.10 (±3.43); **p=N.S.**
Return to activities	n/a	n/a	n/a

[39] Reported p-values pertain to between-arm comparisons.

[40] The Modified Cincinnati Score is divided into 3 parts: knee function (6-30 points), clinical pathology (0-20 points), highest activity level without pain (0-50 points).

[41] Baseline values are based on whole study sample, whereas changes from baseline are calculated based on the sample that remained at follow-up, only.

[42] The Modified ICRS (International Cartilage Repair Society) Score consists of ratings by patient (pain, functional status of knee) and surgeon (functional status knee, classification + crepitation).

[43] The IKDC (International Knee Documentation Committee) scoring system includes 10 items investigating symptoms, function and return to sporting activities.

[44] The WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) scoring system includes pain, stiffness and physical function, measured on a visual analogue scale (VAS). Only the subscale scores for stiffness, function and pain were presented.

Author, year	Anders 2013 [37]	Sharma 2013 [39]	Shive 2014 [36] (Stanish 2013 [38])
Quality of life	n/a	n/a	*SF-36 v2* ***physical component*** [45]: Baseline: n/a Change after 3; 6 months: n/a Change after 12 months: ø +13.02 (±1.5) vs. +14.76 (±1.52); **p=N.S.** Change after 24; 36, 48 months:n/a Change after 60 months: ø +13.12 (±1.63) vs. +14.48 (±1.42); **p=N.S** *SF-36 v2* ***mental component*** [45]: Baseline: n/a Change after 3; 6 months: n/a Change after 12 months: ø +3.54 (±1.56) vs. +0.84 (±1.58); **p=N.S.** Change after 24; 36, 48 months:n/a Change after 60 months: ø +2.72 (±1.3) vs. -0.17 (±1.76); **p=N.S**
Pain	*VAS (0-100)*[46]: Baseline: ø 46/48 vs. 54; p=n/a Change after 3; 6 months: n/a Change after 12 months: ø -32 (±n/a)/-32 (±n/a) vs. -35(±n/a); **p=N.S.** Change after 24 months: ø -37 (±n/a)/-38 (±n/a) vs. -49 (±n/a); **p=N.S.** Change after 36; 48; 60 months: n/a	*Severity*[47]: Baseline ø 54.3 (±16.4) vs. 54 (±21); p=n/a. Change after 3 months: ø -29 (±n/a) vs. -34.7 (±n/a); p=n/a Change after 6 months: ø -32.1 (±n/a) vs. -15.3 (±n/a); p=n/a Change after 12; 24; 36; 48; 60 months: n/a *Frequency*[47]: Baseline: ø 77 (±20.3) vs. 84.3 (±24.5); p=n/a. Change after 3 months: ø -41 (±n/a) vs. -62.6 (±n/a); p=n/a Change after 6 months: ø -52.9 (±n/a) vs. -41 (±n/a); p=n/a Change after 12; 24; 36; 48; 60 months: n/a	*WOMAC subscale score* ***pain*** *(0-50)*[44]: Baseline: ø 22.4 (±10.3) vs. 22.9 (±9.1); **p=N.S.** Change after 3; 6 months: n/a Change after 12 months: ø -16.16 (±1.16) vs. -16.91 (±1.21); **p=N.S.** Change after 24; 36, 48 months:n/a Change after 60 months: ø -15.37 (±1.47) vs. -16.56 (±1.19); **p=N.S.**
Necessity of total joint replacement, n (%)	0/1 (8) vs. 0; p=n/a	n/a	n/a

[45] The Short-Form Health Survey (SF-36) version 2 is an eight-scale profile of functional health and well-being scores plus summary components of physical and mental health. Only the subscale scores for the physical and mental component were presented.

[46] Pain was measured on a visual analogue scale (VAS).

[47] It was not stated on which scale or scoring system the frequency and severity of pain were measured.

Author, year	Anders 2013 [37]	Sharma 2013 [39]	Shive 2014 [36] (Stanish 2013 [38])
Safety			
Overall complications, n (%)	n/a	n/a	*12 months follow-up (41 vs. 37 pts.):* 40 (98)[48] vs. 36 (92)[49]; **p=N.S.** *60 months follow-up (34 vs. 26 pts.):* 13 (19) vs. 18 (27)[50]; p=n/a
Procedure-related complications, n (%)	0/0 vs. 0	1 (7)[51] vs. 0, p=n/a	*12 months follow-up (41 vs. 37 pts.):* 38 (93) vs. 30 (77)[52]; p=n/a *60 months follow-up (34 vs. 26 pts.):* 2 (6) vs. 2 (8)[52]; p=n/a
Device-related complications, n (%)	0/0 vs. -	n/a vs. -	*12 months follow-up (41 vs. 37 pts.):* 9 (22)[53] vs. - *60 months follow-up (34 vs. 26 pts.):* 1 (3)[52] vs. -
Re-operation rate, n (%)	n/a	n/a	n/a
Procedure-related mortality, n (%)	n/a	0 vs. 0	0 vs. 0

Abbreviations: cm=centimetre; CT = (non-randomised) controlled trial; MFx = microfracturing; n = number (of patients); n/a = data not available; N.S. = statistically not significant; pts. = patients, RCT = randomised controlled trial; vs. = versus; yrs. = years

[48] 5 patients experienced severe adverse events. Most frequent (mild to moderate) events: arthralgia, pain and nausea.

[49] 1 patient experienced a severe adverse event. Most frequent (mild to moderate) events: arthralgia and pain.

[50] Most frequent event in both groups: pain (11% vs. 17%).

[51] Mild haemarthrosis in one patient.

[52] Kind of complications not stated.

[53] Kind of complications not clearly stated.

Risk of bias tables

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA [44] and in the Guidelines of EUnetHTA [45].

Table A-2: Risk of bias – study level (randomised controlled studies)

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating Physician			
Anders 2013 [37]	Yes	Yes	No (not possible)	No (not possible)	No[54]	No[55]	High
Shive 2014 [36] (Stanish 2013 [38])[56]	Yes (Yes)	Unclear (Unclear)	No (not possible) (No (not possible))	No (not possible) (No (not possible))	Yes (Yes)	No[57] (No[58])	High (High)

Table A-3: Risk of bias –study level (non–randomised controlled studies)

Study reference/ID	Bias due to confounding	Bias selection of participants into the study	Bias in measurement of intervention	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Sharma 2013 [39]	Serious[59]	Serious[60]	Low	Moderate[61]	Moderate[62]	Serious[63]	Moderate[64]	Serious	-

[54] No study protocol. Incomprehensive safety reporting, unclear approach for assessing Modified ICRS.

[55] Data from interim analysis of an open-label trial. Adherence to/use of concomitant interventions not reported (i.e. to physiotherapy/rehabilitation and pain killers).

[56] Since data for 12 months follow-up were retrieved from Stanish 2013, the risk of bias of this study was also assessed.

[57] Originally, planned follow-up was 12 months and after this period the follow-up was extended to 60 months. However, there was an extra screening and enrolment for the extension study. Adherence to/use of concomitant interventions not reported (i.e. to physiotherapy/rehabilitation and pain killers).

[58] No adherence of possible effect of physiotherapy / rehabilitation or pain killers.

[59] Relevant baseline characteristics not comprehensively provided or controlled for.

[60] Study protocol was switched from "randomised" to "non-randomised". Furthermore, it is unclear whether patients were recruited consecutively or not.

[61] Adherence to concomitant treatment not reported. Concomitant medication (e.g. painkillers) not reported.

[62] Values for IKDC Score were not reported (only summarised in a Figure).

[63] Subjective outcome measures, patients and trial personnel aware of intervention received.

[64] No study protocol available.

Applicability table

Table A-4: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	All studies included patients with chondral defects in the knee. The patients had defects grade 3-4 of the Outerbridge Classification (stated in one study). There was no study that exclusively included patients with osteochondral lesions (or with osteochondritis dissecans) in the knee. The inclusion criteria and the population in the studies seem to be in accordance with the intended patient population for the technology.
Intervention	The implantation of the scaffolds was either performed by miniarthrotomy or by an arthroscopy. The devices were inserted under general anaesthetics. Patients in the included studies received Chondro-Gide® or BST-CarGel®. In one study, it was not stated which product was used, however, based on the compounds, it could have been GelrinC®. In all studies it was stated that patients received postoperative physiotherapy or rehabilitation.
Comparators	In all studies the control group received microfracturing alone. To date, there are no published studies in which the single-step scaffold-assisted treatment of cartilage defects in combination with microfracturing has been compared with (matrix-assisted) autologous chondrocyte implantation/transplantation (MACI/ACI).
Outcomes	A range of clinically relevant outcome criteria was applied in the studies and have shown objective and/or subjective benefits from single-step scaffold-based cartilage repair combined with microfracturing. For the assessment of safety, procedure-, and/or device-related adverse events were recorded. However, the presented data in the studies is limited, especially due to small study samples, short time horizons for follow-up, and obviously different approaches to the reporting/recording of complications (becoming apparent in a high variability in complication rates between studies).
Setting	With one exception, the studies were carried out in Europe: Germany, Italy and the Netherlands. One study was a multi-centre study carried out in Canada, Spain and South Korea. Patients were recruited and the operations were performed at orthopaedic centres. Study centres had experience in the technology used, as well as in clinical research in general. The settings of the studies reflect the clinical setting in which the technology is intended to be used in an appropriate way.

List of ongoing randomised controlled trials

Table A-5: List of ongoing randomised controlled trials

Source	Identifier/ Trial name	Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date
ClinicalTrials.gov	NCT01458782	A Randomized Trial Comparing Autologous Chondrocyte Implantation Using Collagen Membrane (ACI-C) Versus (Autologous Matrix Induced Chondro-genesis) AMIC for Repair of Cartilage Defects in the Knee	Age between 18-60 yrs, symptomatic cartilage defect in the knee >2 square cm	Autologous matrix induced chondrogenesis	Autologous chondrocyte implantation using collagen membrane (ChondroGide)	Perceived treatment efficacy as change from baseline in KOOS score	October 2014
ClinicalTrials.gov	NCT01282034	Multicenter Randomized Controlled Trial for the Treatment of Knee Chondral and Osteochondral Lesions: Marrow Stimulation Techniques vs MaioRege	Patients aged between 18 and 60 years; Knee symptomatic chondral lesion of grade III/IV (according to Outerbridge Classification) or osteochondral lesion; Not re-fixable OCD lesions; Lesion between 2-9 cm^2; Single lesion;	MaioRegen Surgery	Marrow stimulation - Drilling or Microfractures	IKDC Subjective Knee Evaluation Form-2000	July 2015
WHO-ICTRP	DRKS00005100	Evaluation der Rekonstruktion osteochondraler Läsionen am Talus.	Age 18+, osteochondral lesions of the talus	Autologous matrix induced chondrogenesis	MACI/debridement + drilling	Pain	n/a
BioTissue AG (information was transmitted by manufacturer)	n/a	A Randomized Open-Label Study on Safety and Efficacy of chondrotissue in Micro-fracture Treatment of Local Femoral Cartilage Defects	Local femoral defect at the knee joint, defect size: 1-4 cm^2, age 18-60	Chondrotissue + microfracture	Microfrature alone	cartilage tissue formation after 12 weeks as assessed by MRI	December 2017

Literature search strategies

Search strategy for The Cochrane Library

Search Date: 14/01/2016	
ID	Search
#1	MeSH descriptor: [Cartilage Diseases] explode all trees
#2	cartilage near (damage* or disorder* or defect* or lesion* or disease*) (Word variations have been searched)
#3	MeSH descriptor: [Cartilage, Articular] explode all trees and with qualifier(s): [Abnormalities – AB, Injuries – IN, Pathology – PA, Physiology – PH, Physiopathology – PP]
#4	#1 or #2 or #3
#5	MeSH descriptor: [Knee Joint] explode all trees
#6	Knee*
#7	MeSH descriptor: [Ankle Joint] explode all trees
#8	Ankle*
#9	MeSH descriptor: [Knee Injuries] explode all trees
#10	MeSH descriptor: [Ankle Injuries] explode all trees
#11	MeSH descriptor: [Knee] explode all trees
#12	MeSH descriptor: [Ankle] explode all trees
#13	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
#14	#4 and #13
#15	MeSH descriptor: [Osteochondritis Dissecans] explode all trees
#16	osteochondritis dissecans (Word variations have been searched)
#17	OCD:ti,ab,kw (Word variations have been searched)
#18	osteochondr* near (damage* or disorder* or defect* or lesion* or disease*) (Word variations have been searched)
#19	#15 or #16 or #17 or #18
#20	#14 or #19
#21	MeSH descriptor: [Chondrogenesis] explode all trees
#22	autologous near chondrogenes* (Word variations have been searched)
#23	Matrix-Induced Chondrogenesis (Word variations have been searched)
#24	AMIC (Word variations have been searched)
#25	osteochondral regeneration* (Word variations have been searched)
#26	OCD regeneration (Word variations have been searched)
#27	Chondro-Gide (Word variations have been searched)
#28	Chondrotissue (Word variations have been searched)
#29	Chondro-Tissue (Word variations have been searched)
#30	Hyalofast (Word variations have been searched)
#31	MaioRegen (Word variations have been searched)
#32	"CaRes-1s" (Word variations have been searched)
#33	#21 or #24 or #25 or #26 or #32
#34	#4 and #33
#35	#20 and #33
#36	#34 or #35
Total: 8Hits	

Search strategy for CRD (DARE, NHS-EED, HTA)

Search Date: 14/01/2016	
#1	(Chondrogenesis)
#2	(autologous NEAR chondrogenes*)
#3	(Matrix-Induced Chondrogenesis)
#4	(AMIC)
#5	(osteochondral regeneration*)
#6	(OCD regeneration)
#7	(Chondro-Gide)
#8	(Chondrotissue)
#9	(Chondro-Tissue)
#10	(Hyalofast)
#11	(MaioRegen)
#12	(CaRes-1)
#13	#1 OR #12
Total:2 Hits	

Search strategy for Embase

No.	Query Results	Results	Date
#37	'chondropathy'/exp/mj OR cartilage NEAR/4 (damage* OR disorder* OR defect* OR lesion* OR disease*) OR 'articular cartilage'/mj AND ('knee'/exp OR knee* OR 'ankle'/exp OR ankle* OR 'knee injury'/exp OR 'ankle injury'/exp) OR 'osteochondritis dissecans'/exp OR 'osteochondritis dissecans' OR ocd OR osteochondr* NEAR/5 (damage* OR disorder* OR defect* OR lesion* OR disease*) AND ('chondrogenesis'/exp AND ('collagen'/exp/dm_dt,dm_th OR 'collagen'/exp/dd_dt,dd_ad) OR autologous NEAR/5 chondrogenes* OR 'matrix-induced chondrogenesis' OR amic OR 'osteochondral regeneration' OR 'ocd regeneration' OR 'chondro-gide' OR chondrotissue OR 'chondro-tissue' OR hyalofast OR maioregen OR cares:dn OR cares:df)	147	14 Jan 2016
#36	'chondrogenesis'/exp AND ('collagen'/exp/dm_dt,dm_th OR 'collagen'/exp/dd_dt,dd_ad) OR autologous NEAR/5 chondrogenes* OR 'matrix-induced chondrogenesis' OR amic OR 'osteochondral regeneration' OR 'ocd regeneration' OR 'chondro-gide' OR chondrotissue OR 'chondro-tissue' OR hyalofast OR maioregen OR cares:dn OR cares:df	485	14 Jan 2016
#35	cares:df	1	14 Jan 2016
#34	cares:dn	28	14 Jan 2016
#33	maioregen	15	14 Jan 2016
#32	hyalofast	6	14 Jan 2016
#31	'chondro-tissue'	3	14 Jan 2016
#30	chondrotissue	14	14 Jan 2016
#29	'chondro-gide'	54	14 Jan 2016
#28	'ocd regeneration'	1	14 Jan 2016
#27	'osteochondral regeneration'	58	14 Jan 2016
#26	amic	308	14 Jan 2016
#25	'matrix-induced chondrogenesis'	68	14 Jan 2016
#24	autologous NEAR/5 chondrogenes*	81	14 Jan 2016
#23	'chondrogenesis'/exp AND ('collagen'/exp/dm_dt,dm_th OR 'collagen'/exp/dd_dt,dd_ad)	6	14 Jan 2016
#22	'collagen'/exp/dm_dt,dm_th OR 'collagen'/exp/dd_dt,dd_ad	2,271	14 Jan 2016

#21	'collagen'/exp/dd_dt,dd_ad	2,271	14 Jan 2016
#20	'collagen'/exp/dm_dt,dm_th	1,905	14 Jan 2016
#19	'chondrogenesis'/exp	7,077	14 Jan 2016
#18	'chondropathy'/exp/mj OR cartilage NEAR/4 (damage* OR disorder* OR defect* OR lesion* OR disease*) OR 'articular cartilage'/mj AND ('knee'/exp OR knee* OR 'ankle'/exp OR ankle* OR 'knee injury'/exp OR 'ankle injury'/exp) OR 'osteochondritis dissecans'/exp OR 'osteochondritis dissecans' OR ocd OR osteochondr* NEAR/5 (damage* OR disorder* OR defect* OR lesion* OR disease*)	26,925	14 Jan 2016
#17	'osteochondritis dissecans'/exp OR 'osteochondritis dissecans' OR ocd OR osteochondr* NEAR/5 (damage* OR disorder* OR defect* OR lesion* OR disease*)	16,594	14 Jan 2016
#16	osteochondr* NEAR/5 (damage* OR disorder* OR defect* OR lesion* OR disease*)	5,317	14 Jan 2016
#15	ocd	9,937	14 Jan 2016
#14	'osteochondritis dissecans'	2,654	14 Jan 2016
#13	'osteochondritis dissecans'/exp	2,132	14 Jan 2016
#12	'chondropathy'/exp/mj OR cartilage NEAR/4 (damage* OR disorder* OR defect* OR lesion* OR disease*) OR 'articular cartilage'/mj AND ('knee'/exp OR knee* OR 'ankle'/exp OR ankle* OR 'knee injury'/exp OR 'ankle injury'/exp)	12,380	14 Jan 2016
#11	'knee'/exp OR knee* OR 'ankle'/exp OR ankle* OR 'knee injury'/exp OR 'ankle injury'/exp	234,561	14 Jan 2016
#10	'ankle injury'/exp	10,442	14 Jan 2016
#9	'knee injury'/exp	24,314	14 Jan 2016
#8	ankle*	74,687	14 Jan 2016
#7	'ankle'/exp	23,988	14 Jan 2016
#6	knee*	173,200	14 Jan 2016
#5	'knee'/exp	51,895	14 Jan 2016
#4	'chondropathy'/exp/mj OR cartilage NEAR/4 (damage* OR disorder* OR defect* OR lesion* OR disease*) OR 'articular cartilage'/mj	55,586	14 Jan 2016
#3	'articular cartilage'/mj	10,491	14 Jan 2016
#2	cartilage NEAR/4 (damage* OR disorder* OR defect* OR lesion* OR disease*)	15,301	14 Jan 2016
#1	'chondropathy'/exp/mj	35,781	14 Jan 2016

Search strategy for Medline via OVID

Database: Ovid MEDLINE(R) <1946 to January Week 1 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <January 13, 2016>, Ovid MEDLINE(R) Daily Update <January 13, 2016>, Ovid OLDMEDLINE(R) <1946 to 1965>	
Search Strategy:	
1	exp Cartilage Diseases/(11,591)
2	(cartilage adj5 (damage* or disorder* or defect* or lesion* or disease*)).mp. (13,334)
3	exp *Cartilage, Articular/ab, in, pa, ph, pp [Abnormalities, Injuries, Pathology, Physiology, Physiopathology] (6,639)
4	1 or 2 or 3 (25,002)
5	exp Knee Joint/(47,920)
6	Knee*.mp. (125,592)
7	exp Ankle Joint/(12,123)
8	Ankle*.mp. (49,692)
9	exp Knee Injuries/(16,867)
10	exp Ankle Injuries/(8,245)
11	5 or 6 or 7 or 8 or 9 or 10 (166,243)
12	4 and 11 (7,529)

13	exp Osteochondritis Dissecans/(1,360)
14	osteochondritis dissecans.mp. (1,948)
15	OCD.mp. (6,692)
16	(osteochondr* adj5 (damage* or disorder* or defect* or lesion* or disease*)).mp. (3,881)
17	13 or 14 or 15 or 16 (11,543)
18	12 or 17 (17,962)
19	exp Chondrogenesis/(3346)
20	exp *Collagen/ad, tu [Administration & Dosage, Therapeutic Use] (2,466)
21	19 and 20 (8)
22	(autologous adj10 chondrogenes*).mp. (64)
23	Matrix-Induced Chondrogenesis.mp. (48)
24	AMIC.mp. (174)
25	osteochondral regeneration*.mp. (47)
26	OCD regeneration.mp. (1)
27	27 Chondro-Gide.mp. (24)
28	28 Chondrotissue.mp. (4)
29	29 Chondro-Tissue.mp. (1)
30	30 Hyalofast.mp. (0)
31	31 MaioRegen.mp. (3)
32	32 CaRes.mp. (2,901)
33	33 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 31 or 32 (3,179)
34	34 18 and 33 (106)
Search date: 13/01/2016	

Search strategy for PubMed

(((((((Cartilage Diseases[MesH] OR cartilage damage* OR cartilage disorder* OR cartilage defect* OR cartilage lesion* OR cartilage disease* OR "Cartilage, Articular/abnormalities"[Mesh] OR "Cartilage, Articular/injuries"[Mesh] OR "Cartilage, Articular/pathology"[Mesh] OR "Cartilage, Articular/physiology"[Mesh] OR "Cartilage, Articular/physiopathology"[Mesh])))) AND (Knee Joint[MesH] OR Knee* OR Ankle Joint[MesH] OR Ankle* OR Knee Injuries[MesH] OR Ankle Injuries[MesH])))) OR (Osteochondritis Dissecans[MesH] OR osteochondritis dissecans OR osteochondral damage* OR osteochondral disorder* OR osteochondral defect* OR osteochondral lesion* OR osteochondral disease*))) AND ((Chondrogenesis[MesH] OR "Collagen/administration and dosage"[Mesh] AND "Collagen/therapeutic use"[Mesh]) OR autologous chondrogenes* OR Matrix-Induced Chondrogenesis OR AMIC OR osteochondral regeneration* OR OCD regeneration OR Chondro-Gide OR Chondrotissue OR Chondro-Tissue OR Hyalofast OR MaioRegen OR CaRes)
200 Hits
Search date: 15/01/2016