Single-/two-step scaffold-based cartilage repair in the knee and ankle joint

Systematic Review

1st Update 2019

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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
ADL .....Activities of daily living
AMIC .....Autologous Matrix-Induced Chondrogenesis
AWMF .....Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.
CE.....Conformité Européenne (European Conformity)
CT.....Clinical trial
CRD .....Centre for Reviews and Dissemination
EQ-5D .....EuroQual-5D (questionnaire for quality of life)
GRADE.....Grading of Recommendations Assessment, Development and Evaluation
ICRS.....International Cartilage Repair Society
IKDC.....International Knee Documentation Committee
KOOS .....Knee Injury and Osteoarthritis Outcome Score
LBI-HTA .....Ludwig Boltzmann Institute for Health Technology Assessment
MACI .....Matrix-Induced Autologous Chondrocyte Implantation
MFx.....Microfracture/Microfracturing
MOCART .....Magnetic Resonance Observation of Cartilage Repair Tissue
MP.....Mosaicplasty
MRI .....Magnetic Resonance Imaging
n.....Number
n/a .....Data not available
NR .....Not reported
NRCT.....Non-randomised controlled trial
n.s. .....Not significant
OATS .....Osteochondral autograft transplantation
OCD .....Osteochondritis dissecans
POP .....Planned and Ongoing Projects database
pts.....Patients
QoL .....Quality of life
RCT.....Randomised controlled trial
RoB.....Risk of bias
s.s. .....Statistically significant
TAS .....Tegner Activity Score
VAS .....Visual Analogue Scale
WOMAC .....Western Ontario and McMaster Universities Osteoarthritis Index
yrs.....Years

Executive summary

Introduction

Health problem

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

focus: defects in the knee & ankle joint

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.

cartilage is a thin layer of connective tissue

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).

cartilage damages due to traumatic events or degeneration

Description of technology

AMIC

In the single-step scaffold-based treatment (AMIC) 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 three-dimensional structure. The matrix decomposes over time.

single-step scaffold-based treatment in combination with microfracturing (MFx)

MACI

In the two-step scaffold-based treatment (MACI) of cartilage defects, firstly, intact cartilage is sampled arthroscopically from a non-weight-bearing 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. Chondrocytes are pre-seeded in a scaffold matrix (e.g., collagen matrix, hyaluronan matrix), which is then implanted in the defect.

two-step scaffold based treatment: cell-free matrix as support for settlement of cells

Research question

In this report, we analysed whether the single- or the two-step scaffold-based cartilage repair (AMIC/MACI) is more effective and safe in comparison to microfracturing (MFx) or as effective but safer in comparison to autologous chondrocyte implantation (ACI).

MFx & autologous chondrocyte implantation (ACI) as comparator

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.

systematic literature search, selection, extraction, and quality appraisal by at least two authors

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.

mobility/joint functionality, quality of life, pain and necessity for joint replacement for effectiveness

Domain safety

severe adverse events, complications and re-operation rate for safety

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

Results

Available evidence

no controlled evidence for ankle joint

We could not identify any controlled trials comparing the single- or the two-step scaffold-assisted treatment of (osteo)chondral defects in the ankle joint.

5 RCTs & 1 NRCT for AMIC (187 vs. 127 pts.), 5 RCTs for efficacy of MACI (184 vs. 146), 5 RCTs for safety of MACI (191 vs. 155)

The only studies that met our inclusion criteria were five randomised controlled trials (RCTs) and one non-randomised controlled trial (NRCT) of the single-step scaffold-assisted treatment (AMIC) in the knee joint (scaffold groups) in combination with MFx (187 patients), compared to MFx alone (127 patients) (MFx groups). For the evaluation of the efficacy of the two-step scaffold-assisted treatment (MACI), five RCTs with a total of 330 patients (184 vs. 146 [92 with MFx, 54 with ACI]) were included. For the safety assessment nearly the same five RCTs with a total of 346 patients (191 vs. 155 [101 with MFx, 54 with ACI]) were included.

Clinical effectiveness

AMIC

no statistically significant differences between study groups for functionality, quality of life and pain

Different scores measuring the effect of AMIC on mobility/joint functionality, quality of life and pain in comparison to MFx were reported in the included studies. With regard to mobility/joint functionality, inconsistent results were reported across the scores. For quality of life, the intervention groups showed an improvement; however, this improvement was not statistically significant. For pain, similar improvements were reported between the study groups across the studies.

1 necessity of total joint replacement reported in 1 study

Furthermore, in only one study, the necessity of a total joint replacement was addressed. In this study, one total knee arthroplasty was reported after 12 months.

MACI

MACI vs. MFx: partly statistically significant improvements in intervention groups

Different scores measuring the effect of MACI on mobility/joint functionality, quality of life and pain were reported in the included studies. For the comparison, MACI versus MFx, some statistically significant improvements in joint functionality, quality of life and pain were reported for the intervention groups across scores and studies.

1 necessity of total joint replacement reported in 1 study

Moreover, in only one study, the necessity of a total joint replacement was addressed. In this study, one total knee arthroplasty was reported after 12 months.

MACI vs. ACI: inconsistent results regarding functionality, no significant results for pain

For the comparison, MACI versus ACI, inconsistent results regarding improvements in joint functionality were reported across scores and studies. For pain, no statistically significant differences between the study groups could be identified. There was no evidence available regarding the outcomes quality of life and necessity of a total joint replacement.

Safety

AMIC

Complications were reported in all extracted studies. Severe adverse event rates ranged from 0-12.2% in the intervention groups and from 0-3.8% in the control groups of three studies. Procedure-related adverse events occurred in 0-93.0% of the patients in the intervention groups (0-77.0% in the control groups) across four studies. The rates for device-related complications differed from 3.0 to 22.0% across three studies.

AMIC vs. MFx: severe adverse events: 0-12.2% vs. 0-3.8%, procedure-related: 0-93.0% vs. 0-77.0%, device-related: 3.0-22.0% in intervention group

MACI

Complications were reported in all three studies comparing MACI to MFx. Severe adverse event rates ranged from 4.8-15.3% in the intervention groups and from 11.1-26.4% in the control groups across the three studies. Procedure-related adverse events occurred in 0-34.7% of the patients in the scaffold groups (0-38.9% in the control groups) across three studies. No evidence was available for device-related complications. In addition, re-operation rates were reported in three RCTs ranging from 2.5-8.3% versus 0-9.7%.

MACI vs. MFx: severe adverse events: 4.8-15.3% vs. 11.1-26.4%, procedure-related: 0-34.7% vs. 0-38.9%, re-operation: 2.5-8.3% vs. 0-9.7%

Furthermore, complications were reported in both studies comparing MACI to ACI. Severe adverse event rates ranged from 0-9.0% in the intervention groups, while zero events occurred in the control groups of the studies. No procedure-related adverse events were reported in the two RCTs. The rates for device-related complications differed from 12.5-36.4% in the intervention groups and from 9.0-140% in the control groups. The reported re-operation rates ranged from 6.4-27.3% versus 6.8-10.0% between the study groups.

MACI vs. ACI: severe adverse events: 0-9.0% vs. 0%, device-related: 12.5-36.4% vs. 9.0-140%, re-operation: 6.4-27.3% vs. 6.8-10.0%

Upcoming evidence

Currently, there are six registered ongoing RCTs of the single-step/two-step scaffold-based cartilage repair (AMIC/MACI) versus MFx. However, the majority of these studies will not provide long-term follow-up of more than 24 months, and thus, will not fill the gap of long-term evidence exceeding 24 months.

6 ongoing RCTs for AMIC/MACI vs. MFx

No ongoing RCTs or NRCTs investigating the clinical efficacy and safety of AMIC/MACI compared to ACI could be identified. Further, no ongoing RCTs or NRCTs for the assessment of both interventions for the ankle joint could be identified.

no ongoing RCTs or NRCTs for AMIC/MACI vs. ACI, or the ankle joint

Reimbursement

At this point in time, the single-step repair (AMIC) of cartilage defects or osteochondritis dissecans (OCD) or (osteo)chondral lesions in the knee or ankle joint is not reimbursed by the Austrian health care system. The two-step matrix-induced procedure (MACI) can be billed with the code for the cultivation of autologous chondrocytes and therefore, it is included in the Austrian hospital benefit catalogue.

AMIC not reimbursed in Austria, MACI included in hospital benefit catalogue

Discussion

quality of evidence AMIC: moderate efficacy and low safety, quality of evidence MACI: low efficacy and very low safety

Overall, the strength of evidence for the efficacy and safety of the single-step scaffold-based cartilage repair (AMIC) of the knee in combination with MFx compared to MFx alone is moderate and low, respectively. The strength of evidence for the efficacy and safety of the two-step scaffold-assisted cartilage repair (MACI) of the knee in compared to MFx or ACI is low and very low, respectively.

AMIC vs. MFx alone: few pts. and short follow-ups

Regarding the evidence of AMIC versus MFx alone, major limitations of the identified trials were the low number of patients of each study and the short follow-up periods (below five years) in the majority of the studies. Only two out of five studies had a follow-up of at least five years.

MACI vs. MFx/ACI: few pts. and short follow-ups

With reference to the evidence of MACI versus MFx or ACI, similar to the AMIC studies, a major issue of the identified studies was the low number of patients. Furthermore, only one study (in comparison to MFx) had a follow-up longer than 24 months. Therefore, long-term evidence is lacking.

patient-reported efficacy outcomes – level of subjectiveness

The majority of the efficacy outcomes (mobility/joint functionality, quality of life, pain and activities of daily living) were patient-reported outcomes, and thus, might be confounded. Therefore, the level of subjectiveness was taken into account within the risk of bias assessment.

in addition, inconsistent adverse event reporting

Moreover, due to the incomprehensive or inconsistent screening, recording and/or reporting of adverse events across the majority of included studies for all comparisons aggregated statements on the safety were barely possible.

lacking long-term efficacy and safety results

Overall, reliable data of long-term efficacy and safety-related outcomes are missing.

Conclusion

evidence not sufficient → reliable conclusion not possible

The current evidence is not sufficient to conclude that the single- or the two-step matrix-assisted cartilage repair is more effective and safer than MFx or as effective, but safer than ACI.

no evidence for the ankle joint → no recommendation

As no controlled evidence could be identified for the cartilage repair of the ankle joint, it was not possible to give a recommendation about whether AMIC and/or MACI should be considered for the inclusion into the Austrian hospital benefit catalogue for the ankle joint.

poor quality of evidence → AMIC & MACI currently not recommended for reimbursement

Due to inconsistent outcome reporting, the included studies showed partly poor quality of evidence and high risk of bias. Hence, it is not possible to draw a reliable conclusion on the clinical effectiveness and safety for both interventions investigated. As a result, AMIC and MACI are currently not recommended for the inclusion in the Austrian hospital benefit catalogue.

studies with larger patient numbers & longer follow-up needed

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

re-evaluation AMIC after 2022; re-evaluation MACI after 2021

A re-evaluation for AMIC is recommended not before 2022 since there are still ongoing RCTs. For MACI a re-evaluation might be reasonable not before 2021, as the technique seems to be promising compared to MFx.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

In der vorliegenden systematischen Übersichtsarbeit liegt der Fokus auf der Behandlung von chondralen und osteochondralen Läsionen im Knie- und Sprunggelenk.

Fokus: Defekte im Knie- und Sprunggelenk

Der Gelenksknorpel ist eine dünne Bindegewebsschicht. Diese bietet eine glatte Oberfläche für die Artikulation und erleichtert die Kraftübertragung auf den darunterliegenden (subchondralen) Knochen.

Knorpel ist eine dünne Schicht aus Bindegewebe

Eine Schädigung des Knorpels kann durch traumatische Ereignisse, einer Degeneration des Gelenks oder durch Osteochondritis dissecans (OCD) entstehen. Die Schädigung kann auch den darunterliegenden Knochen beeinflussen (osteochondrale Läsion).

Knorpelschäden durch traumatische Ereignisse oder Degeneration

Beschreibung der Technologie

Einzeitiges Verfahren (AMIC)

Bei der einzeitigen Matrix-basierten Behandlung von Knorpeldefekten (AMIC) wird nach einer durchgeführten Mikrofrakturierung (MFx) im Bereich des geschädigten Knorpels eine Matrix implantiert. Die verwendete Matrix fungiert als temporäre Struktur, um das Keimen der Zellen zu unterstützen und dadurch eine dreidimensionale Struktur aufzubauen. Die Matrix zersetzt sich im Laufe der Zeit.

einzeitige Behandlung mit Hilfe einer Matrix in Kombination mit Mikrofrakturierung

Zweizeitiges Verfahren (MACI)

Bei der zweizeitigen Matrix-unterstützten Behandlung von Knorpeldefekten (MACI) wird in einem ersten Schritt intakter Knorpel arthroskopisch aus einem nicht belasteten Bereich des betroffenen Knorpels entnommen. In einem zweiten Schritt werden die Zellen (Chondrozyten) in vitro auf einer Matrix (z. B. Kollagenmatrix, Hyaluronmatrix) kultiviert, bis genügend Zellen vorhanden sind, um anschließend in den geschädigten Knorpel re-implantiert zu werden.

zweistufige Behandlung mit Hilfe einer zellfreien Matrix als Unterstützung für die Zell-ansiedlung

Forschungsfrage

Ziel des Berichtes war es, zu untersuchen, ob die ein- oder zweizeitige Matrix-unterstützte Knorpelreparatur (AMIC bzw. MACI) im Vergleich zur Mikrofrakturierung (MFx) effektiver und sicherer bzw. im Vergleich zur autologen Chondrozytenimplantation (ACI) zumindest gleich wirksam und sicherer ist.

AMIC bzw. MACI versus MFx bzw. ACI

Methode

Die Beantwortung der Forschungsfragen bezüglich der Wirksamkeit und Sicherheit von AMIC bzw. MACI beruhte auf einer systematischen Literaturrecherche in verschiedenen Datenbanken und einer zusätzlichen Handsuche. Die Auswahl der Studien, die Datenextraktion und die Bewertung der Qualität der Studien wurden von zwei Autorinnen unabhängig voneinander durchgeführt.

systematische Literaturrecherche, -auswahl, -extraktion und -bewertung von mindestens zwei Autorinnen

Klinische Wirksamkeit

entscheidungsrelevante Endpunkte für Wirksamkeit

Die folgenden entscheidungsrelevanten Endpunkte wurden für die Bewertung der Wirksamkeit herangezogen: Mobilität/Gelenksfunktionalität, Lebensqualität, Schmerz und Notwendigkeit eines totalen Gelenkersatzes.

Sicherheit

entscheidungsrelevante Endpunkte für Sicherheit

Die folgenden entscheidungsrelevanten Endpunkte wurden für die Bewertung der Sicherheit berücksichtigt: schwerwiegende unerwünschte Ereignisse, eingriffsbezogene Komplikationen, Komplikationen im Zusammenhang mit der Matrix (implantatsbezogen) und Re-operationsraten.

Ergebnisse

Verfügbare Evidenz

keine kontrollierten Studien zum Sprunggelenk

Es konnten keine kontrollierten Studien identifiziert werden, in denen die ein- oder zweizeitige Matrix-gestützte Behandlung von (osteo)chondralen Defekten im Sprunggelenk untersucht wurde.

5 RCTs & 1 NRCT für AMIC (187 vs. 127 PatientInnen), 5 RCTs für Wirksamkeit von MACI (184 vs. 146 PatientInnen), 5 RCTs für Sicherheit von MACI (191 vs. 155 PatientInnen)

In Bezug auf die einzeitige Matrix-unterstützte Knorpelreparatur (AMIC) im Kniegelenk erfüllten lediglich fünf randomisierte kontrollierte Studien (RCTs) und eine nicht randomisierte kontrollierte Studie (NRCT) die Einschlusskriterien. Insgesamt umfassten die sechs Studien 187 PatientInnen, die dem einzeitigen Verfahren unterzogen wurden, und 127 PatientInnen, die lediglich die alleinige MFx erhielten. Bezüglich der zweizeitigen Matrix-unterstützten Behandlung (MACI) im Kniegelenk erfüllten jeweils fünf RCTs die Einschlusskriterien. Insgesamt umfassten die fünf RCTs zur Bewertung der Wirksamkeit 330 PatientInnen (184 vs. 146 [92 mit MFx, 54 mit ACI]). Die fünf RCTs zur Bewertung der Sicherheit umfassten 346 PatientInnen (191 vs. 155 [101 mit MFx, 54 mit ACI]).

Klinische Wirksamkeit

Einzeitiges Verfahren (AMIC)

keine statistisch signifikanten Unterschiede zwischen den Studiengruppen hinsichtlich Funktionalität, Lebensqualität und Schmerzen

In den sechs eingeschlossenen Studien wurden unterschiedliche Scores zur Messung der Wirksamkeit von AMIC im Vergleich zur alleinigen MFx berichtet: In Bezug auf den Wirksamkeitsendpunkt „Mobilität/Gelenkfunktionalität“ resultierte die Auswertung der Scores in inkonsistenten Ergebnissen. Bezüglich des Endpunktes „Lebensqualität“ konnte für die Interventionsgruppen eine Verbesserung festgestellt werden. Diese Verbesserung war jedoch nicht statistisch signifikant. In Bezug auf den Endpunkt „Schmerz“ wurden über die Studien hinweg ähnliche Verbesserungen zwischen den Studiengruppen berichtet.

1 totaler Gelenkersatz in einer Studie

In einer der sechs eingeschlossenen Studien wurde der Endpunkt „Notwendigkeit eines vollständigen Gelenkersatzes“ berichtet. In dieser Studie wurde ein totaler Kniegelenksersatz nach 12 Monaten gemeldet (Studiengruppe unklar).

Zweizeitiges Verfahren (MACI)

In den fünf eingeschlossenen Studien wurden unterschiedliche Scores zur Messung der Wirksamkeit von MACI bezüglich der Mobilität/Gelenksfunktionalität, der Lebensqualität und der Schmerzen herangezogen. Für den Vergleich, MACI versus MFx, wurden für die Interventionsgruppen teilweise statistisch signifikante Verbesserungen der Gelenkfunktionalität, der Lebensqualität und der Schmerzen berichtet.

MACI vs. MFx: teilweise statistisch signifikante Verbesserungen der Wirksamkeit in den Interventionsgruppen

In nur einer Studie (MACI vs. MFx) wurde der Endpunkt „Notwendigkeit eines vollständigen Gelenkersatzes" berichtet. In dieser Studie wurde nach 12 Monaten ein Fall eines totalen Kniegelenksersatzes in der Interventionsgruppe gemeldet.

1 totaler Gelenkersatz in einer Studie

Für den Vergleich, MACI versus ACI, wurden über die unterschiedlichen Scores und Studien hinweg inkonsistente Ergebnisse in Bezug auf Verbesserungen der Gelenkfunktionalität berichtet. In Bezug auf den Endpunkt „Schmerz" konnten keine statistisch signifikanten Unterschiede zwischen den Studiengruppen festgestellt werden. Für die Wirksamkeitsendpunkte „Lebensqualität" und „Notwendigkeit eines totalen Gelenkersatzes" lag keine Evidenz vor.

MACI vs. ACI: inkonsistente Ergebnisse in Bezug auf die Funktionalität, keine signifikanten Ergebnisse für Schmerzen

Sicherheit

Einzeitiges Verfahren (AMIC)

In allen extrahierten Studien wurden Komplikationen berichtet. Die Rate zu schwerwiegenden unerwünschten Ereignissen wurde in drei Studien berichtet und lag in den Interventionsgruppen zwischen 0 und 12,2 % und in den Kontrollgruppen zwischen 0 und 2,8 %. Eingriffsbezogene Komplikationen wurden in vier Studien berichtet und traten bei 0 bis 93,0 % der PatientInnen in den Interventionsgruppen und bei 0 bis 77,0 % der PatientInnen in den Kontrollgruppen auf. Die Raten zu den implantatsbezogenen Komplikationen lagen in drei Studien zwischen 3,0 und 22,0 %.

schwere unerwünschte Ereignisse: 0-12,2 % vs. 0-3,8 %, eingriffsbedingt: 0-93,0 % vs. 0-77,0 %, implantatsbedingt: 3,0-22,0 % in der Interventionsgruppe

Zweizeitiges Verfahren (MACI)

Komplikationen wurden in allen drei Studien berichtet, in denen MACI mit MFx verglichen wurde. Die Rate zu schwerwiegenden unerwünschten Ereignissen wurde in allen drei Studien berichtet und lag in den Interventionsgruppen zwischen 4,8 und 15,3 % und in den Kontrollgruppen zwischen 11,1 und 26,4 %. In allen drei Studien traten auch eingriffsbezogene Komplikationen bei 0-34,7 % der PatientInnen in den Interventionsgruppen und bei 0-38,9 % der PatientInnen in den Kontrollgruppen auf. In keiner der drei Studien wurde von implantatsbezogenen Komplikationen berichtet. Jedoch wurden in den drei RCTs von Re-operationsraten zwischen 2,5-8,3 % in den Interventionsgruppen und 0-9,7 % in den Kontrollgruppen berichtet.

MACI vs. MFx: schwere unerwünschte Ereignisse: 4,8-15,3 % vs. 11,1-26,4 %, eingriffsbedingt: 0-34,7 % vs. 0-38,9 %, Re-operationen: 2,5-8,3 % vs. 0-9,7 %

In beiden Studien, in denen MACI mit ACI verglichen wurde, wurden Komplikationen berichtet. Die Rate zu schwerwiegenden unerwünschten Ereignissen lag in den Interventionsgruppen zwischen 0 und 9,0 %, während in den Kontrollgruppen der Studien keine schwerwiegenden Ereignisse auftraten. In beiden RCTs wurden keine eingriffsbezogenen Komplikationen berichtet. Die Raten zu implantatsbezogenen Komplikationen lagen in den Interventionsgruppen zwischen 12.5 und 36,4 % und in den Kontrollgruppen zwischen 9,0 und 140 %. Die angegebenen Re-operationsraten reichten von 6,4-27,3 % der PatientInnen in den Interventionsgruppen und von 6,8-10,0 % der PatientInnen in den Kontrollgruppen.

MACI vs. ACI: schwere unerwünschte Ereignisse: 0-9,0 % vs. 0 %, eingriffsbedingt: 12,5-36,4 % vs. 9,0-140 %, Re-operationen: 6,4-27,3 % vs. 6,8-10,0 %

Laufende Studien

6 laufende RCTs zu AMIC/MACI vs. MFx, jedoch Laufzeit meist nur bis 24 Monate

Derzeit sind sechs RCTs zur einzeitigen bzw. zweizeitigen Matrix-basierten Knorpelreparatur im Vergleich zu MFx registriert. Die Mehrheit dieser Studien sieht jedoch keine Nachbeobachtungszeiträume von länger als 24 Monate vor und wird somit die Evidenzlücke an Langzeitdaten (>24 Monate) nicht füllen können.

keine laufenden RCTs oder NRCTs zu AMIC/MACI vs. ACI oder das Sprunggelenk

Es konnten keine laufenden RCTs oder NRCTs identifiziert werden, die die klinische Wirksamkeit und Sicherheit von AMIC/MACI im Vergleich zu ACI untersuchen. Des Weiteren konnten keine laufenden RCTs oder NRCTs für die Beurteilung beider Verfahren bei Knorpelschäden im Sprunggelenk identifiziert werden.

Kostenerstattung

AMIC aktuell in Österreich nicht erstattet, MACI im Leistungskatalog enthalten

Zum Zeitpunkt des Verfassens des vorliegenden Berichts wird das einzeitige Matrix-basierte Reparaturverfahren (AMIC) von Knorpeldefekten, Osteochondritis dissecans (OCD) oder (osteo)chondralen Läsionen im Knie- oder Sprunggelenk vom österreichischen Gesundheitssystem nicht erstattet. Die zweizeitige Matrix-basierte Knorpelreparatur (MACI) kann mit dem Code zur Kultivierung autologer Chondrozyten abgerechnet werden und ist demnach im Leistungskatalog enthalten.

Diskussion

Evidenzqualität AMIC: moderat bis gering Evidenzqualität MACI: gering bis sehr gering

Insgesamt ist die Qualität der Evidenz für die Wirksamkeit und Sicherheit der einzeitigen Matrix-basierten Knorpelreparatur – in Kombination mit MFx – (AMIC) des Kniegelenks im Vergleich zur alleinigen MFx als moderat bzw. gering einzustufen. Die Qualität der Evidenz für die Wirksamkeit und Sicherheit der zweizeitigen Matrix-gestützten Knorpelreparatur (MACI) des Kniegelenks im Vergleich zur MFx oder zu ACI ist gering bzw. sehr gering.

AMIC vs. MFx: geringe Pat.-Anzahl und kurze Nachbeobachtungszeiträume

Die wesentlichen Limitationen der Evidenz bezüglich AMIC versus MFx alleine umfassen die geringen Stichprobengrößen und die kurzen Nachbeobachtungszeiträume (bis zu fünf Jahre) in der Mehrzahl der Studien. Nur zwei von fünf Studien hatten eine Nachbeobachtungszeit von mindestens fünf Jahre.

MACI vs. MFx/ACI: wenige PatientInnen und kurze Nachbeobachtungszeiträume

Wie in den AMIC-Studien, waren die wesentlichen Limitationen der Studien zu MACI versus MFx oder ACI die geringe Anzahl von PatientInnen und die kurzen Nachbeobachtungszeiträume. Lediglich eine Studie (im Vergleich zu MFx) hatte eine Nachbeobachtungszeit von mehr als 24 Monaten, weshalb langfristige Evidenz mangelhaft ist.

PatientInnen-berichtete Wirksamkeitsendpunkte – Subjektivität

Die Mehrzahl der Wirksamkeitsendpunkte (Mobilität/Gelenkfunktionalität, Lebensqualität, Schmerzen und Aktivitäten des täglichen Lebens) wurden von den PatientInnen selbst berichtet und könnten dadurch verzerrt sein. Aus diesem Grund wurde der Grad der Subjektivität bei der Beurteilung des Bias-Risikos berücksichtigt.

aggregierte Aussagen zur Sicherheit nur limitiert möglich

Darüber hinaus waren aufgrund der unvollständigen oder inkonsistenten Berichterstattung, Erfassung bzw. Meldung unerwünschter Ereignisse in der Mehrzahl der eingeschlossenen Studien aggregierte Aussagen zur Sicherheit kaum möglich.

langfristige Wirksamkeits- und Sicherheitsergebnisse fehlen

Insgesamt fehlen zuverlässige Daten zur langfristigen Wirksamkeit und Sicherheit der beiden Verfahren (AMIC & MACI).

Zusammenfassung und Empfehlung

Auf der Grundlage der verfügbaren Evidenz können keine Schlussfolgerungen gezogen werden, ob die ein- bzw. zweizeitige Matrix-unterstützte Knorpelreparatur wirksamer und sicherer ist als MFx oder zumindest genauso wirksam und sicherer ist als ACI.

Evidenz nicht ausreichend → verlässliche Aussage nicht möglich

Da keine kontrollierten Studien für die Knorpelreparatur des Sprunggelenks identifiziert werden konnten, konnte keine Empfehlung bezüglich der Aufnahme von AMIC und/oder MACI bei Knorpelreparaturen des Sprunggelenks in den österreichischen Leistungskatalog formuliert werden.

keine Evidenz für das Sprunggelenk → keine Empfehlung

Aufgrund der inkonsistenten Ergebnisberichterstattung der Knorpelreparatur im Kniegelenk zeigten die eingeschlossenen Studien eine teilweise schlechte Qualität der Evidenz und ein hohes Verzerrungspotenzial. Daher kann für beide Interventionen keine verlässliche Aussage hinsichtlich der klinischen Wirksamkeit und Sicherheit getroffen werden. Aus diesem Grund werden AMIC und MACI bei Knorpelreparaturen im Kniegelenk derzeit nicht für die Aufnahme in den österreichischen Leistungskatalog empfohlen.

schwache Qualität der Evidenz zum Knie → AMIC & MACI derzeit nicht für Erstattung empfohlen

Neue Studienergebnisse, insbesondere aus Studien mit einer höheren Anzahl an PatientInnen und längeren Nachbeobachtungszeiträumen (z. B. zehn Jahren), könnten die Effektschätzung der beiden Interventionen erheblich beeinflussen.

Studien mit größeren Pat.-Populationen & längerem Follow-up erforderlich

Eine Re-evaluierung für AMIC wird nicht vor 2022 empfohlen, da laufende RCTs noch ausständig sind. Für MACI könnte eine Re-evaluierung nach 2021 sinnvoll sein, da das Verfahren im Vergleich zur MFx vielversprechend erscheint.

Re-evaluierung von AMIC nach 2022; Re-evaluierung von MACI nach 2021

Summary of the assessment 2016

Scope

erste systematische Übersichtsarbeit von 2016

The systematic review "Single-step scaffold-based cartilage repair in the knee" was performed by the Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA) on behalf of the Austrian Ministry of Health in the year 2016 [1]. The aim was to answer the following research questions:

PIKO-Fragen von 2016

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

Einschlusskriterien von 2016

The following inclusion criteria for relevant studies summarised in Table 1 were considered.

Table 1: Inclusion criteria

Population	✿ Adult patients with indications for surgical cartilage repair in the knee ✿ Grades 3-4 (Outerbridge Classification) localised cartilage damages/defects/disorders in the knee ✿ Grades 3-4 (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
Intervention	✿ Single-step cell-free scaffold-based cartilage repair in combination with microfracture ✿ Alternative terms (selection): ✿ Autologous matrix-induced chondrogenesis (AMIC) ✿ Cell-free matrix-induced chondrogenesis ✿ Cell-free (collagen) matrices/matrix ✿ Product names: ✿ BST-CarGel® ✿ CaReS®-1S ✿ Chondro-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 ❖ Necessity 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)

Description of the technology

einzeitige Knorpelreparatur in Kombination mit Mikrofrakturierung

In the single-step scaffold-based treatment in combination with microfracture 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 three-dimensional structure. The matrix decomposes over time.

Mikrofrakturierung + (M)ACI als Vergleich

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

Description of the health problem

Fokus: (Knochen-) Knorpelschäden im Knie

The systematic review of 2016 [1] focused on the treatment of chondral and osteochondral lesions in the knee.

Knorpel ist Gleitschicht

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.

Knorpelschäden durch Trauma oder Abnutzung

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).

Results

wichtige Wirksamkeitsendpunkte für Empfehlung

In the report from 2016, the following outcomes were defined as crucial to derive a recommendation:

Outcomes for clinical effectiveness:

- Mobility/joint functionality measured by different scores [2]:
  - Knee Injury and Osteoarthritis Outcome Score (KOOS),
  - International Knee Documentation Committee (IKDC) Subjective Knee Form,
  - Western Ontario McMaster University Osteoarthritis Index (WOMAC),

- Modified Cincinnati Knee Rating Systems,
- Lysholm scoring scale,
- Modified International Cartilage Repair Society (ICRS) Score.

- Quality of life measured by different scores:
  - EQ-5D,
  - Short-Form Health Survey (SF-36, SF-12, SF-8).
- Pain measured with several instruments:
  - Visual Analogue Scale (VAS).
- Necessity of a total joint replacement

A further outcome not considered crucial, but used to answer the effectiveness-related research questions, was "return to activities".

zusätzlicher Endpunkt nicht relevant für Empfehlung

Outcomes for safety:

- Procedure-related complications associated with the surgical intervention, e.g., events associated with anaesthesia, infections, damages to nerves or blood vessels, bleeding, or the occurrence of blood clots.
- Device-related complications associated with the implantation of the scaffold, e.g., movement or release of the scaffold or allergic reactions.
- Procedure-related mortality considering cases up to ten days postoperatively.
- Re-operation rate.

wichtige Sicherheitsendpunkte für Empfehlung

For the clinical effectiveness, no controlled trials comparing AMIC with (M)ACI could be identified. However, three randomised controlled trials (RCTs) [3-5] and one non-randomised controlled trial (NRCT) [6], with a total of 136 patients assessing the clinical effectiveness of AMIC (scaffold groups) in combination with microfracture (MFx) compared to MFx alone (MFx groups), could be identified. The mean age of the patients ranged from 33 to 38 years in the scaffold groups and from 37 to 41 years in the MFx groups across trials. Patients had grade III-IV (Outerbridge Classification) of chondral defects with a mean lesion size of 2.3-3.7 cm^2 in the scaffold groups and 2.0-2.9 cm^2 in the MFx groups. The follow-up of the studies was 6, 24 and up to 60 months (five years). In one RCT [4], Chondro-Gide®, in the other two RCTs [3, 5] BST-CarGel®, and in the non-randomised clinical trial (CT) [6] a polyethylene glycol diacylate hydrogel were applied. No studies were available assessing the clinical effectiveness of other products like CaReS®-1S, Chondrotissue®, MaioRegen™ or MeRG® that met the inclusion criteria. For the safety evaluation, RCTs, prospective non-randomised CT, and prospective single-arm studies with at least 50 patients and a follow-up of at least 24 months were considered. No additional prospective single-arm studies met the inclusion criteria; the same four studies [3-6] as for clinical effectiveness were thus considered for safety.

keine RCTs:
AMIC vs. (M)ACI,
3 RCTs and 1 NRCT:
AMIC vs. MFx alleine,
Durchschnittsalter:
33-41 Jahre,
durchschn. Defektgrößte: 2,3-3,7 cm^2,
Leistungen:
Chondro-Gide®,
BST-CarGel®, etc.

keine zusätzlichen Beobachtungsstudien eingeschlossen

The clinical effectiveness and safety of AMIC could only be evaluated compared to MFx, as no studies were available for the comparison to (M)ACI. In the three included RCTs [3-5], the effect on mobility or joint functionality was measured by five different scoring systems. In one RCT [4], it was measured with the Modified Cincinnati Score (scale: 6-100) and with a modified ICRS score. For both scores, no statistically significant differences between the study groups could be identified. In the second RCT [3, 5], joint functionality was measured with the WOMAC subscale scores for stiffness (scale: 0-20) and for function (scale: 0-170). The changes of the WOMAC sub-scores be-

Mobilität/Funktionalität gemessen mit 5 Scores in 3 RCTs,

tween the study groups were statistically not significant at any time point. In the NRCT [6], joint functionality was measured with the IKDC Score; however, no statistically significant differences of the score changes between the study groups could be stated.

Lebensqualität gemessen mit einem Score in 2 RCTs,

Schmerz gemessen mit 2 Scores in 2 RCTs,

Notwendigkeit eines totalen Knorpelaustausches in 1 RCT berichtet,

Nebenwirkungen in allen inkludierten Studien berichtet: 0-93 %

With regard to quality of life, one RCT [3, 5] measured the generic quality of life using the mental components of the SF-36 (version 8); however, no differences in changes of the scores between the study groups were statistically significant. In another RCT [3, 5], the disease-specific quality of life was measured with the physical component of the SF-36 (version 2); however, the differences in changes of the scores between the study groups were not statistically significant. Regarding the outcome "pain", one RCT [4] measured pain on a VAS (scale: 0-100). In the other RCT [3, 5], pain was measured with the WOMAC subscale score for pain (scale: 0-50). In both RCTs, no statistically significant differences in changes of the pain scores could be identified. The necessity of a total joint replacement was reported in one RCT [4] and showed one patient who received a joint replacement after AMIC. In the MFx group, the joint did not need to be replaced in any of the patients. None of the included studies reported on the outcome "return to activities". Two RCTs [3-5] and the non-randomised CT [6] reported on adverse events related to the surgical procedure. The reported rates ranged from 0 to 93% in the scaffold groups and from 0 to 77% in the MFx groups. Adverse events related to the device were reported in 0 to 22% in two RCTs [3-5]. None of the included studies clearly stated the kind of adverse events, as well as if any re-operations were necessary.

Evidenzstärke für AMIC vs. MFx als „niedrig" eingestuft

Overall, the strength of evidence evaluating the effectiveness and safety of AMIC in combination with MFx, compared to MFx alone, was "low", indicating that the confidence in the effect estimate is limited, according to the GRADE rating scheme.

Recommendation

AMIC vorerst nicht empfohlen für die Aufnahme in den Leistungskatalog

The evidence included in the 2016 report was not sufficient to conclude that the single-step matrix-assisted cartilage repair combined with MFx (AMIC) is more effective and safer than MFx. No evidence was available to compare AMIC with the (matrix-assisted) autologous chondrocyte implantation. Therefore, it was concluded in the report that the inclusion of the single-step matrix-assisted cartilage repair combined with MFx (AMIC) was currently not recommended for inclusion in the Austrian hospital benefit catalogue.

UPDATE 2019

1 Scope

1.1 PICO question

Anpassung der Forschungsfragen

According to the Austrian Ministry of Health, there have been changes of the original PICO from 2016, including one additional indication, as well as changes in the intervention and control groups. This resulted in the following adapted research questions:

PICO-Fragen für Update 2019

1. Is the single-step scaffold-based cartilage repair (AMIC) in combination with MFx more effective and safer in comparison to MFx alone in patients with indications for cartilage surgery in the knee or ankle concerning the outcomes listed in Table 1-1.
2. Is the single-step scaffold-based cartilage repair (AMIC) in combination with MFx as effective, but safer in comparison to the two-step cartilage repair procedure, autologous chondrocyte implantation without matrix (ACI), in patients with indications for cartilage surgery in the knee or ankle concerning the outcomes listed in Table 1-1.
3. Is the two-step scaffold-based cartilage repair procedure, matrix-induced autologous chondrocyte implantation (MACI), more effective and safer in comparison to MFx in patients with indications for cartilage surgery in the knee or ankle concerning the outcomes listed in Table 1-1.
4. Is the two-step scaffold-based cartilage repair procedure, matrix-induced autologous chondrocyte implantation (MACI), as effective, but safer in comparison to the two-step cartilage repair procedure, autologous chondrocyte implantation without matrix (ACI), in patients with indications for cartilage surgery in the knee or ankle concerning the outcomes listed in Table 1-1.

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien für Update

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

Table 1-1: Inclusion criteria

Population	✿ Adult patients with indications for surgical cartilage repair in the knee and ankle joints ✿ Grades 3-4 (Outerbridge Classification) localised cartilage damages/defects/disorders in the knee ✿ Grades 3-4 (ICRS classification) (osteo)chondral lesions ✿ Osteochondritis dissecans (OCD) ✿ Contraindications: ✿ Defect size <1 and >10 cm² ✿ Allergies of the used material(s) ✿ Inflammatory cartilage diseases ✿ Malposition of the knee ≥5 degrees ICD-10 codes:M17.9, M24.1, M24.17, M94.8, M94.9, M93.2	
Intervention	✿ Single-step cell-free scaffold-based cartilage repair in combination with microfracture ✿ Alternative terms (selection): ✿ Autologous matrix-induced chondrogenesis (AMIC) ✿ Cell-free matrix-induced chondrogenesis ✿ Cell-free (collagen) matrices/matrix ✿ Product names: ✿ BST-CarGel® ✿ CaReS®-1S ✿ Chondro-Gide® ✿ Chondrotissue® ✿ GelrinC® ✿ Hyalofast® ✿ MaioRegen™ ✿ MeRG® ✿ Novocart Basic® ✿ Chondrofiller® ✿ JointRep™	✿ Two-step scaffold-based cartilage repair in combination with microfracture ✿ Alternative terms (selection): ✿ Matrix-induced autologous chondrocyte implantation/ transplantation (MACI/T) ✿ Product names: ✿ Spherox® ✿ BioSeed®-C ✿ NeoCart
Control	✿ Microfracture surgery/microfracturing ✿ Autologous chondrocyte implantation/transplantation (ACI/ACT)	
Outcomes		
Efficacy	✿ Mobility/joint functionality ✿ Pain ✿ Quality of life ✿ Necessity of total joint replacement ✿ Complete defect filling ✿ Return to daily activities/sports/physical activity	
Safety	✿ Adverse events ✿ Mortality (up to ten 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	

2 Methods

2.1 Research questions

Description of the technology	
Element ID	**Research question**
B0001	What is AMIC/MACI and the comparator(s)?
A0020	For which indications has AMIC/MACI received marketing authorisation or CE marking?
B0002	What is the claimed benefit of AMIC/MACI in relation to the comparators?
B0003	What is the phase of development and implementation of AMIC/MACI and the comparator(s)?
B0004	Who administers AMIC/MACI and the comparators, and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use AMIC/MACI and the comparator(s)?
B0009	What supplies are needed to use AMIC/MACI and the comparator(s)?
A0021	What is the reimbursement status of AMIC/MACI?

Health problem and current use	
Element ID	**Research question**
A0001	For which health conditions, and for what purposes is AMIC/MACI 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?
A0023	How many people belong to the target population?
A0011	How much is AMIC/MACI utilised?

Clinical Effectiveness	
Element ID	**Research question**
D0005	How does AMIC/MACI affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the AMIC/MACI affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of AMIC/MACI on patients' body functions?
D0016	How does the use of AMIC/MACI affect activities of daily living?
D0012	What is the effect of AMIC/MACI on generic health-related quality of life?
D0013	What is the effect of AMIC/MACI on disease-specific quality of life?
D0017	Was the use of AMIC/MACI worthwhile?

Safety	
Element ID	**Research question**
C0008	How safe is AMIC/MACI in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying AMIC/MACI?
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 AMIC/MACI?
C0007	Are AMIC/MACI and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of AMIC/MACI and the comparator?
D0001	What is the expected beneficial effect of AMIC/MACI on mortality?
D0003	What is the effect of AMIC/MACI on the mortality due to causes other than the target disease?

2.2 Sources

Description of the technology

Quellen: systematische Suche, Handsuche sowie Informationen der Hersteller und Einreicher

- Hand search in the POP, AdHopHTA and CRD databases for Health Technology Assessments, and in Google
- Background publications identified in database search: see Section 2.3
- Documentation provided by the manufacturers
- Information provided by the submitting hospitals.

Health problem and current use

Quellen: systematische Suche, Handsuche, sowie Informationen der Hersteller und Einreicher

- Hand search in the UpToDate database, POP, AdHopHTA and CRD databases for Health Technology Assessments, and in Google
- Background publications identified in database search: see Section 2.3
- Documentation provided by the manufacturers
- Information provided by the submitting hospitals
- Hand search for management guidelines in the Trip Database[1] and in the database of the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF).

systematische Literatursuche für Wirksamkeit und Sicherheit

For the domains of clinical effectiveness and safety, a systematic literature search and hand search were conducted, as described in detail in the following chapter.

[1] Since the National Guideline Clearinghouse (NGC) database no longer exists, the Trip Database is a valuable alternative, as it undertakes the existing guidelines from NGC.

2.3 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted from the 7th until the 14th of December 2018 in the following databases:

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

Suche eingegrenzt nach Sprache und Studiendesign: 323 Treffer

The systematic search was not limited to years, but it was limited to articles published in English or German and to only (non-) randomised controlled trials or prospective observational studies. After deduplication, a total of 323 citations were included. The specific search strategy employed can be found in the Appendix (Chapter "Literature search strategies").

28 Publikationen von Herstellern

Manufacturers from the most common products (CaReS®-1S, Chondro-Gide®, Chondrotissue®, Hyalofast®, JointRep™, Spherox®) submitted 28 publications, from which two new citations were identified.

1 zusätzliche Publikation vom Report 2016

From the hand search of the original report [1], one additional relevant study could have been identified.

11 systematische Übersichtsarbeiten, jedoch ausgeschlossen,

22 zusätzliche Studien identifiziert

insgesamt 374 Treffer identifziert

A total of eleven systematic reviews and health technology assessments (HTAs) on the surgical management (AMIC, [M]ACI) of (osteo)chondral defects in the knee and ankle joint could be identified through the systematic literature search. However, due to methodological differences (e.g., other study purposes, inclusion of retrospective studies) of the reviews, we decided to exclude the systematic reviews and HTAs from our analysis. Nonetheless, we searched through the reviews to see if they identified studies that we did not find via our systematic literature search. Most of the reviews provided relevant background information for this report and 22 additional studies were identified, resulting in 374 hits (after deduplication) overall.

keine neue Publikation

The submitting hospital sent seven publications, from which no new citations were identified.

Suche nach laufenden Studien: 6 Treffer

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trial registries (ClinicalTrials.gov, WHO-ICTRP, EU Clinical Trials [EudraCT]) was conducted from the 14th until 16th of January 2019, resulting in 85 hits. Of those 85 hits, six were identified as potentially relevant trials (RCTs) and included in the Appendix (see Chapter "List of ongoing randomised controlled trials"). The other 79 ongoing trials were excluded because of other study designs (e.g., single-arm), other interventions or other populations.

2.4 Flow chart of study selection

Literaturauswahl: 13 Studien eingeschlossen, davon 3 „Erweiterungsstudien"

Overall, 374 hits (after deduplication) 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.

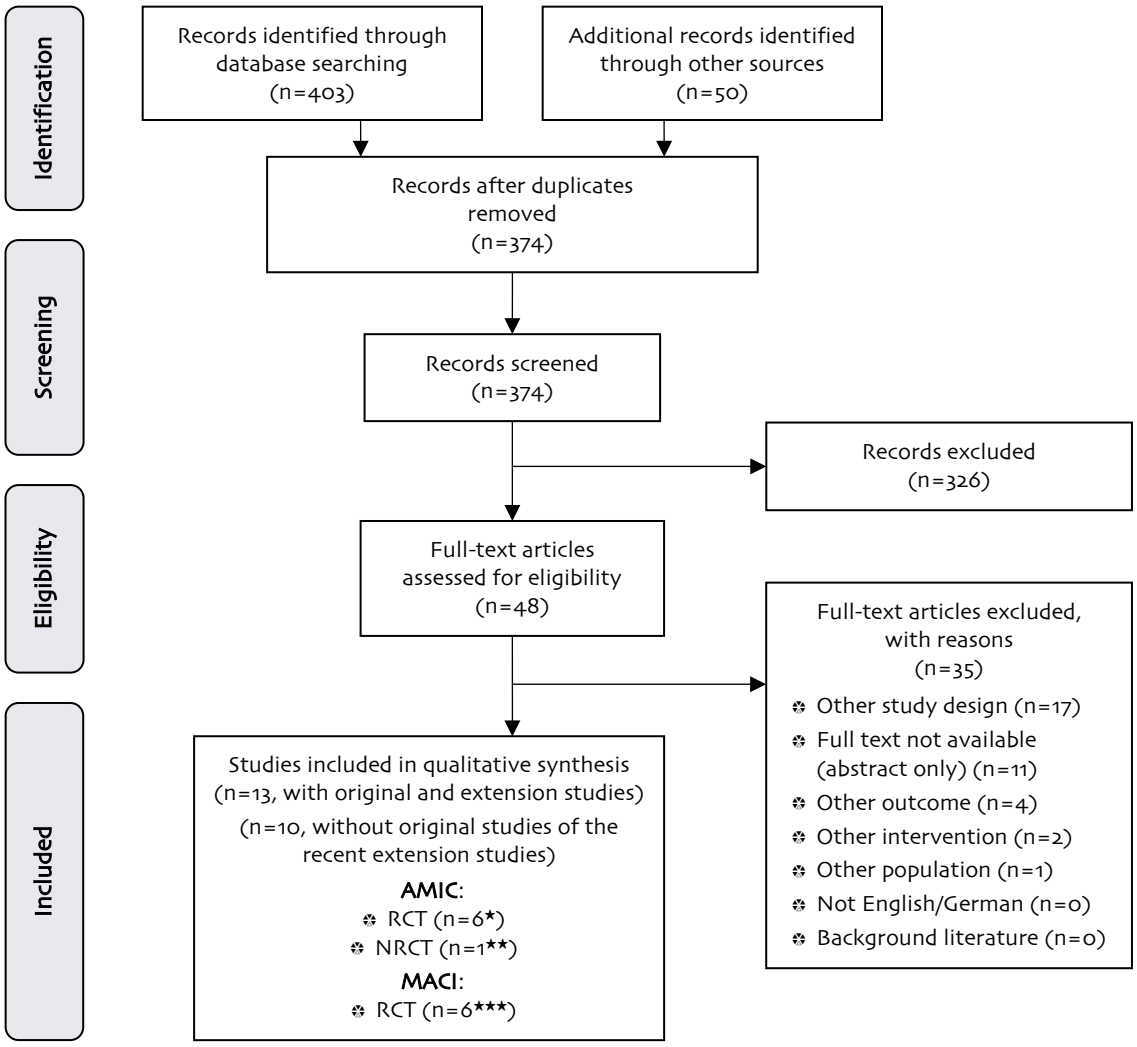

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

* *Two of the six RCTs were interim analyses of the included two extension studies (Volz 2017 [7] & Anders 2013 [4]; Shive 2015 [3] & Stanish 2013 [5]). For Volz/Anders only the data of Volz 2017 were considered for the analysis due to longer follow-up and larger patient population. For Shive/Stanish, the data from both studies are presented: from Stanish after 12 months and from Shive after 60 months, since Shive had a longer follow-up but included fewer patients.*

** *This study, Sharma 2013 [6], was initiated as a RCT.*

*** *One of the six RCTs was an interim analysis of the included extension study (Saris 2014 [8] & Brittberg 2018 [9]). Efficacy data were extracted from Brittberg 2018 and safety data from Saris 2014.*

2.5 Analysis

Datenextraktion und Bewertung des Bias-Risikos laut Cochrane RoB-Tool und ROBINS-I

The data retrieved from the selected studies (see Chapter 2.4) were systematically extracted into data extraction tables (see Appendix Table A-1, Table A-2, Table A-3 and Table A-4). No further data processing (e.g., indirect comparison) was applied. The studies were systematically assessed for quality and risk of bias (RoB) by two independent researchers (SW, KR) using the Cochrane Collaboration's tool for assessing risk of bias for randomised controlled studies [10] and the Risk Of Bias In Non-randomised Studies of Interventions assessment tool (ROBINS-I) [11] presented in the Appendix (see Table A-5, Table A-6, and Table A-7).

2.6 Synthesis

Evidenzsynthese mittels GRADE

Based on the data extraction tables (see Appendix Table A-1, Table A-2, Table A-3 and Table A-4), data on each selected outcome category were synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [12]. The research questions were answered in plain text format with reference to GRADE evidence tables that are included in the Appendix; results were summarised in Table A-8 and Table A-9.

3 Description and technical characteristics of technology

Features of the technology and comparators

B0001 – What is the technology and the comparator(s)?

MFx stimuliert Knochenmark

The standard single-step cartilage repair technique is the microfracture technique (MFx) [13, 14]. It consists of 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 [15, 16]. It is used for small defects (≤ 2 cm^2).

Fokus: einzeitiges (AMIC) und zweizeitiges (MACI) Verfahren für Knorpelreparatur in Kombination mit Mikrofrakturierung (MFx)

This systematic review focuses on approaches where the MFx technique is combined with the implantation of a scaffold, like *the single-step scaffold-based treatment* of cartilage defects. This technique uses a matrix which is implanted in the area of the damaged cartilage to cover the blood clot after MFx. Thus, it is also called *the autologous matrix-induced chondrogenesis (AMIC)* [13, 15-17]. 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 three-dimensional structure. The used matrices are cell-free scaffolds; however, the material and configuration of the scaffolds vary between the individual products, and decompose over time [1, 18].

MACI speziell für größere Defekte (≤ 10 cm^2)

zellfreie Matrix als Unterstützung für Zellansiedlung

For larger defects (≤ 10 cm^2), the autologous chondrocyte implantation (ACI) is indicated, which can also be used in combination with a matrix (so-called matrix-induced autologous chondrocyte implantation [MACI]). These techniques include two steps. In a first step, intact cartilage is sampled arthroscopically from a non-weight-bearing 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. Chondrocytes are applied onto the damaged area in combination with a membrane (tibial periosteum or biomembrane) or pre-seeded in a scaffold matrix (e.g., collagen matrix, hyaluronan matrix) [1].

MFx und ACI als Vergleichsinterventionen

In the present review, MFx and ACI, both treatments without a matrix, were considered as the comparators.

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

8 AMIC Hersteller in Bericht aus 2016

In the original systematic review from 2016, eight products from eight manufacturers were listed for the single-step intervention, AMIC (Table 3-1):

Table 3-1: Manufacturers and products of the single-step procedure of the original assessment in 2016

Manufacturer	Product	Characteristics	CE marking
Pirimal Enterprises Limited, Canada	BST-CarGel®	Gel that consists of a chitosan solution (a natural polymer) and a buffer.	Yes (2014)
Arthro Kinetics AG, Germany	CaReS®-1S	A collagen type I matrix for the treatment of chondral lesions.	Yes (year unknown)
Geistlich Pharma, Switzerland	Chondro-Gide®	A bilayer matrix made from porcine collagen type I/III for the treatment of traumatic chondral and osteochondral lesions. Besides AMIC, the product can also be used for MACI (matrix-assisted autologous chondrocyte implantation).	Yes (2010)
BioTissue Technologies GmbH, Switzerland	Chondrotissue®	The matrix is made from polyglycolic acid fleece and freeze-dried sodium hyaluronate for the treatment of chondral lesions.	Yes (year unknown)
Regentis Biomaterials Ltd., Israel	GelrinC®	A hydrogel of polyethylene glycol di-acrylate (PEG-DA) and denatured fibrinogen, crosslinked with UVA light in-situ, for the treatment of chondral defects.	Yes (2013)
Anika Therapeutics, Inc., USA	Hyalofast®	A biodegradable, hyaluronan-based (HYAFF) scaffold; it is intended for the repair of chondral or osteochondral lesions.	Yes (2013)
Fin-Ceramica Faenza S.p.A., Italy	MaioRegen™	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 magnesium-enriched hydroxyapatite (Mg-HA) and stimulates the subchondral bone structure.	Yes (year unknown)
Bioteck S.p.A., Italy	MeRG®	A microfibrilla collagen membrane that is inserted in the chondral lesion after microfracture.	Yes (2012)

3 zusätzliche Produkte im aktuellen Bericht

For the present systematic review, three additional products from three manufacturers could be identified for the single-step intervention (AMIC) (Table 3-2):

Table 3-2: Additional manufacturers and products of the single-step procedure

Manufacturer	Product	Characteristics	CE marking
B. Braun	Novocart Basic®	Biphasic, three-dimensional collagen-based matrix inserted after microfracture technique.	Yes (year unknown)
Amedrix GmbH	Chondrofiller®	Biological cartilage implant made of high-purity, native collagen, available as a cell-free matrix in the form of a gel or a liquid.	Gel: Yes (2012) Liquid: Yes (2013)
Oligo Medic	JointRep™	Injectable hydrogel from chitosan/glucosamine to fill in cartilage defects.	Yes (2013)

3 Produkte für MACI Verfahren identifziert

Furthermore, three additional products from three manufacturers for the two-step intervention (MACI) were added to this report (in the original assessment of 2016 MACI was only included as a comparator) (Table 3-3):

Table 3-3: Additional manufacturers and products of the two-step procedure

Manufacturer	Product	Characteristics	CE marking
BioTissue Technologie GmbH, Germany	BioSeed®-C	Autologous three-dimensional chondrocyte transplantation.	Yes (year unknown)
CO.DON AG	Spherox®	Matrix-associated endogenous three-dimensional cartilage cell transplantation.	Authorised as ATMP (07/2017)
Histogenics®	NeoCart®	Cells seeded on a unique three-dimensional collagen scaffold and cultured under exacting conditions of high pressure, oxygen concentration and perfusion in their proprietary Tissue Engineering Processor (TEP).	NR

Abbreviations: ATMP – Advanced therapy medicinal product, NR – not reported

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

AMIC: Behandlung größerer Defekte vs. MFx; einzeitiger Eingriff → weniger Komplikationen & geringere Kosten vs. ACI

The single-step scaffold-based treatment of cartilage damages (AMIC) enables the treatment of larger cartilage defects than MFx alone. Furthermore, it provides a better microenvironment and structure for cell proliferation [19, 20]. In comparison to ACI, AMIC claims the advantage of the single-step procedure, sparing the need for a second intervention (one for the biopsy and one for the implant), resulting in fewer complications and lower costs, but at comparable effectiveness with regards to clinical outcomes [1, 20, 21].

MACI einfachere Operation als ACI & verbesserte Zellansiedlung als MFx, aber kostenintensiver vs. MFx

The two-step matrix-induced procedure (MACI), in contrast to ACI, claims an easier intraoperative handling (e.g., no need for the extraction of periosteal flap), resulting in shorter duration of the surgery and the development of a stable hyaline cartilage. In addition, MACI might lead to fewer hypertrophies of the transplant compared to ACI. Furthermore, in comparison to matrix-free techniques (e.g., MFx), the use of an autologous matrix seems to enhance the cell proliferation. However, compared to the single-step interventions (e.g., MFx), during (M)ACI, healthy cartilage needs to be damaged and it is more cost-intensive [1, 20, 21].

B0003 – What is the phase of development and implementation of the technology and the comparator(s)?

No evidence was available to answer this research question for both interventions (AMIC & MACI).

3 Generationen des ACI Verfahrens:
- ACI-P (Periost)
- ACI-C (Collagen)
- ACI 3. Generation (MACI)

There are three generations of the ACI procedure. According to the original ACI technique, the cartilage defect is covered by a periosteal flap removed from the tibia, the so-called ACI-P technique. To avoid removal of periosteum from the tibia, a more advanced ACI technique was developed. A membrane of porcine type I/III collagen is used to cover the lesion filled with cultured chondrocytes (ACI-C). In the third ACI generation, chondrocyte cells are implanted on a membrane by using a membrane consisting of a porcine type I/III collagen bilayer seeded with chondrocytes. However, problems in the cultivation of chondrocytes are the slow growth and the dedifferentiation of cells, including a switch of collagen synthesis from type II to type I [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?

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)?

Operationen an Gelenksknorpel von OrthopädInnen auszuführen, steriler OP erforderlich, für MACI zusätzlich Labor

Both techniques of the present review (AMIC & MACI) should be performed by an orthopaedic surgeon with the support of two persons from the nursing staff. The procedures can be performed under general or spinal anaesthesia. For the surgery, a sterile operation theatre and several instruments are required. For both techniques, matrices are needed, while for MACI a laboratory for cell culturing and expansion is additionally required [1, 21, 24-26].

Regulatory & reimbursement status

A0021 – What is the reimbursement status of the technology?

zum Zeitpunkt des Berichts 2016 wurde AMIC nicht erstattet

At the time of the first report in 2016, the single-step scaffold-based repair (AMIC) of cartilage defects or osteochondritis dissecans (OCD) or (osteo)-chondral lesions in the knee joint was not included in the Austrian hospital benefit catalogue and, therefore, was not reimbursed by the Austrian health care system [1].

aktuell keine Erstattung von AMIC in Österreich

Currently, the single-step scaffold-based repair (AMIC) of cartilage defects or osteochondritis dissecans (OCD) or (osteo)chondral lesions in the knee or ankle joint, are not included in the Austrian DRG system (Leistungsorientierte Krankenanstaltenfinanzierung/LKF). Therefore, the intervention itself is still not reimbursed by the Austrian health care system. However, the intervention could be billed with other codes, e.g., for arthroscopic operations of the knee or ankle joint (Code NF020 – Arthroskopische Operation des Kniegelenks; Code NG020 – Arthroskopische Operation des Sprunggelenks) [27].

Erstattung von MACI mit Code NF130

The two-step matrix-induced procedure (MACI) can be billed with the code for the cultivation of autologous chondrocytes (Code NF130 – Kultivierung autologer Chondrozyten) and therefore, it is included in the Austrian DRG system [27].

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?

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

The described AMIC and MACI techniques are intended for the treatment of articular chondral or osteochondral lesions, a debilitating condition, Outerbridge grade III-IV [1, 14, 16, 24] (additional information from the submitting hospitals). The scope of the present assessment comprises matrix-assisted treatments (AMIC and MACI) of cartilage defects in the knee and talus (ankle joint).

Behandlung (osteo)chondraler Defekte

Fokus auf Knie- und Sprunggelenk

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. Damage of the cartilage can occur due to traumatic events, such as sport injuries or incorrect weight-bearing, degeneration of the joint that mostly occurs in elderly people or due to osteochondritis dissecans (OCD). OCD is an acquired idiopathic lesion of subchondral bone characterised by osseous resorption, collapse, and sequestrum formation, thus, it can also cause an osteochondral lesion [1, 14, 26, 28].

Knorpel ist dünne Gewebsschicht

Risikofaktoren: Trauma (z. B. Sportverletzung), Abnutzung, Osteochondritis dissecans

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

(Osteo)chondral lesions can occur in nearly every phase of life. Besides older persons with degenerative cartilage damage, especially young and active persons are likely to acquire such damages. 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 [1, 24, 29].

Defekte v. a. bei älteren und jungen, sportlich aktiven Personen

geringes intrinsisches Heilungsvermögen

(Osteo)chondral defects and OCD (of both, knees and ankles) can be graded via different systems, which are mainly determined by the type of diagnostic examination (e.g., MRI or arthroscopy), such as [1]:

verschiedene Klassifikationssysteme

- The classification of chondral effects by ICRS [1, 30]:

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 (cartilage defects >50% of cartilage depth)
4	Severely abnormal (through the subchondral bone)

Abbreviation: *ICRS – International Cartilage Regeneration & Joint Preservation Society*

- The classification of chondral defects by Outerbridge [1, 30]:

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

- The classification of OCD and osteochondral defects by Kramer [1, 31]:

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

Abbreviation: *OCD – Osteochondritis dissecans*

- The classification of OCD and osteochondral defects by Guhl [1, 32]:

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

Abbreviation: *OCD – Osteochondritis dissecans*

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, Osteoarthritis bis hin zu Gelenksersatz

Patients with (osteo)chondral defects are suffering from pain and impaired mobility, leading to a lower quality of life [17]. In severe cases, it can lead to degenerative osteoarthritis and further progression accompanied with the requirement of a joint replacement [1, 24, 25].

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

~ 80.000 OPs am Knie- bzw. ~3.000 am Sprunggelenk in Ö

In Austria, 78,277 surgeries of the knee joint and 2,855 surgeries of the talus were performed in 2016 [33]. Out of the surgeries of the knee joint, a total of 37,364 interventions were arthroscopic surgeries [34].

keine Daten zu AMIC oder MACI Interventionen

However, neither information on the number of AMIC or MACI interventions of the knee joint or talus performed, nor information regarding the prevalence or incidence of cartilage disorders or OCD have been identified.

zusätzliche gesellschaftliche Kosten

Furthermore, a vast majority of the patients suffering from defect cartilage of the knee or ankle are in their productive age. As a result, some of the patients are incapacitated for work, which can be assumed to result in additional societal costs.

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?

3 Leitlinien identifiziert

zunächst klinische Diagnostik, danach Einsatz bildgebender Verfahren

There is a German guideline for the diagnosis (and treatment) of OCD available that was conducted in cooperation of the German and the Austrian Association for trauma surgery. In addition, one international guideline for the diagnosis and treatment of OCD and one for articular cartilage lesions were identified for the report of 2016 [1, 35-38][2]: According to the guidelines, the first step is a *physical examination* of the affected joint, including an inspection (swelling of the joint, gait, etc.), a palpation (pressure pain, extrusion in the joint, etc.) and specific tests for functioning and pain (motion, Wilson's test[2], etc.). Secondly, the affected joint should be examined by *diagnostic imaging*, i.e., X-rays and/or magnetic resonance imaging (MRI). Alternative diagnostic imaging techniques, like ultrasound, computed tomography, or arthroscopy, can also be used.

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

zahlreiche Behandlungsoptionen

The guidelines listed above [35-37] also cited several treatment alternatives for (osteo)chondral lesions or OCD after diagnosis, starting with conservative treatment followed by surgical interventions.

Ziele: Vermeidung/ Verlangsamung einer Progression, Schmerzreduktion

konservative und chirurgische Behandlungsoptionen

geeignete Methode abhängig von verschiedenen Faktoren (z. B. Defektgröße, Alter)

Generally, the treatments aim for pain reduction, regaining joint mobility, reactivating the affected area, preventing/slowing the progression and prevention of osteoarthritis, and avoiding total joint replacement. *Conservative therapies* include physical therapy, partial weight-bearing or activity restrictions, dietary supplements or pain management (e.g., non-steroidal anti-inflammatory drugs). A variety of *surgical techniques* exist, for example, arthroscopic lavage (or debridement), bone marrow stimulating techniques like MFx, (M)ACI, autologous osteochondral transplantation or osteochondral allografts or total knee/joint replacement in later stages of (osteo)chondral lesions. For example, during an osteochondral transplantation (OCT), a cartilage-bone cylinder is removed from a less burdensome area of the joint and planted in the appropriate, drilled defect area. However, none of the international guidelines recommends one specific surgical intervention, as it depends on factors such as the defect size and localisation, the age of the patient, and/ or the grade of discomfort [1, 35-38].

Target population

A0007 – What is the target population in this assessment?

PatientInnen mit (osteo)chondralen Defekten ...

In the systematic review from 2016, patients older than 18 years of age with chondral or osteochondral lesions or OCD of the knee joint, with an ICRS or Outerbridge 3-4, a defect size of 1-8 cm^2 were considered for the evaluation. Patients with two or more corresponding cartilage defects or an allergy to one of the scaffold components were excluded.

[2] For the current assessment, these guidelines were found to be still valid or received a revision. No additional guidelines could be identified.

... im Bereich Knie- und Sprunggelenk

In the present update of the systematic review from 2016, next to chondral or osteochondral lesions or OCD of the knee joint, the ankle joint was also considered. Furthermore, due to the inclusion of a second intervention (MACI), a defect size of 1-10 cm^2 instead of 1-8 cm^2 was determined. The other inclusion criteria stayed constant.

A0023 – How many people belong to the target population?

keine Daten zu Prävalenz oder Inzidenz identifiziert

No information on the Austrian, European or international data for the prevalence or incidence of (osteo)chondral defects or OCD was identified to inform this research question. Similarly, the frequency of AMIC and MACI interventions conducted in Austria is currently unknown.

A0011 – How much are the technologies utilised?

geschätzte Erbringung in Gesamtösterreich:
- AMIC 30-50 p.a.
- MACI >20 p.a.

According to the submitting hospitals, the estimated annual utilisation of the AMIC intervention in their institutions ranged from 5-15 and is estimated for MACI to be about five interventions.

The estimated annual utilisation of the AMIC intervention in Austria ranged from 30-50 and more than 20 for the MACI intervention (information from the submitting hospitals in 2018).

5 Clinical effectiveness

5.1 Outcomes

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

entscheidende Endpunkte für Wirksamkeit

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

The outcomes chosen represent the aims of a treatment of chondral and osteochondral defects: regaining joint mobility, reactivation of the affected area, pain reduction, prevention/delay of disease progression, and prevention of osteoarthritis and/or avoiding total joint replacement.

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

Mobility and joint functionality can be measured by different scores:

Mobilität/Funktion des Gelenks gemessen anhand von 7 Scores

- Knee Injury and Osteoarthritis Outcome Score (KOOS):
  42 items in five separately scored subscales:
  (1) Pain (nine items)
  (2) Other symptoms (seven items)
  (3) Function in daily living (ADL) (17 items)
  (4) Function in sport and recreation (sport/rec) (five items)
  (5) Knee-related quality of life (QoL) (four items).
  A Likert scale is used and all items have five possible answer options scored from 0 (no problems) to 4 (extreme problems), and each of the five scores is calculated as the sum of the items included. Scores are transformed to a 0-100 scale, 0 representing extreme problems and 100 representing no problems [39].
- International Knee Documentation Committee (IKDC) Subjective Knee Form designed to assess patients with a variety of knee disorders, including ligamentous and meniscal injuries, as well as patellofemoral pain and osteoarthritis. A patient-completed tool, which contains sections on knee symptoms (seven items), function (two items), and sports activities (two items). Scores range from 0 points (lowest level of function or highest level of symptoms) to 100 points (highest level of function and lowest level of symptoms) [40].
- Western Ontario McMaster Universities Osteoarthritis Index (WOMAC): a self-administered questionnaire consisting of 24 items divided into three subscales:
  (1) *Pain (five items):* during walking, using stairs, in bed, sitting or lying, and standing upright
  (2) *Stiffness (two items):* after first waking and later in the day
  (3) *Physical Function (17 items):* using stairs, rising from sitting, standing, bending, walking, getting in/out of a car, shopping, putting on/taking off socks, rising from bed, lying in bed, getting in/out of bath, sitting, getting on/off toilet, heavy domestic duties, light domestic duties.
  The test questions are scored on a scale of 0-4, which correspond to: none (0), mild (1), moderate (2), severe (3), and extreme (4). The scores for each subscale are summed up, with a possible score range of 0-20

for pain, 0-8 for stiffness, and 0-68 for physical function. Higher scores indicate worse pain, stiffness, and functional limitations [41].

- Modified Cincinnati Knee Rating System
  consists of 12 questions, eight of which are included in the summary score. These scored questions cover the domains of pain, swelling, function and activity level. The total score is calculated as the sum of all questions responses, with 100 representing the best/excellent knee function, and 0 representing the worst/poor knee function [42].
- Lysholm scoring scale:
  a patient-reported outcome measure (PROM) consisting of eight items that measure: pain (25 points), instability (25 points), locking (15 points), swelling (10 points), limp (5 points), stair climbing (10 points), squatting (5 points), and need for support (5 points). Every question response has been assigned an arbitrary score on an increasing scale. The total score is the sum of each response to the eight questions and may range from 0-100. Higher scores indicate a better outcome with fewer symptoms or disability [43].
- Short Form Health Survey (SF-8, SF-12, SF-36):
  a patient-reported survey of patient health consisting of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale. A score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability. A shorter version is the SF-12; for the case, only adequate physical and mental health summary scores are of interest [44].
- The (modified) International Cartilage Repair Society (ICRS)
  macroscopic score (consisting of ratings by patient and surgeon): due to the lacking scoring instructions, the interpretation of reported scores was not possible.

Quality of life can be measured by different scores:

Lebensqualität gemessen anhand von 3 Scores

- Knee Injury and Osteoarthritis Outcome Score (KOOS):
  see more information above.
- EQ-5D consists of a descriptive system and the EQ Visual Analogue Scale (VAS), and comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The five dimensions are rated via the VAS scale, numbered from 0 to 100: 100 meaning the best health imaginable and 0 meaning the worst health [45].
- Short Form Health Survey (SF-8, SF-12, SF-36):
  see more information above.

Pain can be measured by different scores:

Schmerzen gemessen anhand von 3 Scores

- Knee Injury and Osteoarthritis Outcome Score (KOOS):
  see more information above.
- Visual Analogue Scale (VAS): The VAS [0-100 mm scale] for pain intensity is most commonly anchored by “no pain” (score of 0) and “pain as bad as it could be” or “worst imaginable pain” (score of 100).
- Western Ontario McMaster Universities Osteoarthritis Index (WOMAC): see more information above.

Necessity of total joint replacement:

Notwendigkeit eines Gelenkersatzes

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 re-placement was considered as a crucial long-term outcome.

The following outcomes were *not* considered as *crucial* to derive a recommendation, but were used to answer the effectiveness-related questions:

weitere (nicht entscheidungsrelevante) Endpunkte zur Beantwortung der Fragen

- Activities of daily living, which can be measured with the KOOS score (see more information above) or the Tegner Activity Score (a one-item score that graded activity based on work and sports activities on a scale of 0-10. Zero represents disability because of knee problems and 10 represents national or international level soccer).
- Complete defect filling can be measured with the magnetic resonance observation of cartilage repair tissue (MOCART) score (lower MOCART scores indicate more positive/normal MRI diagnostic findings of the cartilage repair).

In the following sections of this report, the results of the included studies are presented separately for the AMIC (Chapters 5.2 and 5.3) and the MACI intervention (Chapters 5.4 and 5.5).

5.2 Included studies: AMIC

For evaluating efficacy-related outcomes, we exclusively considered RCTs and prospective NRCTs (see Chapter 1.2).

kontrollierte Studien für Wirksamkeitsendpunkte

No controlled trials comparing the single-step scaffold-based treatment (AMIC) of (osteo)chondral defects in the ankle joint with MFx or ACI could be identified.

keine Studien für das Sprunggelenk

Further, no controlled trials comparing the single-step scaffold-assisted technique (AMIC) of (osteo)chondral defects in the knee with ACI could be identified.

keine Studien im Vergleich zu ACI

The only studies that met our inclusion criteria were five RCTs[3] [3, 5, 7, 46, 47] and one NRCT [6], with a total of 314 patients, assessing the clinical effectiveness of the single-step scaffold-assisted chondral repair (AMIC) in the knee joint, compared to MFx alone. Out of these patients, 43 were lost to follow-up across the studies.

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

Study characteristics

In all five RCTs[3], the intervention (AMIC) was performed with products of different manufacturers. In one study, it was performed with Chondro-Gide® [7], in one study with MaioRegen™ [47], in one study with JointRep™ [46], in another with BST-CarGel® [3, 5], and in the NRCT, a polyethylene glycol diacylate hydrogel (comparable to GelrinC®) was applied [6].

Produkte: Chondro-Gide®, MaioRegen™, JointRep™, BST-CarGel®

[3] In total, six RCTs were included; two of the six RCTs were interim analyses of the included two extension studies (Volz 2017 [7] & Anders 2013 [4]; Shive 2015 [3] & Stanish 2013 [5]). For Volz/Anders, only the data of Volz 2017 were considered for the analysis due to longer follow-up and larger patient population. For Shive/Stanish, the data from both studies are presented: from Stanish after 12 months and from Shive after 60 months, since Shive had a longer follow-up, but included fewer patients.

keine Studien zu anderen Produkten

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

RCTs in zahlreichen Ländern durchgeführt

One RCT was assessed in nine countries (Italy, Sweden, Belgium, Switzerland, Austria, Germany, Poland, South Africa) [47], one RCT in Italy [46], one RCT in Canada, Spain and South Korea respectively [3, 5], and the other RCT in Germany [7]. The NRCT was assessed in Germany, Italy and the Netherlands [6]. One of the five included studies [46] did not report any funding of the study.

Patient characteristics

PatientInnen: Ø 34.0-54.5 vs. 35.2-56.6 Jahre, 20.6-43.9 vs. 23.1-52.2 % Frauen, Stadium 3-4, Nachbeobachtungszeit 6-60 Monate

The mean age of patients ranged from 34.0-54.5 years in the intervention groups and from 35.2-56.6 years in the control groups across the RCTs [3, 5, 7, 46, 47]; in the NRCT, the age of patients ranged from 20.0-59.0 years in the treatment group versus 40.0-49.0 in the control group [6]. Between 20.6 and 43.9% of the patients in the intervention groups and 23.1-52.2% of the patients in the control groups were females across trials. Patients had grades 3-4 (Outerbridge Classification) of chondral defects with a mean lesion size of 2.3-3.9 cm^2 in the intervention groups and 1.9-3.5 cm^2 in the control groups. The follow-up of the studies was six months [6], 24 [46, 47] and up to 60 months (five years) [3, 5, 7].

Ein- und Ausschlusskriterien

Three of the included studies considered only patients aged 18 to 55 years [3, 5-7], whereas one study included patients between 26 and 72 years of age [46]. One study did not report on inclusion or exclusion criteria [47]. In three studies, osteoarthritis or any form of inflammatory arthritis, as well as multiple lesions or kissing lesions, were defined as exclusion criteria [3, 5-7]. All of the studies reported on postoperative rehabilitation programs [3, 5-7, 46] or isometric and isotonic exercises and electrical neuromuscular stimulation [47].

postoperative Maßnahmen (z. B. Physiotherapie) in allen Studien berichtet

Extraktionstabellen in Anhang

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2, and in the evidence profile in Table A-8.

5.3 Efficacy results: AMIC

Wirksamkeit *nur* für Kniegelenk

Since we could not identify any controlled studies regarding AMIC for cartilage repair for the ankle joint, the results presented are exclusively for AMIC for the knee joint.

Morbidity

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

Beantwortung anhand Endpunkt „Schmerzen" und „vollständige Defektfüllung"

Answering this research question was based on the outcome "pain" and "complete defect filling".

The effect on **pain** was measured in five studies by two different scoring systems comparing the single-step scaffold-assisted cartilage repair (AMIC) plus MFx with MFx alone [3, 5, 6, 46, 47].

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

(1) VAS scale *(0-100, lower scores indicate lower pain)*

One study [47] stated a mean reduction of -26.3 points in the intervention group versus -23.9 for the control group after 12 months (p=n/a), and -23.6 vs. -29.9 points after 24 months (p=n/a).

The NRCT [6] reported changes after three and six months on severity and frequency of pain. The changes for *severity* for the intervention versus the control group were: -29.0 vs. -34.7 points, and -32.1 vs. -15.3 points at three and six months, respectively. The changes for *frequency* assessed for the intervention versus the control group were: -41.0 vs. -62.6 points, and -52.9 vs. -41.0 points at three and six months, respectively. The study did not mention whether the changes were statistically significant between the groups (p=n/a).

1 RCT, 1 NRCT: Verminderung Schmerzen in beiden Gruppen, jeweils keine Angabe, ob statistisch signifikante Unterschiede zwischen Gruppen

(2) WOMAC scale *(subscale: pain, 0-20, lower scores indicate lower pain)*

The first study [46] reported changes after six, 12 and 24 months. After six months, a change of -11.3 vs. -5.2 was reported for the intervention versus the control group, both statistically significant compared to baseline (p<0.0001; p<0.0001). After 12 months, the change from baseline was only statistically significant for the intervention group with -11.6 (p<0.0001) vs. the control group with -1.5 (p=0.3154). After 24 months, there was a mean reduction in pain for the intervention group of -12.1 (p<0.0001) vs. the control group of -0.1 (p=0.9446) compared to baseline. The interim and extension studies [3, 5][4] reported slightly poorer changes for the intervention versus the control group: -16.2 vs. -16.9, and -15.4 vs. -16.6 at 12 and 60 months compared to baseline, respectively. However, the study did not state whether the changes were statistically significant between the groups (p=n/a).

Across the scoring systems, the improvements for pain were higher in the intervention groups (after >6 months). However, the differences between the study groups were not statistically significant [3, 5].

3 RCTs: Verminderung Schmerzen jeweils für beide Gruppen berichtet; keine Angabe ob statistisch signifikante Unterschiede zwischen Gruppen

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

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

keine Evidenz

The effect on **complete defect filling** was measured in two studies by two scoring systems comparing the single-step scaffold-assisted cartilage repair (AMIC) plus MFx with MFx alone [7, 47].

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

(1) Unknown scoring system

One RCT [7] only describes that 35.0-50.0% of the patients had a defect filling of $\geq^2/_3$ after 12 months. After 24 months, the defect filling was more complete in the AMIC groups, where at least 60.0% of the patients had a defect filling of $>^2/_3$ compared to only 25.0% of the patients in the MFx group. At 60 months follow-up, defect filling was the lowest in the MFx group versus both AMIC groups (sutured & glued).

1 RCT: Defektfüllung war vollständiger in AMIC Gruppe (>60 %) vs. MFx nach 24 und 60 Monaten

[4] In this study, the WOMAC subscales were reported in the VAS format of 0 to 10 cm length. Scores had a maximum value of 50 points for pain, 20 points for stiffness, and 170 points for function.

(2) MOCART scale
(*subscale: defect filling, 0-20, higher scores indicate more complete filling*)

1 RCT: vollständige Defektfüllung häufiger in AMIC Gruppe vs. MFx Gruppe (nach 6 Monaten); nach 12 & 24 Monaten besser in MFx Gruppe

The other RCT [47] describes a complete filling of the defect after 12 and 24 months. After six months, 53.3% of patients had a complete defect filling in the intervention group versus 39.5% in the control group. After 12 and 24 months, a complete defect filling was assessed more frequently in the control group with 55.6 and 65.9% of patients, in comparison to the intervention group with 40.8 and 49.0%. No statistically significant differences were obtained in the MRI scores between the groups.

Across the two studies, contradictory results appeared: a complete defect filling was described more often for the intervention group in [7], as opposed to [47], where a complete defect filling was reported more frequently for the control group (after 12 and 24 months).

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

keine Evidenz

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

Do006 – How does AMIC affect progression (or recurrence) of the disease or health condition?

Beantwortung anhand Endpunkt „Notwendigkeit eines Gelenksersatzes"

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

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

1 RCT berichtet von 1 totalen Kniearthroplastik

Only one RCT addressed this outcome [46]. In this study, there was one total knee arthroplasty reported after 12 months, without mentioning in which study group this event occurred.

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

Function

Do011 – What is the effect of AMIC on patients' body functions?

Beantwortung anhand Endpunkt „Mobilität/ Gelenksfunktionalität"

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

The effect on **mobility or joint functionality** was measured in six studies by five different scoring systems comparing the single-step scaffold-assisted cartilage repair (AMIC) plus MFx with MFx alone [3, 5-7, 46, 47].

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

(1) IKDC scale (*0-100, higher scores indicate better function*)

1 RCT: geringfügig stärkere Verbesserung in Interventionsgruppe

The IKDC score was reported in one RCT [47] and the NRCT [6]. In the RCT, the score improved in all study groups over time. After 12 months, the score improved by 17.5 and 20.7 points in the intervention and control group compared to baseline, respectively. After 24 months, the score increased slightly more to 23.5 in the intervention group and to 22.5 in the control group compared to baseline. There were no p-values given in the study. Overall, the improvement in the RCT was slightly higher in the intervention group for all follow-ups.

The NRCT [6] only mentions that there were no statistically significant changes from baseline after three and six months.

NRCT: keine Unterschiede berichtet

(2) WOMAC scale (*lower scores indicate better function*)

WOMAC stiffness subscale (0-8):

Three studies assessed the WOMAC stiffness subscale [3, 5, 46]. In the studies, the score improved in all study groups over time. In one RCT [46], the score improved after 12 and 24 months by -5.3 and -5.4 in the intervention group and by -1.9 and -1.9 in the control group, respectively. These mean reductions were statistically significant in both groups compared to baseline ($p<0.0001$, $p<0.0001$ vs. $p=0.0024$, $p=0.0004$). The interim and extension studies [3, 5][4] reported similar improvements after 12 and 60 months compared to baseline: -5.9 and -5.6 for the intervention group and -6.6 and -6.7 for the control group, respectively. As the baseline scores were very high in this study, the changes were not statistically significant in either group ($p=$n/a).

1 RCT: signifikante Verbesserungen in beiden Studiengruppen

2 weitere Studien: stärkere Verbesserung in Kontrollgruppe, jedoch Unterschiede nicht statistisch signifikant

WOMAC physical function subscale (0-68):

Three studies reported the WOMAC physical function subscale [3, 5, 46]. In the studies, the score improved in all study groups over time. In the first RCT [46], the score improved after 12 and 24 months compared to baseline by -35.1 and -36.0 in the intervention group and by -10.6 and -6.3 in the control group, respectively. These mean reductions were statistically significant in both groups compared to baseline ($p<0.0001$, $p<0.0001$ vs. $p=0.0001$, $p=0.044$). The interim and extension studies [3, 5][4] also reported improvements after 12 and 60 months compared to baseline: -55.9 and -56.5 for the intervention group and -60.6 and -62.1 for the control group. As the baseline scores were very high in these studies, the changes were not statistically significant in either group; no statistically significant differences were reported between the groups ($p=$n/a).

1 RCT: signifikante Verbesserungen in beiden Studiengruppen

2 weitere Studien: stärkere Verbesserung in Kontrollgruppe, jedoch nicht statistisch signifikant

Overall, contradictory results across the studies were found for both WOMAC subscales: one RCT had higher improvements for the intervention group [46], whereas the interim and extension studies had higher improvements for the control group [3, 5]. However, the higher improvements in the control group were not statistically significant.

(3) Modified Cincinnati Knee score (*0-100, higher scores indicate better function*)

Only one study reported on this scoring system [7]. The mean scores improved similarly after 12 and 24 months compared to baseline by 37.0 | 19.0 and n/a | 37.0 for the intervention groups (AMIC sutured | AMIC glued) versus 34.0 and 36.0 for the control group. After 60 months, the study only stated that the score was stable or improving in both AMIC groups, whereas a significant decrease was observed for the MFx group ($p=$n/a).

1 RCT: Verbesserung in beiden Studiengruppen; nach 60 Monaten Verschlechterung unter MFx

(4) Short Form Health Survey
(*subscale: physical components, 0-100, higher scores indicate better function*)

In two studies [3, 5] there were improvements for the SF-36 subscale in all study groups. The changes were not statistically significant, but with slightly better improvements for the control group: 13.0 and 13.1 in the intervention group and 14.8 and 14.5 in the control group after 12 and 60 months compared to baseline, respectively.

2 Studien: geringfügig stärkere Verbesserung in Kontrollgruppe, jedoch nicht signifikant

(5) (Modified) ICRS macroscopic score

Due to lacking scoring instructions, it was not possible to interpret the reported scores in one study [7].

1 RCT: Werte nicht interpretierbar

Across all scoring types, for the comparison of AMIC + MFx versus MFx alone, improvements in functionality were reported for the intervention groups, as well as the control groups after six, 12, 24 and 60 months.

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

keine Evidenz

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

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

Beantwortung anhand Endpunkt „Aktivitäten des täglichen Lebens"

Answering this research question was based on the outcome "activities of daily living".

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

1 RCT: Verbesserung nach 12/24 Monaten in beiden Gruppen

This outcome was addressed only in one RCT [47] and was measured with the Tegner Activity Score (TAS). All study groups showed improvements after 12 and 24 months compared to baseline. In both groups, the mean improvements were +1.0 after 12 months and +1.0 after 24 months (p=n/a). Overall, no differences occurred between the intervention and the control group.

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

keine Evidenz

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

Health-related quality of life

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

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

Beantwortung anhand Endpunkt „Lebensqualität"

Answering these research questions was based on the outcome "quality of life".

The effect on **quality of life (QoL)** was measured only in the interim and extension studies [3, 5] by one scoring system comparing the single-step scaffold-assisted cartilage repair (AMIC) plus MFx with MFx alone.

(1) Short Form Health Survey
(*subscale: mental components, 0-100, higher scales indicate better function*)

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

2 Studien: Verbesserung in Interventionsgruppe nach 12 und 60 Monaten, nicht signifikant

The two studies [3, 5] assessed improvements on the SF-36: +3.5 and +2.7 in the intervention group and +0.8 and -0.2 in the control group after 12 and 60 months compared to baseline, respectively. The changes were not statistically significant (p=n/a).

Overall, for the comparison of AMIC + MFx versus MFx alone, better improvements in QoL were reported for the intervention group after 12 and 60 months.

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

keine Evidenz

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

Patient satisfaction

D0017 – Was the use of AMIC worthwhile?

keine Evidenz

There was no evidence to answer this research question.

5.4 Included studies: MACI

keine kontrollierte Studien zum Sprunggelenk

No controlled trials comparing the two-step scaffold-based treatment (MACI) of (osteo)chondral defects in the ankle with MFx or ACI could be identified.

5 RCTs zu zweizeitiger matrix-assistierter Behandlung von Knorpeldefekten im Kniegelenk

The only studies that met the inclusion criteria (see Chapter 1.2) were five RCTs [9, 22, 23, 48, 49][5] with a total of 330 (184 vs. 146) patients assessing the clinical efficacy of the two-step scaffold-assisted chondral repair of the knee joint (MACI) compared to MFx [9, 48, 49] or ACI [22, 23].

Study characteristics

unterschiedliche Produkte von unterschiedlichen Herstellern

In all five RCTs, the intervention (MACI) was from another manufacturer. In three studies, collagen type I/III matrices [9, 22, 48], in another study a bovine type I collagen matrix [49], and in the fifth study, a rectangular resorbable scaffold of polyglactin 910 and poly-p-dioxanone [23] were applied.

zweizeitiges Verfahren: Studien zu 3 Produkten

There were only studies assessing the clinical effectiveness of products like Spherox®, BioSeed®-C and NeoCart® that met the inclusion criteria (see Chapter 1.2).

4 europäische & 1 US-amerikanische Studie(n)

One study was assessed in seven European countries (n/a) [9], two studies in Germany [23, 48], one study in England [22] and one study in the USA [49]. One of the five studies [48] did not report on the funding of the study.

Patient characteristics

Ø 29.1-41.0 vs. 29.5-39.0 Jahre, 10.0-45.5 vs. 0-33.0 % Frauen, Stadium 3-4, Nachbeobachtung 24-60 Monate

The mean age of patients ranged from 29.1-41.0 years in the intervention groups and from 29.5-39.0 in the control groups across the studies. Between 10.0 and 45.5% of the patients in the intervention groups and between 0 and 33.0% of the control groups were female across the studies. Patients had grades 3-4 (Outerbridge or ICRS Classification) of chondral defects with a mean lesion size of 2.9-6.1 cm^2 in the intervention groups and 2.5-6.0 cm^2 in the control groups. The follow-up of the studies was 24 and 60 months (five years).

Ein- & Auschlusskriterien, Rehabilitations-programm in allen Studien

Three of the included studies only considered patients aged 18 to 55 years [9, 48, 49], whereas two studies included patients between 15 and 50 years of age [22, 23]. All five studies considered osteoarthritis or any form of inflammatory arthritis as an exclusion criterion and reported a postoperative rehabilitation program.

Extraktionstabellen im Anhang

Detailed study characteristics and results of included studies are displayed in Table A-3 and Table A-4, and in the evidence profile in Table A-9.

[5] In total, six RCTs were included. One of the six RCTs was an interim analysis of the included extension study (Saris 2014 [8] & Brittberg 2018 [9]). Efficacy data were extracted only from Brittberg 2018.

5.5 Efficacy results: MACI

Wirksamkeit *nur* für Kniegelenk

Since we could not identify any controlled studies regarding MACI for cartilage repair for the ankle joint, the results presented are exclusively for MACI for the knee joint.

Morbidity

Dooo5 – How does MACI affect symptoms and findings (severity, frequency) of the disease or health condition?

Beantwortung anhand "Schmerzen" und "kompletter Defektfüllung"

Answering this research question was based on the outcomes "pain" and "complete defect filling".

The effect on **pain** was measured in four studies by three different scoring systems comparing the scaffold-based two-step cartilage repair (MACI) with MFx [9, 49] or with ACI [22, 23].

Schmerzen: in 4 Studien anhand 3 Scores berichtet

(1) KOOS score *(subscale: pain, 0-100, higher scales indicate lower pain)*

Two-step scaffold-based treatment vs. MFx:

2 RCTs: verbesserte Schmerzscores (KOOS) in der Interventionsgruppe, jedoch nur in 1 Studie statistisch signifikant

In one RCT [9], the KOOS score (pain) increased in all study groups over time. After 24 months, the score improved by 45.1 and 36.6 points in the intervention and control group compared to baseline, respectively. After 60 months, the score improved by 45.1 points in the intervention group and by 38.8 points in the control group. However, the higher increase in the control groups for both follow-ups was not statistically significant (p=n/a). Another study [49] reported a significant score improvement in the intervention group (+12.06, 95% CI 2.388-21.74, p<0.05) after 24 months.

Overall, the two RCTs reported a score improvement for the intervention group; however, the improvement was statistically significant only in one study.

Two-step scaffold-based treatment vs. ACI:

keine Evidenz

There was no evidence available assessing the KOOS score (pain) of a two-step scaffold-assisted cartilage repair, compared to ACI.

(2) Visual analogue scale *(0-100, lower scales indicate lower pain)*

1 RCT: signifikante Schmerzverbesserung (VAS) in Interventionsgruppe

Two-step scaffold-based treatment vs. MFx:

One RCT [49] reported significant pain improvements in the intervention group after 24 months (p<0.05).

Two-step scaffold-based treatment vs. ACI:

1 RCT: verbesserte Schmerzscores (VAS) in der Interventionsgruppe

In one study [22], a deterioration of the scale from baseline to follow-up (n/a) was reported for the intervention group (-1.9), as well as for the control group (-1.7). However, the difference was not statistically significant.

insgesamt in beiden RCTs verbesserte VAS Scores in den Interventionsgruppen

Overall, in both RCTs, the VAS showed an improvement of pain in the intervention group. However, this improvement was only statistically significant in one study [49].

(3) Short Form Health Survey
(subscale: pain, 0-100, higher scores indicate lower pain)

Two-step scaffold-based treatment vs. MFx:

keine Evidenz

There was no evidence available assessing the Short Form Health Survey (pain) of a two-step scaffold-assisted cartilage repair, compared to MFx.

Two-step scaffold-based treatment vs. ACI:

One RCT [23] reported that there was no significant difference between the intervention and the control group after 12 and 24 months.

1 RCT: keine signifikanten Unterschiede zwischen Studiengruppen und Follow-ups

Overall, no conclusions can be made for the pain outcome with the Short Form Health Survey.

Across all scores, some statistically significant pain improvements were reported in the intervention groups.

The effect on complete effect filling was measured in two studies by three different scoring systems comparing the scaffold-based two-step cartilage repair (MACI) with MFx [48] or with ACI [23].

2 RCTs: komplette Defektfüllung in 2 Studien nach 3 Scores berichtet

(1) Unknown scoring system

Two-step scaffold-based treatment vs. MFx:

There was no evidence available assessing the complete defect filling of a two-step scaffold-assisted cartilage repair on an unknown score, compared to MFx.

keine Evidenz

Two-step scaffold-based treatment vs. ACI:

In one study [23], a complete defect filling could be diagnosed after six months via MRI imaging technique in 50.0% of the intervention group versus 11.1% of the control group.

1 RCT: höhere Defektfüllungsrate in Interventionsgruppe

(2) MOCART score
(subscale: defect filling, 0-20, higher points indicate more complete filling)

Two-step scaffold-based treatment vs. MFx:

keine Evidenz

There was no evidence available assessing the MOCART score of a two-step scaffold-assisted cartilage repair, compared to MFx.

Two-step scaffold-based treatment vs. ACI:

In one study [23], 6.3 points and 8.4 points were reported for the intervention and control group, respectively, at 12 months. After 24 months, the filling did not change in the intervention group (a stable 6.3 points), while the filling deteriorated in the control group to 6.8 points. However, the differences in points between the study groups were not statistically significant at both follow-up.

1 RCT: stabile Defektfüllung in Interventionsgruppe von 12 auf 24 Monaten, jedoch reduzierte Defektfüllung in der Kontrollgruppe

Overall, the reported points indicate a defect fill of >50% of the defect (5-10 points) in both study groups for both 12 and 24 months [50].

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

Answering this research question was based on the outcome "necessity of total joint replacement". Thus, the higher the rate of the total joint replacement, the less the effect of the intervention on the disease progression is.

Beantwortung anhand Notwendigkeit eines Gelenkersatzes

Two-step scaffold-based treatment vs. MFx:

The effect on necessity of total joint replacement was measured in one study comparing the scaffold-based two-step cartilage repair (MACI) with MFx [49]. In the study, one case of total knee arthroplasty was reported in the intervention group (4.8%) versus zero cases in the control group.

1 RCT: 1 Fall eines Gelenkersatzes in Interventionsgruppe

Two-step scaffold-based treatment vs. ACI:

There was no evidence available assessing the necessity of total joint replacement of a two-step scaffold-assisted cartilage repair, compared to ACI.

keine Evidenz

Function

D0011 – What is the effect of MACI on patients' body functions?

Beantwortung anhand Mobilität und Gelenk-funktion in allen 5 Studien durch 6 Scores

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

The effect on **mobility or joint functionality** was measured in all five studies by six different scoring systems comparing the scaffold-based two-step cartilage repair (MACI) with MFx [9, 48, 49] or with ACI [22, 23].

(1) KOOS score *(subscale: sport/rec, 0-100, higher scores indicate better function)*

Two-step scaffold-based treatment vs. MFx:

2 RCTs: signifikante Verbesserung der Funktion (KOOS) in den Interventionsgruppen

In one RCT [9], the KOOS score (sport/rec) increased in all study groups over time. After 24 months, the score improved by 45.1 and 37.0 points in the intervention and control group, respectively. After 60 months, the score improved by 46.5 points in the intervention group and by 38.8 points in the control group. The higher increase in the intervention group after 60 months was statistically significant (p=0.0122). In another RCT [49], the difference in the KOOS scores (sport/rec) from baseline to 24 months was statistically significantly higher in the intervention group compared to the control group.

Two-step scaffold-based treatment vs. ACI:

keine Evidenz

There was no evidence available assessing the KOOS score (sport/rec) of a two-step scaffold-assisted cartilage repair, compared to ACI.

(2) IKDC score *(0-100, higher scores indicate better function)*

Two-step scaffold-based treatment vs. MFx:

2 RCTs: verbesserte Funktion (IKDC) in den Interventionsgruppen, jedoch nur in 1 Studie statistisch signifikant

In one RCT [9], the IKDC score increased in all study groups over time. After 24 months, the score improved by 32.2 and 30.8 points in the intervention and control group, respectively. After 60 months, the score increased slightly more to 35.4 points in the intervention group and to 32.5 points in the control group. However, the differences between the study groups were not statistically significant (p=0.113) at 60 months. In another RCT [49], the difference in the adjusted means (IKDC score) at 24 months was statistically significantly higher in the intervention group (+11.59 points, 95% CI 1.353-21.82, p=0.028).

Two-step scaffold-based treatment vs. ACI:

1 RCT: verbesserte Scores (IKDC) in der Kontrollgruppe (nicht signifikant)

In one RCT [23], the IKDC score increased in all study groups over time. At 24 months, the score improved by 19.0 points and 25.2 points in the intervention and control group, respectively. However, the difference in improvement was not statistically significant (p=0.4994).

insgesamt Verbesserung in Interventionsgruppe vs. MFx bzw. Verschlechterung bei Vergleich mit ACI

Overall, the three RCTs reported similar improvements from baseline to follow-up in the score. However, in two of the three RCTs, the improvement was higher in the intervention group, whereas in one RCT the improvement was higher in the control group (not significant).

(3) Modified Cincinnati Knee score *(0-100, higher scores indicate better function)*

Two-step scaffold-based treatment vs. MFx:

1 RCT: signifikante Verbesserung in der Interventionsgruppe nach 60 Monaten

In one RCT [9], the Modified Cincinnati Knee score improved in all study groups over time. After 24 and 60 months, the score improved by 3.3 and 3.6 points in the intervention group and by 2.5 and 2.8 points in the control group, respectively. The higher increase in the intervention group after 60 months was statistically significant (p=0.035).

Two-step scaffold-based treatment vs. ACI:

In another RCT [22], the score increased in all study groups over time. After 12 months, the score improved by 19.6 points in the intervention group and by 17.5 points in the control group. However, the difference between the study groups was not statistically significant (p=0.32).

1 RCT: höhere Scores in der Interventionsgruppe (nicht signifikant)

Overall, the two RCTs reported different improvements in the score from baseline to follow-up. However, in both studies, the improvement was higher in the intervention group for all follow-up. Across the studies, the score was 1.5 points higher in the intervention group compared to the control group.

insgesamt durchschnittl. Verbesserung von 1.5 Punkten in den Interventionsgruppen beider Studien

(4) Lysholm score *(0-100, higher scores indicate better function)*

Two-step scaffold-based treatment vs. MFx:

In one RCT [48], the Lysholm score increased in all study groups over time. After 24 months, the score improved by 40.0 points in the intervention group and by 14.0 points in the control group. There was a statistically significant improvement in the intervention group after 24 months (p=0.005).

1 RCT: bessere Funktion (Lysholm) in Interventionsgruppe

Two-step scaffold-based treatment vs. ACI:

In another RCT [23], the score increased in all study groups over time. At 24 months, the score improved by 1.2 points in the intervention group and by 22.7 points in the control group. There was a significantly higher increase for the control group after 24 months (p=0.0487).

signifikant bessere Funktion (Lysholm) in Kontrollgruppe nach 24 Monaten

Overall, the RCTs reported very inconsistent results regarding the improvement in the score between intervention and control groups and between the two studies. In one study, the improvement was higher in the intervention group, whereas in the other study the improvement was higher in the control group (statistically significant).

insgesamt kontroverse Resultate zwischen Studiengruppen und zwischen Studien

(5) Short Form Health Survey
(subscale: physical components, 0-100, higher scores indicate better function)

Two-step scaffold-based treatment vs. MFx:

In one RCT [9], negative scores of the SF-12, which were not translated on a 0-100 score, were reported. Thus, these negative values could not be interpreted.

1 RCT: berichtete Scores nicht interpretierbar

Two-step scaffold-based treatment vs. ACI:

In another RCT [23], it was only reported that the differences in the changes of scores from baseline to 12 and 24 months between the study groups were not statistically significant.

1 RCT: keine statistisch signifikanten Unterschiede

(6) ICRS macroscopic score *(subjective and objective scales)*

Two-step scaffold-based treatment vs. MFx:

Due to lacking scoring instructions, it was not possible to interpret the reported scores in one study [48].

1 RCT: Werte nicht interpretierbar

Two-step scaffold-based treatment vs. ACI:

Due to lacking scoring instructions, it was not possible to interpret the reported scores in one study [22].

1 RCT: Werte nicht interpretierbar

Across all scoring types, for the comparison MACI versus MFx, (partly statistically significant) improvements in joint functionality were reported for the intervention groups after 24 and 60 months [9, 48, 49]. For the comparison MACI versus ACI, inconsistent results about improvements in joint functionality were reported [22, 23].

insgesamt verbesserte Gelenksfunktion in Interventionsgruppe vs. MFx, inkonsistente Resultate vs. ACI

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

Beantwortung anhand „Aktivität des täglichen Lebens", gemessen in 3 Studien mit 2 Scores

Answering this research question was based on the outcome "activities of daily living".

The effect on **activities of daily living (ADL)** was measured in three studies by two different scoring systems comparing the scaffold-based two-step cartilage repair (MACI) with MFx [9, 48] or with ACI [23].

(1) KOOS score *(subscale: ADL, 0-100, higher scores indicate improved ADL)*

Two-step scaffold-based treatment vs. MFx:

1 RCT: signifikante bessere tägliche Aktivität in der Interventionsgruppe nach 60 Monaten

In one RCT [9], the score improved by 43.7 points in the intervention group and by 34.4 points in the control group after 24 months. After 60 months, the improvement in the intervention group decreased to 42.8 points and increased to 37.4 points in the control group.

Overall, the improvements were higher in the intervention group for both 24 and 60 months, but statistically significant only after 60 months (p=0.007).

Two-step scaffold-based treatment vs. ACI:

keine Evidenz

There was no evidence available assessing the KOOS score (ADL) of a two-step scaffold-assisted cartilage repair, compared to ACI.

(2) TAS *(0-10, higher scores indicate better daily activities):*

Two-step scaffold-based treatment vs. MFx:

1 RCT: signifikante Verbesserung in der Interventionsgruppe

In one RCT [48], a significantly better improvement in the daily activity was reported for the intervention group at 24 months (p=0.04).

Two-step scaffold-based treatment vs. ACI:

1 RCT: verbesserte tägliche Aktivität (TAS) in beiden Gruppen nach 12 & 24 Monaten

In one RCT [23], the score increased by 0.1 points in the intervention group and by 0.9 points in the control group after 12 months. After 24 months, the improvement was slightly higher in the intervention group (+0.6 points from baseline) and in the control group (+1.7 points from baseline). However, the differences in improvements between the study groups were not statistically significant for both follow-ups (p=0.4063 vs. p=0.1043).

insgesamt Verbesserung (TAS) in Interventionsgruppe vs. MFx, jedoch Verschlechterung vs. ACI

Overall, the two RCTs reported inconsistent results about the effect on daily activity. On the one hand, the daily activity improved in the intervention group [48]; on the other hand, the daily activity score was higher in the control group (not significant) – indicating better daily activity [23].

Health-related quality of life

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

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

Beantwortung anhand Endpunkt "Lebensqualität" gemessen in 3 Studien durch 3 Scores

These research questions were answered based on the outcome "quality of life".

The effect on **quality of life (QoL)** was measured in three of the five RCTs by three different scoring systems comparing the scaffold-based two-step cartilage repair (MACI) with MFx [9, 49] or with ACI [23].

(1) KOOS scale *(subscale: QoL, 0-100, higher scores indicate better QoL)*

Two-step scaffold-based treatment vs. MFx:

In one RCT [9], the KOOS score (QoL) increased for all study groups over time. After 24 months, the score improved by 35.5 points in the intervention group and by 30.7 points in the control group. After 60 months, the score improved slightly more by 39.9 points and 35.3 points in the intervention and the control group, respectively (p=n/a). In another RCT [49], a marginal improvement in the score for the intervention group after 24 months was reported (p=0.05).

Overall, in both studies, the improvement was higher in the intervention group for all follow-up.

2 RCTs: höhere Lebensqualität (KOOS) in den Interventionsgruppen

Two-step scaffold-based treatment vs. ACI:

There was no evidence available assessing the KOOS score (QoL) of a two-step scaffold-assisted cartilage repair, compared to ACI.

keine Evidenz

(2) EQ-5D score *(0-100, higher scores indicate higher QoL)*

Two-step scaffold-based treatment vs. MFx:

In one RCT [9], the EQ-5D scores increased in both study groups over time. After 24 and 60 months, the score improved by 16.2 and 20.1 points in the intervention group and by 1.4 and 19.1 in the control group, respectively. There was a statistically significant improvement (+1 point) in the intervention group after 60 months (p=0.043).

1 RCT: statistisch signifikante Verbesserung der Lebensqualität in der Interventionsgruppe nach 60 Monaten

Two-step scaffold-based treatment vs. ACI:

There was no evidence available assessing the EQ-5D score of a two-step scaffold-assisted cartilage repair, compared to ACI.

keine Evidenz

(3) Short Form Health Survey
(subscale: mental components, 0-100, higher scores indicate better QoL)

Two-step scaffold-based treatment vs. MFx:

In one RCT [9], negative scores of the SF-12, which were not translated on a 0-100 score, were reported. Thus, these negative values could not be interpreted and this study could not be graded for this outcome.

1 RCT: berichtete Scores nicht interpretierbar

Two-step scaffold-based treatment vs. ACI:

One study [23] reported that there was no statistically significant difference in the scores between the study groups after 12 and 24 months. Score values were not described.

1 RCT: keine signifikanten Unterschiede zwischen Studiengruppen

Across all scoring types, for the comparison MACI versus MFx, (partly statistically significant) improvements of QoL were reported for the intervention groups after 24 and 60 months. For the comparison MACI versus ACI, no conclusions can be made regarding the effect on QoL.

insgesamt verbesserte Lebensqualität in der Interventionsgruppe (vs. MACI), unklar (vs. ACI)

Patient satisfaction

D0017 – Was the use of MACI worthwhile?

There was no evidence to answer this research question.

keine Evidenz

6 Safety

6.1 Outcomes

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

entscheidende Endpunkte für Sicherheit:

- **Severe adverse events,** which were rated as such in the study.
- **Procedure-related adverse events**: Complications that were 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).
- **Device-related adverse events:** Complications that were associated with the implantation of the scaffold. Possible complications are movement or release of the scaffold or allergic reactions.
- **Re-operation rate**, which shows how often patients had to undergo additional surgeries.

schwerwiegende Komplikationen

eingriffsbezogene Komplikationen

implantatsbezogene Komplikationen

Re-Operationsrate

The following outcome was *not* considered as *crucial* to derive a recommendation, but was used to answer the safety-related questions:

weiterer Endpunkt zur Beantwortung der Fragen: eingriffsbezogene Mortalität

- **Procedure-related mortality**

6.2 Included studies: AMIC

For evaluating safety-related outcomes, we considered RCTs and prospective NRCTs (see Chapter 1.2).

(un)kontrollierte Studien für Sicherheit

In order to assess safety-related outcomes of AMIC, we identified the same five RCTs [3, 5, 7, 46, 47] and the same NRCT [6] as for efficacy, with a total of 187 patients treated with AMIC and 127 patients with MFx. Patient and study characteristics are described in Chapter 5.2.

gleiche Studien wie für Wirksamkeit eingeschlossen

No controlled trials comparing the single-step scaffold-based treatment of (osteo)chondral defects in the ankle joint with MFx or ACI could be identified.

keine kontrollierten Studien für das Sprunggelenk

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

keine Studien im Vergleich zu ACI

Study characteristics and results of included studies are displayed in Table A-1, Table A-2, and in the evidence profile in Table A-8.

6.3 Safety results: AMIC

Sicherheit *nur* zum Kniegelenk

Since we could not identify any controlled studies regarding AMIC for the ankle joint, the results presented are exclusively for AMIC for the knee joint.

Patient safety

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

Answering this research question was based on the outcome "severe adverse events", "procedure-related adverse events", "device-related adverse events" and "re-operation rate".

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

Severe adverse events

4 Studien: schwerwiegende Komplikationen: 0-12.2 % vs. 0-3.8 %

Severe adverse events were reported in four studies [3, 5, 7, 47]. The reported rates ranged from 0-12.2% in the intervention groups and from 0-3.8% in the control groups (slightly favouring the control groups).

Procedure-related adverse events

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

Adverse events *related to the procedure*, in comparison to MFx, were reported in four studies [3, 5, 7, 47] and the NRCT [6]. The rates ranged from 0-93.0% in the intervention groups and from 0-77.0% in the control groups.

keine umfangreichen Details zu Komplikationen

Only in one RCT was it clearly stated that the most reported procedure-related adverse events were inflammation, joint adhesion or persistent pain in the intervention group and joint instability in the control group [47]. None of the other identified studies clearly described which kind of adverse events occurred.

Device-related adverse events

3 Studien, 1 NRCT: implantatsbezogene Komplikationen: 0-22 %

Adverse events *related to the device* were reported in three studies [3, 5, 47] and the NRCT [6], and occurred in 3.0-22.0% of the patients. Only one study [47] stated that the event occurred due to failures of the scaffold. Since the control groups did not receive a scaffold, no device-related complications occurred.

Re-operation rate

1 RCT nach 12 Monaten: 1 vs. 1 Re-Operation

Re-operations were stated in two RCTs [3, 7]. One study reported no re-operations in the AMIC sutured group, one in the AMIC glued versus one in the MFx group after 12 months [7]. The other study [3] reported no re-operations in the intervention group versus one in the control group after 60 months.

1 RCT nach 60 Monaten: 0 vs. 1 Re-Operation

Overall, one re-operation was stated for the intervention groups and two re-operations for the control groups across the studies.

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

keine Evidenz

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

C0002 – Are the harms related to dosage or frequency of applying AMIC?

keine Evidenz

No direct evidence was found to answer this research question.

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

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

keine verlässliche Evidenz

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

No direct evidence was found to answer this research question.

keine Evidenz

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

No direct evidence was found to answer this research question.

keine Evidenz

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of AMIC and the comparator?

No direct evidence was found to answer this research question.

keine Evidenz

Mortality

D0001 – What is the expected beneficial effect of AMIC on mortality?

Answering this research question was based on the outcome "procedure-related mortality".

Beantwortung anhand Endpunkt „eingriffsbezogene Mortalität"

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

Data on procedure-related mortality was only reported in three studies: the interim and extension studies [3, 5] and the NRCT [6]. No patient deaths were reported either in the intervention or in the control groups (0 vs. 0).

3 Studien: keine eingriffsbezogenen Todesfälle aufgetreten

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

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

keine Evidenz

D0003 – What is the effect of AMIC on the mortality due to causes other than the target disease?

No direct evidence was found to answer this research question.

keine Evidenz

6.4 Included studies: MACI

RCTs und NRCTs

For evaluating safety outcomes, we also exclusively considered RCTs and prospective NRCTs.

keine Evidenz für Knöchel – Sicherheit zum Knie

Again, no controlled trials comparing the two-step scaffold-based treatment of (osteo)chondral defects in the ankle with MFx or ACI could be identified for safety. Thus, the following questions are only answered for cartilage defects of the knees.

5 Studien für Wirksamkeit inkludiert: 3 Studien vs. MFx & 2 Studien vs. ACI

Nearly the same five RCTs [8, 22, 23, 48, 49][6], with a total of 346 (191 vs. 155) patients assessing the clinical efficacy of the two-step scaffold-assisted chondral repair of the knee joint (MACI) compared to MFx [8, 48, 49] or ACI [22, 23] were also included for safety.

Detailed study characteristics are described before (see Chapter 5.4) and displayed in Table A-3, Table A-4, and in the evidence profile in Table A-9.

6.5 Safety results: MACI

Patient safety

Cooo8 – How safe is MACI in comparison to the comparators?

Beantwortung anhand von mehreren Endpunkten berichtet in allen 5 Studien

Answering this research question was based on the outcome "severe adverse events", "procedure-related adverse events", "device-related adverse events" and "re-operation rate".

Adverse events were reported in all five RCTs comparing the scaffold-based two-step cartilage repair (MACI) with MFx [8, 48, 49] or with ACI [22, 23].

Two-step scaffold-based treatment vs. MFx:

Severe adverse events

3 RCTs: schwerwiegende Nebenwirkungen: 0 %-15.3 % vs. 0 %-26.4 %

Severe adverse events were reported in all three RCTs comparing MACI with MFx [8, 48, 49]. In one RCT [48], there were no severe adverse events in any study group. In the other two RCTs [8, 49], the reported rates ranged from 4.8% to 15.3% in the intervention groups and from 11.1% to 26.4% in the control groups. The two RCTs reported on severe adverse events, like treatment failure, cartilage injury and arthralgia [8], and total knee arthroplasty and one case of cancer of gynaecologic origin; however, the relation to the procedure was unknown [49].

Procedure-related adverse events

2 RCTs: eingriffsbezogene Nebenwirkungen: 0 %-34.7 % vs. 0 %-38.9 %

Adverse events *related to the surgical procedure* were reported in two RCTs [8, 49]. In one of the two studies [49], no procedure-related adverse events occurred in any study group. The other RCT [8] reported on rates of 34.7% and 38.9% in the intervention and control group, respectively. Thereof, the most common adverse events were treatment failure, arthralgia and joint swelling.

[6] In total, six RCTs were included. One of the six RCTs was an interim analysis of the included extension study (Saris 2014 [8] & Brittberg 2018 [9]). Safety data were extracted only from Saris 2014, because only this study reported on safety outcomes.

Device-related adverse events

Adverse events *related to the scaffold* were not reported in any of the three RCTs [8, 48, 49].

keine Evidenz

Re-operation rates

Re-operation rates were reported in all three studies [8, 48, 49], ranging from 2.5% to 8.3% in the intervention groups and from 0% to 9.7% in the control groups.

Overall, across the three RCTs, the rates for the different adverse event categories (severe, procedure-related, re-operation) were higher in the control groups. However, the differences in rates between the intervention and control groups were not statistically significant.

3 RCTs:
Re-Operationsraten:
2.5 %-8.3 % vs.
0 %-9.7 %
insgesamt höhere Nebenwirkungsraten in den Kontrollgruppen (jedoch nicht statistisch signifikant)

Two-step scaffold-based treatment vs. ACI:

Severe adverse events

Severe adverse events were reported in both RCTs comparing MACI with ACI [22, 23]. In one RCT [22], there were no severe adverse events in any study group. In the other RCT [23], one severe case of inability to work was reported in the intervention group (9.0%).

2 RCTs: schwerwiegende Nebenwirkungen:
0 %-9 % vs. 0 %

Procedure-related adverse events

None of the two RCTs [22, 23] reported *procedure-related* adverse events.

keine Evidenz

Device-related adverse events

Adverse events *related to the scaffold* were reported in both RCTs [22, 23]. The rates ranged from 12.5% to 36.4% in the intervention groups and from 9.0% to 140% (as one patient could suffer from several adverse events) in the control groups. The most reported device-related adverse events in the RCTs were symptomatic hypertrophy, painful catching, wound infection and graft failure.

2 RCTs:
implantatsbezogene Nebenwirkungen:
12.5 %-36.4 % vs.
9.0 %-140 %

Re-operation rates

Re-operation rates were also reported in both RCTs [22, 23], ranging from 6.4% to 27.3% in the intervention groups and from 6.8% to 10.0% in the control groups.

Overall, across the two RCTs, the rates for the different adverse event categories (severe, procedure-related, device-related, re-operation) were inconsistent. While the maximum rates for severe adverse events and re-operations were higher in the intervention groups, the maximum rate of procedure-related adverse events was higher in the control groups. However, the difference between the study groups within a study showed different conclusions: e.g., for device-related adverse events, in one study [22] the rate was higher in the intervention group, whereas in the other RCT [23], the rate was higher in the control group. The opposite held true for the re-operation rates.

2 RCTs:
Re-Operationsraten:
6.4 %-27.3 % vs.
6.8 %-10.0 %
insgesamt inkonsistente Resultate zwischen den Studiengruppen vs. ACI

C0002 – Are the harms related to dosage or frequency of applying MACI?

No direct evidence was found to answer this research question.

keine Evidenz

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

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

keine verlässliche Evidenz

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

keine Evidenz

No direct evidence was found to answer this research question.

C0007 – Are MACI and comparators associated with user-dependent harms?

keine Evidenz

No direct evidence was found to answer this research question.

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of MACI and the comparators?

keine Evidenz

No direct evidence was found to answer this research question.

Mortality

D0001 – What is the expected beneficial effect of MACI on mortality?

D0003 – What is the effect of MACI on the mortality due to causes other than the target disease?

1 RCT: keine eingriffs-bezogenen Todesfälle in MACI-Gruppe

One of the five studies [8] reported on procedure-related mortality. According to the study, no patients died due to the two-step scaffold-assisted surgery (MACI).

7 Quality of evidence

The risk of bias (RoB) for individual studies was assessed with the Cochrane Collaboration tool for assessing risk of bias for randomised controlled studies [51] and the Risk Of Bias In Non-randomized Studies of Interventions assessment tool (ROBINS-I) [11], and is presented in Table A-5, Table A-6, and Table A-7 in the Appendix.

RoB bewertet mit Cochrane Collaborations Tool (RCTs) sowie ROBINS-I (NRCT)

The four RCTs (and two interim studies) for AMIC were graded with a *high* and the NRCT was graded with a *serious* RoB. The five RCTs (and one interim study) for MACI were also graded with a *high* RoB.

hoher RoB in den eingeschlossen Studien

The main reasons for downgrading were no blinding of patients and outcome assessors, incomplete outcome data (e.g., no statistical analyses of outcomes between groups, missing confidence intervals and p-values), unclear reporting of confounding variables (e.g., no adherence of possible effect of physiotherapy/rehabilitation or pain killers), and possible conflicts of interests of the authors.

Hauptgründe: fehlende Verblindung, unvollständige Daten, Interessenskonflikte etc.

The strength of evidence was rated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme [12] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved to resolve the difference. A more detailed list of the criteria applied can be found in the recommendations of the GRADE Working Group [12].

Qualität der Evidenz nach GRADE

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.

The ranking according to the GRADE scheme for the research question can be found in the summary of findings tables below (Table 7-1 and Table 7-2) and in the evidence profile in the Appendix (Table A-9).

GRADE Tabelle nächste Seite

As the outcomes were measured with different scores, each score for the specific outcome was graded individually. Due to lacking data, the following scores could not be graded for AMIC (KOOS sport/rec & QoL & pain, Lysholm score, EQ-5D) and for MACI (WOMAC stiffness & physical function & pain). With regard to the AMIC and MACI studies, the ICRS score was not interpretable, due to missing scoring instructions. Additionally, three AMIC studies [3, 5, 46] reported on the WOMAC score; however, different scales were used. Thus, the WOMAC scores were graded separately for the two studies. With regard to the MACI studies, negative scores of the SF-12, which were not translated on a 0-100 score, were reported in one study [9]. Consequently, the reported negative values could not be interpreted and this study could not be graded.

nicht alle Endpunkte/ Scores mittels GRADE evaluiert, aufgrund fehlender Daten bzw. unmöglicher Interpretation der berichteten Daten

AMIC vs. MFx: moderate Evidenzstärke für Wirksamkeit und niedrige für Sicherheit

Overall, the strength of evidence for the efficacy and safety of the single-step scaffold-based cartilage repair of the knee in combination with MFx in comparison to MFx alone is “moderate” and “low”, respectively. For the comparison to ACI, no evidence was available (Table 7-1).

MACI vs. MFx/ACI: niedrige Evidenzstärke für Wirksamkeit und sehr niedrige für Sicherheit

Overall, the strength of evidence for the efficacy and safety of the two-step scaffold-assisted cartilage repair of the knee in comparison to MFx or ACI is “low” and “very low”, respectively (Table 7-2).

Table 7-1: Summary of findings table of AMIC compared to MFx for cartilage repair in the knee

Outcomes	Anticipated absolute effects			Relative effect	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with MFx or ACI	Risk with AMIC	Difference				
Efficacy							
Mobility/joint functionality: **improvement** from baseline assessed with: IKDC Scale from: 0 to 100 follow-up: mean 24 months	NR	NR	MD **1 point higher in AMIC group** [a]	Not estimable	100 (1 RCT)	⊕⊕⊕◯ MODERATE [b,c]	Higher score indicates better function
Mobility/joint functionality: **improvement** from baseline assessed with: WOMAC stiffness Scale from: 0 to 8 follow-up: mean 24 months	NR	NR	MD **3.5 points lower in AMIC group** [a]	Not estimable	69 (1 RCT)	⊕⊕⊕◯ MODERATE [b]	Lower score indicates less stiffness
Mobility/joint functionality: **reduction** from baseline assessed with: WOMAC stiffness Scale from: 0 to 20 follow-up: mean 60 months	NR	NR	MD **1.1 points higher in AMIC group** [a]	Not estimable	80 (1 RCT)	⊕⊕⊕◯ MODERATE [b]	Lower score indicates less stiffness
Mobility/joint functionality: **improvement** from baseline assessed with: WOMAC physical function Scale from: 0 to 68 follow-up: mean 24 months	NR	NR	MD **29.7 points lower in AMIC group** [a]	Not estimable	69 (1 RCT)	⊕⊕⊕◯ MODERATE [b]	Lower score indicates better function
Mobility/joint functionality: **reduction** from baseline assessed with: WOMAC physical function Scale from: 0 to 170 follow-up: mean 60 months	NR	NR	MD **5.6 points higher in AMIC group** [a]	Not estimable	80 (1 RCT)	⊕⊕⊕◯ MODERATE [b]	Lower score indicates better function
Mobility/joint functionality: **reduction** from baseline assessed with: Modified Cincinnati Knee Rating System Scale from: 0 to 100 follow-up: mean 12 months	NR	NR	MD **6.0 points lower in AMIC group** [a]	Not estimable	47 (1 RCT)	⊕⊕◯◯ LOW [b,c,,f]	Higher score indicates better function
Mobility/joint functionality: **reduction** from baseline assessed with: SF-12, SF-36 Scale from: 0 to 100 follow-up: mean 60 months	NR	NR	MD **1.4 points lower in AMIC group** [a]	Not estimable	80 (1 RCT)	⊕⊕⊕◯ MODERATE [b,c]	Higher score indicates better function
Quality of life: **improvement** from baseline assessed with: SF-36 Scale from: 0 to 100 follow-up: mean 60 months	NR	NR	MD **2.9 points higher in AMIC group** [a]	Not estimable	80 (1 RCT)	⊕⊕⊕◯ MODERATE [b,c]	Higher score indicates better QoL
Pain: **improvement** from baseline assessed with: VAS Scale from: 0 to 100 follow-up: mean 24 months	NR	NR	MD **6.3 points lower in AMIC group** [a]	Not estimable	100 (1 RCT)	⊕⊕⊕◯ MODERATE [b,c]	Higher score indicates worse pain

Outcomes	Anticipated absolute effects			Relative effect	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with MFx or ACI	Risk with AMIC	Difference				
Pain: **improvements** from baseline assessed with: WOMAC pain Scale from: 0 to 20 follow-up: mean 24 months	NR	NR	MD **12.0 points fewer in AMIC group** [a]	Not estimable	69 (1 RCT)	⨁⨁⨁◯ MODERATE [b]	Lower score indicates less pain
Pain: **reduction** from baseline assessed with: WOMAC pain Scale from: 0 to 50 follow-up: mean 60 months	NR	NR	MD **1.2 points higher in AMIC group** [a]	Not estimable	80 (1 RCT)	⨁⨁⨁◯ MODERATE [b]	Lower score indicates less pain
Necessity of total joint replacement assessed with: in % of pts.	At 12 months: 1 total knee arthroplasty (study group N/A).			N/A	69 (1 RCT)	⨁⨁⨁◯ MODERATE [b,c]	-
Safety							
Safety: Severe adverse events (SAE) assessed with: in % of pts. follow-up: range 24 months to 60 months	30 per 1,000	62 per 1,000	N/A	**RR 2.1** [a]	227 (3 RCTs)	⨁◯◯◯ VERY LOW [b, g,h]	-
Safety: Procedure-related adverse events assessed with: in % of pts. follow-up: range 24 months to 60 months	347 per 1,000	381 per 1,000	N/A	**RR 1.1** [a]	227 (3 RCTs)	⨁◯◯◯ VERY LOW [b,g,h]	-
Safety: Device-related adverse events assessed with: in % of pts. follow-up: range 24 months to 60 months	0 per 1,000	0 per 1,000	N/A	Not estimable	180 (2 RCTs)	⨁⨁⨁◯ MODERATE [b,]	-
Safety: Re-operation rate assessed with: in % of pts. follow-up: range 12 months to 60 months	38 per 1,000	13 per 1,000	N/A	**RR 0.34** [a]	127 (2 RCTs)	⨁⨁◯◯ LOW [b,h]	-

Abbreviations: *CI: Confidence interval; MD: Mean difference; N/A: not available; RR: Risk ratio.*

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Comments

[a.] *Based on self-calculated mean difference between study groups/relative risk.*

[b.] *There was a serious risk of bias due to possible confounding, missing data, and the use of un-blinded patient-reported outcome measures.*

[c.] *N/A (only one trial).*

[e.] *Different age of pts. between studies.*

[f.] *Low incidence/pts. numbers.*

[g.] *Heterogeneity in reported cases across studies.*

[h.] *Low incidence/pt. numbers in one study.*

Table 7-2: Summary of findings table of MACI compared to MFx or ACI for cartilage repair in the knee

Outcomes	Anticipated absolute effects			Relative effect	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with MFx or ACI	Risk with MACI	Difference				
Efficacy							
Mobility/joint functionality: **improvement** from baseline assessed with: KOOS sport/rec Scale from: 0 to 100 follow-up: mean 60 months	NR	NR	MD **8.1 points higher in MACI group** [a]	Not estimable	158 (2 RCTs)	⨁◯◯◯ VERY LOW [c,d,e,f]	Higher score indicates better function
Mobility/joint functionality: **reduction** from baseline assessed with: IKDC Scale from: 0 to 100 follow-up: mean 24 months	NR	NR	MD **2.4 points fewer in MACI group** [a]	Not estimable	179 (3 RCTs)	⨁◯◯◯ VERY LOW [c,d,e,h]	Higher score indicates better function
Mobility/joint functionality: **improvement** from baseline assessed with: Modified Cincinnati Knee Scoring System Scale from: 0 to 100 follow-up: range 12 months to 60 months	NR	NR	MD **1.5 points higher in MACI group** [a]	Not estimable	219 (2 RCTs)	⨁⨁◯◯ LOW [c,d]	Higher score indicates better function
Mobility/joint functionality: **improvement** from baseline assessed with: Lysholm scoring scale Scale from: 0 to 100 follow-up: mean 24 months	NR	NR	MD **2.3 points higher in MACI group** [a]	Not estimable	81 (2 RCTs)	⨁◯◯◯ VERY LOW [c,d,f]	Higher score indicates better function
Mobility/joint functionality: **change** from baseline assessed with: SF-36 Scale from: 0 to 100 follow-up: mean 24 months	At 12/24 months n.s. difference between study groups.			Not estimable	21 (1 RCT)	⨁⨁◯◯ LOW [c,d,f,m]	Higher score indicates better function
Quality of life: **improvement** from baseline assessed with: KOOS QoL Scale from: 0 to 100 follow-up: mean 60 months	NR	NR	MD **4.6 points higher in MACI group** [a]	Not estimable	158 (2 RCTs)	⨁◯◯◯ VERY LOW [c,d,e,f]	Higher score indicates better QoL
Quality of life: **improvement** from baseline assessed with: EQ-5D Scale from: 0 to 100 follow-up: mean 60 months	NR	NR	MD **1.0 point higher in MACI group** [a]	Not estimable	128 (1 RCT)	⨁⨁⨁◯ MODERATE [c,i]	Higher score indicates better QoL
Mobility/joint functionality: **change** from baseline assessed with: SF-36 Scale from: 0 to 100 follow-up: mean 24 months	At 12/24 months n.s. difference between study groups.			Not estimable	21 (1 RCT)	⨁⨁◯◯ LOW [c,d,f,m]	Higher score indicates better QoL
Pain: **improvement** from baseline assessed with: KOOS pain Scale from: 0 to 100 follow-up: mean 60 months	NR	NR	MD **5.5 points higher in MACI group** [a]	Not estimable	158 (2 RCTs)	⨁◯◯◯ VERY LOW [c,d,e,f]	Higher score indicates less pain

Outcomes	Anticipated absolute effects			Relative effect	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with MFx or ACI	Risk with MACI	Difference				
Pain: **improvement** from baseline assessed with: VAS Scale from: 0 to 100 follow-up: N/A	NR	NR	MD **0.2 points lower in MACI group** [a]	Not estimable	121 (2 RCTs)	⨁◯◯◯ VERY LOW [c,d,e,f]	Higher score indicates worse pain
Pain: assessed with: SF-12, SF-36 follow-up: mean 24 months	N.s. difference between IG vs. CG for 12 and 24 months.			Not estimable	(1 RCT)	⨁⨁◯◯ LOW [c,i,k]	Higher score indicates less pain
Necessity of total joint replacement assessed with: in % of pts.	0 per 1,000	0 per 1,000	N/A	Not estimable	30 (1 RCT)	⨁⨁◯◯ LOW [c,i,k]	-
Safety							
Safety: Severe adverse events (SAE) follow-up: range 24 months to 60 months	7 per 1,000	11 per 1,000	N/A	**RR 1.57** [a]	330 (5 RCTs)	⨁◯◯◯ VERY LOW [c,d,e,h]	-
Safety: Procedure-related adverse events	0 per 1,000	0 per 1,000	N/A	Not estimable	30 (1 RCTs)	⨁⨁◯◯ LOW [c,f, l]	-
Safety: Device-related adverse events follow-up: range 6 months to 24 months	333 per 1,000	173 per 1,000	N/A	**RR 0.52** [a]	112 (2 RCTs)	⨁◯◯◯ VERY LOW [c,d,e,f, g]	-
Safety: Re-operation rate follow-up: mean 24 months	27 per 1,000	44 per 1,000	N/A	**RR 1.59** [a]	330 (5 RCTs)	⨁◯◯◯ VERY LOW [c,d,e,h]	-

Abbreviations: *MD: Mean difference; N/A: not available; RR: Risk ratio*

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Comments

a. *Based on self-calculated mean difference between study groups/relative risk.*
b. *Absolute effect based on one study (Brittberg 2018).*
c. *There was a serious risk of bias due to possible confounding, missing data, and the use of un-blinded patient-reported outcome measures.*
d. *Heterogeneity in reported cases across studies.*
e. *Different defect size in pts. between studies.*
f. *Low incidence/pt. numbers in one study.*
g. *For device-related adverse events, only the studies with ACI as the comparator were considered.*
h. *Low incidence/pt. numbers in two studies.*
i. *N/A (only one trial)*
j. *Absolute effect based on one study (Bartlett 2005).*
k. *Low incidence/pt. numbers.*
l. *Absolute numbers for adverse events given only in one study.*
m. *In one RCT [9], negative scores of the SF-12, which were not translated on a 0-100 score, were reported. Thus, the reported negative values could not be interpreted and this study could not be graded for this outcome.*

8 Discussion

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 isolation from the systemic regulation and lacking vessels plus nerve supply. This contributes to the fact that cartilage healing remains challenging.

Knorpeldefekte schwierig zu behandeln

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.

Defekte am Knorpel bedeuten Schmerzen

The aims of this report were, on the one hand, to assess the clinical efficacy and safety of the single-step matrix-assisted cartilage repair combined with MFx (AMIC) in the knee or ankle joint, compared to MFx alone or ACI. On the other hand, the clinical efficacy and safety of the two-step matrix-assisted cartilage repair (MACI) in the knee or ankle joint was investigated compared to MFx or ACI.

Ziele: Bewertung Wirksamkeit & Sicherheit von AMIC & MACI

Results of the single-step matrix-assisted cartilage repair (AMIC)

No studies investigating the clinical efficacy of AMIC in the ankle joint or in comparison to ACI met the inclusion criteria. Thus, only results for the efficacy and safety of AMIC in the knee joint compared to MFx alone were reported.

keine Studien zum Sprunggelenk bzw. zu ACI als Vergleich

For assessing the clinical efficacy and safety of AMIC combined with MFx in the knee joint compared to MFx alone, six studies (five RCTs[3] and one NRCT) that met our inclusion criteria could be identified, involving 314 patients overall.

6 Studien mit MFx als Vergleich

All trials used different products of scaffolds: Chondro-Gide®, MaioRegen™, JointRep™, BST-CarGel® and another device comparable to GelrinC®.

in Studien 4 Produkte explizit genannt

All of the identified studies included patients with (osteo)chondral defects in the knee. The mean defect sizes were slightly larger in the intervention groups compared to the control groups (2.3-3.9 vs. 1.9-3.5 cm^2). As AMIC is indicated for a defect size of up to 8 cm^2, the patients included in the studies had relatively small defect sizes.

vergleichsweise kleine Defektgrößen

Different scores measuring the mobility/joint functionality (six scores), quality of life (three scores) and pain (three scores) were reported in the included studies. With regard to mobility/joint functionality, inconsistent results were reported across the scores. For quality of life, an improvement was reported for the intervention group; however, this improvement was not statistically significant. For pain, similar improvements were reported between the study groups across the studies. In only one study, the necessity of a total joint replacement was addressed. In this study, one total knee arthroplasty was reported after 12 months.

inkonsistente Resultate für Mobilität, keine signifikanten Unterschiede für Schmerzen und Lebensqualität zwischen den Studiengruppen

Komplikationen: 0-12.2 % vs. 0-3.8 % schwerwiegend, 0-93.0 % vs. 0-77.0 % eingriffsbezogen, 3.5-22.0 % 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. Severe adverse event rates ranged from 0-12.2% in the intervention groups and from 0-3.8% in the control groups of three studies. Procedure-related adverse events occurred in 0-93.0% of the patients in the intervention groups (0-77.0% in the control groups) across four studies [3, 5-7, 47]. The rates for device-related complications differed from 3.0 to 22.0% across three studies [3, 5, 6, 47].

Evidenzstärke moderat bis gering für Wirksamkeit bzw. Sicherheit

Overall, the strength of evidence for the clinical effectiveness and safety of AMIC compared to MFx alone was determined as "moderate" and "low", respectively, by considering only the highest available level of evidence (RCTs). 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.

Interpretation of findings of the single-step matrix-assisted cartilage repair (AMIC)

unzureichende Evidenz zur Überlegenheit AMIC vs. MFx

There is no robust evidence that AMIC leads to better efficacy and safety outcomes than MFx alone. In the following, different aspects that might have influenced these results are presented:

relativ kleine Fallzahlen

- A major issue of the identified trials is the low number of patients of each study. One RCT [47] consisted of 100 patients, whereas the smallest controlled trial included only 18 patients (NRCT [6]). Initially, this study was conducted as a RCT. However, the randomisation was stopped after only three patients were assigned to the control group. This study was thus treated as a NRCT in the present report. Especially for identifying rare (unanticipated) complications, these patient numbers might be insufficient. Furthermore, small patient numbers are likely to have an impact on 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 (six months for the NRCT [6]). Only two of the studies had a follow-up of at least five years. Therefore, reliable data on long-term efficacy and safety-related outcomes are missing, which might have especially impacted the safety results.

Interventionen in Studien wichen teilweise leicht voneinander ab

- The applied interventions (different products) differed slightly between the individual studies. First of all, in two studies 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). Moreover, the MFx-procedure in the control groups was either performed arthroscopically or by mini-arthrotomy.

In addition, some outcomes were reported incomplete or inconsistent and lacked sufficient data:

Notwendigkeit eines Gelenksersatzes in nur einer Studie berichtet

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

- 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 about 93.0% in the treatment group. In another RCT, the rates of procedure-related complications were 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 adverse event rate close to 0% could be questioned. Furthermore, in only one out of five studies was it clearly stated which adverse events occurred.

inkonsistente Angaben zu Komplikationen

Results of the two-step matrix-assisted cartilage repair (MACI)

No studies investigating the clinical efficacy and safety of MACI in the ankle joint met the inclusion criteria. Thus, only results about the efficacy and safety of MACI in the knee joint compared to MFx or ACI could be reported.

keine Studien zum Sprunggelenk

For assessing the clinical efficacy and safety of MACI in the knee joint compared to MFx or ACI, three and two RCTs were identified, respectively, involving a total of 330 patients.

3 Studien vs. MFx & 2 Studien vs. ACI

In three trials, different products of scaffolds were used: Spherox®, BioSeed®-C and NeoCart®.

3 unterschiedliche Produkte

All of the identified studies included patients with chondral defects in the knee. The mean defect sizes were slightly larger in the intervention groups compared to the control groups (2.9-6.1 vs. 2.5-6.0 cm^2). As MACI is indicated for a defect size of up to 10 cm^2, the patients included in the studies had relatively small defect sizes.

vergleichsweise kleine Defektgrößen

Different scores measuring the mobility/joint functionality (six scores), quality of life (three scores) and pain (three scores) were reported in the included studies.

For the comparison to MFx, partly statistically significant improvements in joint functionality and quality of life were reported for the intervention group. For pain, partly statistically significant improvements were also reported in the intervention groups across scores and studies. In only one study, the necessity of a total joint replacement was addressed. In this study, one total knee arthroplasty was reported after 12 months.

vs. MFx: (signifikante) Verbesserung der Funktionalität, Lebensqualität und Schmerzen

For the comparison MACI versus ACI, inconsistent results regarding improvements in joint functionality were reported across scores and studies. Moreover, no evidence was available for quality of life. For pain, no statistically significant differences between the study groups could be identified. There was no evidence for the necessity of a total joint replacement.

vs. ACI: inkonsistente Resultate zur Funktionalität, keine Verbesserung der Schmerzen

Complications were reported in all three studies comparing MACI to MFx. The complication rates between the studies differed considerably, which might be related to the different follow-up periods. Severe adverse event rates ranged from 4.8-15.3% in the intervention groups and from 11.1-26.4% in the control groups across the three studies. Procedure-related adverse events occurred in 0-34.7% of the patients in the scaffold groups (0-38.9% in the control groups) across all three studies. No evidence was available for device-related complications. In addition, re-operation rates were reported in all three RCTs ranging from 2.5-8.3% versus 0-9.7%.

Komplikationen (vs. MFx): 4.8-15.3 % vs. 11.1-26.4 % schwerwiegend, 0-34.7 % vs. 0-38.9 % eingriffsbezogen, 2.5-8.3 % vs. 0-9.7 % Re-Operationsraten

Komplikationen (vs. ACI): 0-9.0% vs. 0 % schwerwiegend, 12.5-36.4 % vs. 9.0-140 % implantatsbezogen, 6.4-27.3 % vs. 6.8-10.0 % Re-Operationsraten

Furthermore, complications were reported in both studies comparing MACI to ACI. Again the complication rates differed considerably between the studies. Severe adverse event rates ranged from 0-9.0% in the intervention groups, while zero events occurred in the control groups of the studies. No procedure-related adverse events were reported in the two RCTs. The rates for device-related complications differed from 12.5-36.4% in the intervention groups and from 9.0-140% in the control groups across the studies. The reported re-operation rates ranged from 6.4-27.3% versus 6.8-10.0% between the study groups of both RCTs.

Evidenzstärke niedrig bis sehr niedrig für Wirksamkeit bzw. Sicherheit

Overall, the strength of evidence for the clinical efficacy and safety of MACI compared to MFx or ACI was determined as “low” and “very low”, respectively. 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.

Interpretation of findings of the two-step matrix-assisted cartilage repair (MACI)

unzureichende Evidenz im Vergleich zu ACI, jedoch mögliche Überlegenheit von MACI vs. MFx

There is no robust evidence that MACI leads to better efficacy and safety outcomes than ACI. However, from the extracted evidence, slightly better improvements (partly statistically significant) in joint functionality, quality of life and pain, as well as slightly lower complications rates, could be identified in the intervention groups compared to MFx. In the following, different aspects that might have influenced these results are presented:

relativ kleine Fallzahlen, speziell in den Studien im Vergleich zu ACI

- Similar to the AMIC studies, a major issue of the identified studies for MACI is the low number of patients in some studies. Only one RCT (in comparison to MFx) [9] consisted of more than 100 patients (n=128), whereas one study (in comparison to ACI) included only 21 patients [23]. Thus, in total, the comparison to MFx involved 218 patients (3 RCTs), whereas the comparison to ACI only included 112 patients (2 RCTs). Especially for identifying rare (unanticipated) complications, these patient numbers, in particular for the comparison to ACI, might be insufficient. The small patient numbers in the studies “MACI vs. ACI” are also likely to have an impact on the trials’ ability to detect between-group differences in efficacy outcomes.

relativ kurze Nachbeobachtungszeiträume in den meisten Studien

- Furthermore, only one study (in comparison to MFx) [9] had a follow-up longer than 24 months. Therefore, reliable data of long-term efficacy and safety-related outcomes are missing, which might have especially impacted the safety results.

Interventionen in Studien wichen teilweise leicht voneinander ab, sowie unterschiedliche Kontrollinterventionen

- The applied interventions (different products) differed slightly between the individual studies. First of all, the material of the used scaffold differed between studies (e.g., bovine vs. porcine collagen matrix). Secondly, in three of the five studies, MACI was compared to MFx, and to ACI, in the remaining two studies. Of these two studies, the first ACI generation, including a periosteal flag matrix, was investigated in one study [23], whereas the third ACI generation [22], involving a porcine derived matrix, was assessed in the second study.

In addition, some outcomes were reported incomplete or inconsistent and lacked sufficient data:

- One outcome defined as crucial – necessity of a total joint replacement – was exclusively reported in only one trial (one patient in the scaffold-group required a new joint) in comparison to MFx. In comparison to ACI, no evidence about the necessity of a total joint replacement was available. However, this outcome is important to assess the long-term efficacy of the treatment of (osteo)chondral defects. Thus, for meaningful prospective data on joint replacement rates, a very long follow-up and/or larger samples might be necessary.

Notwendigkeit eines Gelenksersatzes in nur einer Studie berichtet

- 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 all five studies, the ranges of adverse events were wide within and between study groups. This discrepancy hints at different approaches to safety. It has to be stated that due to the invasive nature of the interventions compared (involving one to two operations), an adverse event rate close to zero could be questioned.

inkonsistente Angaben zu Komplikationen ...

- Moreover, different adverse event rate results between intervention and control groups might also be related to the control group (MFx or ACI). Interestingly, the adverse event rates of MACI compared to MFx were lower in the intervention groups, even though MACI involves two operations, while MFx only one. In comparison to ACI (also a two-step approach), the adverse event rates were partly higher in the control groups. However, this could also be an effect of the smaller patient numbers and shorter follow-up in the studies comparing MACI vs. ACI.

... evtl. bezogen auf Kontrollintervention (MFx vs. ACI)

In 2009, the Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA) in Germany concluded that MACI 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 have been published yet) [52].

scheinbar keine Evidenz zu Überlegenheit von MACI

General discussion points

To date, no RCTs and NRCTs could be identified to assess the clinical effectiveness and safety of AMIC and MACI versus MFx and/or ACI for the ankle joint.

keine RCTs/NRCTs zum Sprunggelenk

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

unklare Angaben zu preoperativen Interventionen

Moreover, all included studies reported on post-operative rehabilitation programmes. However, the effects of these post-operative therapies on the overall efficacy and safety outcomes were not considered. Thus, there is a possible confounding effect on the reported findings.

mögliches Confounding durch postoperative Maßnahmen

In addition, it was barely reported whether 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, such as pain and quality of life.

unklare Angaben zu Medikation

längere Nachbeobachtungszeiträume & größere PatientInnenanzahlen notwendig, um Komplikationen zu identifzieren

Moreover, limited long-term evidence of both interventions (AMIC & MACI) is currently available, as only a few studies had a follow-up longer than 24 months. Thus, it remains questionable whether the interventions have a sustainable effect. Especially in terms of safety and the necessity of a total joint replacement, longer follow-up periods are substantial in order to identify rare adverse events and to investigate the sustainable preservation of the rebuilt cartilage. Besides longer follow-up, larger clinical trials are also necessary to identify serious rare complications and to be able to detect more reliable between-group differences in efficacy and safety outcomes.

v. a. jüngere Personen betroffen → Arbeitsunfähigkeit kann einhergehen, Lebensqualität niedriger → zusätzliche gesellschaftliche Kosten

All studies included relatively young patients of working age. The mean ages in the AMIC studies were slightly higher (34.0-54.5 vs. 35.2-56.6 years) compared to the mean ages in the MACI studies (29.5-41.0 vs. 29.5-39.0 years). Nevertheless, assuming that mean ages in the studies display the mean ages of the general patient population with cartilage defects, these patients might be incapacitated for work, require more sick leave, have to quit their current jobs, including a subsequent need for retraining, or even require early retirement, which might significantly impact their quality of life. Consequently, cartilage defects – or more precisely the challenge of healing cartilage defects – can result in additional societal costs.

zahlreiche Scores zur Effektmessung in Studien, teilweise nicht interpretierbar bzw. untereinander vergleichbar

In all included studies (for AMIC and MACI), efficacy outcomes were measured with various different scores within and across the studies. As a result, the interpretation of the effect of the intervention on one specific outcome was difficult for one study and across all studies and, in some cases, not even possible. For example, the ICRS scores were not interpretable due to lacking scoring instructions. Moreover, one study reported negative SF-12 scores, which were not translated on a 0-100 score. Consequently, the reported negative scores could not be interpreted (see Applicability table).

PatientInnen-berichtete Endpunkte als Confounder in RoB beachtet

Moreover, the majority of the efficacy outcomes (mobility/joint functionality, quality of life, pain and activities of daily living) were patient-reported outcomes and thus may be confounded. Therefore, the level of subjectiveness was taken into account within the risk of bias assessment.

Upcoming evidence

6 laufende Studien zu AMIC/MACI vs. MFx (Beobachtungszeitraum ≤24 Monate, nur 1 RCT mit 36 Monaten)

Six ongoing RCTs (Table A-11) will provide further data on the efficacy and safety of AMIC or MACI (for different products) in comparison to MFx. However, the majority of these studies will not provide long-term follow-up of more than 24 months, and thus will not fill the gap of long-term evidence exceeding 24 months. Only one RCT (NCT01656902) will investigate the safety and effectiveness of the NOVOCART® 3D plus (MACI) compared to MFx for 36 months (estimated completion date May 2019).

keine laufenden kontrollierten Studien zu AMIC/MACI vs. ACI bzw. zum Sprunggelenk

No ongoing RCTs or NRCTs investigating the clinical efficacy and safety of AMIC/MACI compared to ACI could be identified. Further, no ongoing RCTs or NRCTs for the assessment of both interventions for the ankle joint could have been identified.

Limitations to the present report

First of all, we decided to exclusively include studies with a high level of evidence, RCTs and NRCTs, due to the richness of these detected studies. Consequently, we excluded the only study (case series) for the ankle joint that had been identified via the systematic literature and additional hand search.

lediglich RCTs und NRCTs eingeschlossen → keine kontrollierten Studie zum Sprunggelenk

Secondly, 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 retrospektiver Studien

Thirdly, possibly not all appropriate studies could have been identified, although different terms in the systematic literature search were used, the manufacturers contacted for additional studies and a supplemented hand search was conducted. This is mainly due to the inconsistent wording for the assessed technology of cartilage repair. In addition, it is possible that not all manufacturers could have been identified.

Möglichkeit der Nicht-Identifikation von relevanten Studien

Further, we did not distinguish between chondral and osteochondral defects. Therefore, studies investigating other comparative interventions for osteochondral defects, for example osteochondral autograft transplantation (OATS) were not considered in this report.

keine Unterscheidung chondraler/ osteochondraler Defekte

In all included studies (for AMIC and MACI), efficacy outcomes were measured with various different scores within and across the studies. Therefore, for most of the scores, only one study was available for performing the GRADE analysis. This could have had an impact on the explanatory power of the strength of evidence resulting from the analysis.

Aussagekraft der GRADE Analyse evtl. limitiert

Finally, although the present report includes various different comparisons between interventions/control interventions (AMIC vs. MFx; MACI vs. MFx or ACI), the two interventions (AMIC and MACI) as well as the two comparative interventions (MFx and ACI) have not been compared with each other, as this would have been beyond the scope of this assessment. Therefore, additional studies might have been excluded.

kein Vergleich von AMIC vs. MACI, sowie MFx vs. ACI

Conclusion

Overall, no conclusions can be made that the single-step scaffold-assisted cartilage repair combined with MFx (AMIC) leads to better outcomes than MFx alone. No evidence (RCTs and NRCTs) is available for investigating the effect on AMIC compared to ACI.

keine klare Aussage zu AMIC vs. MFx

For the comparison of the two-step scaffold-assisted cartilage repair (MACI) to MFx, slightly better efficacy outcomes (joint functionality, quality of life, pain) were identified in the intervention groups. Moreover, MACI seems to be slightly safer compared to MFx. However, there was no robust evidence that MACI leads to better outcomes compared to ACI.

MACI scheinbar etwas wirksamer und sicherer als MFx, keine Aussage vs. ACI

Because the included studies showed partly poor quality of evidence and high risk of bias, it is not possible to draw a reliable conclusion on the clinical effectiveness and safety for both interventions.

jedoch generell Qualität der Evidenz niedrig

weitere Studien zu Sprunggelenk, zu AMIC vs. ACI, längere Nachbeobachtungszeiträume & größere Studien notwendig

Future RCTs and/or NRCTs investigating, on the one hand, the effect of AMIC and/or MACI for the ankle joint and, on the other hand, the effect of AMIC compared to ACI for the knee joint, need to be reported. Moreover, longer follow-up periods (with a minimum of five years) and larger clinical trials are necessary in order to be able to investigate the sustainable preservation of the rebuilt cartilage, as well as to identify serious rare adverse events.

Effekt von MACI über MFx bestätigen

Further evidence is likewise needed to confirm the possible positive effect of MACI over MFx and to clarify the inconsistent evidence of AMIC compared to MFx and of MACI versus ACI.

9 Recommendation

Table 9-1 shows the scheme for recommendations and highlights the respective choice.

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 single-step scaffold-assisted cartilage repair (AMIC)

The current evidence is not sufficient to conclude that the single-step scaffold-assisted cartilage repair (AMIC) combined with microfracture is more effective and safer than microfracture alone for the treatment of cartilage defects in the knee joint.

AMIC vs. MFx: unzureichende Evidenz zum Kniegelenk

In comparison to the autologous chondrocyte implantation (ACI), no evidence was available to conclude that AMIC is as effective, but safer than ACI for the treatment of cartilage defects in the knee joint.

AMIC vs. ACI: keine Evidenz zum Kniegelenk

Reasoning two-step scaffold-assisted cartilage repair (MACI)

To date, the evidence shows that the two-step scaffold-assisted cartilage repair (MACI) seems to be slightly more effective and safer than microfracture for the treatment of cartilage defects in the knee joint.

MACI scheint wirksamer und sicherer als MFx zu sein

In comparison to ACI, the current evidence is not sufficient to prove that MACI is as effective, but safer than ACI for the treatment of cartilage defects in the knee joint.

MACI vs. ACI: unzureichende Evidenz für das Kniegelenk

Recommendation

As no controlled studies could be identified for the cartilage repair of the ankle joint, it was not possible to give a recommendation about whether AMIC and/or MACI should be considered for the inclusion into the hospital benefit catalogue for the ankle joint.

keine Evidenz zum Sprunggelenk, daher keine Empfehlung dazu

Due to inconsistent outcome reporting, the included studies showed partly poor quality of evidence and high risk of bias. Hence, it is not possible to draw a reliable conclusion on the clinical effectiveness and safety for both interventions. As a result, AMIC and MACI are currently not recommended for the inclusion in the hospital benefit catalogue.

niedrige Evidenzqualität → verlässliche Aussage nicht möglich

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

Studien mit mehr PatientInnen + längerer Nachbeobachtung

A re-evaluation for AMIC is recommended not before 2022, since there are still ongoing RCTs (see Table A-11). For MACI a re-evaluation might be reasonable not before 2021, as the technique seems to be promising compared to MFx.

Re-Evaluierung AMIC 2022 empfohlen; Re-Evaluierung MACI nach 2021 empfohlen

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

*Table A-1: Autologous matrix-induced chondrogenesis in combination with MFx (AMIC) for cartilage repair of **knee joints** Results from randomised controlled trials*

Author, year [Reference]	Kon, 2018 [47]	Pipino, 2018 [46]	Shive, 2015 [3] (Stanish, 2013[7] [5])[8]	Volz, 2017 [7] (Anders, 2013[7] [4])[9]
Country	Italy, Sweden, Belgium, Switzerland, Austria, Germany, Norway, Poland, South Africa	Italy	Canada, Spain, South Korea	Germany
Sponsor	Fin-Ceramica Faenza S.p.A., Italy	None	BioSyntech Canada Inc., Piramal Life Sciences	Geistlich Pharma AG, Switzerland
Intervention/Product	AMIC (MaioRegen™, Fin-Ceramica Faenza S.p.A., Italy): Arthrotomy, nanostructured collagen-hydroxyapatite (coll-HA) multilayer scaffold (osteochondral biomimetic scaffold)	AMIC (JointRep™, Oligo Medic Inc., Laval, Quebec Canada): Microfracture surgery + injectable thermogelling system	AMIC (BST-CarGel®, Piramal Life Sciences, Bio-Orthopaedic Division): Arthroscopy + miniarthrotomy, single-step cartilage repair + microfracture/BST-CarGel®	AMIC (Chondro-Gide®, Geistlich Pharma AG, Wolhusen, Switzerland): Miniarthrotomy + microfracture + collagen type I/III membrane (AMIC® sutured | AMIC® glued)
Comparator	MFx alone	MFx alone	Arthroscopic MFx alone	Arthroscopic MFx alone
Study design	Multicentre randomised controlled trial (RCT)	Matched pair study (RCT)	Multi-centre randomised controlled trial (RCT)	Two-centred, prospective, randomised controlled trial (RCT)
Number of pts., n	100 (51 vs. 49)[10]	69 (46 vs. 23)	80 (41 vs. 39)[12] 60 (34 vs. 26)	47 (17 | 17[11] vs. 13)
Location of lesion, n (%)	Chondral and osteochondral lesions: Condyle: 37 (72.6) vs. 23 (47.0) Trochlea: 2 (3.9) vs. 6 (12.2) Patella: 12 (23.5) vs. 20 (40.8)	Osteochondral defect lesions (NR)	Femoral condyle cartilage lesion[12]: Medial femoral condyle: 40 (97.6) vs. 38 (97.4) Lateral femoral condyle: 1 (2.4) vs. 1 (2.6)	Cartilage defect (NR)

[7] Study already included in initial report DSD98 2016.

[8] Study results after one year were published in Stanish 2013 (assessing 41 vs. 39 pts.) and results after five 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 initial pts. were enrolled in the extension study.

[9] Study results after two years were published in Anders 2013 (assessing 28 vs. 10 pts.) and results after two and five years follow-up were presented in Volz 2017 (assessing 34 vs. 13 pts.). Therefore, only the data from the latest publication are presented.

[10] Per protocol population. Safety population (n=124), 14 drop-outs and protocol violators and ten loss to follow-up.

[11] In 17 patients the scaffold was sutured and in 17 patients the scaffold was glued.

[12] Extracted from Stanish 2013.

Author, year [Reference]	Kon, 2018 [47]	Pipino, 2018 [46]	Shive, 2015 [3] (Stanish, 2013[7] [5])[8]	Volz, 2017 [7] (Anders, 2013[7] [4])[9]
Inclusion criteria	NR	✿ moderate to severe (Outerbridge III–IV) osteochondral lesions in the knee secondary to primary osteoarthritis or trauma and refractory to conservative measures, ✿ pts. with associated conditions such as previous partial meniscectomy, cruciate ligament lesions, or failed microfracture surgery (only in one case) were also included in the study and the associated procedures were performed simultaneously and in addition to the surgical treatment of the chondropathy.	✿ aged 18-55 yrs, ✿ single, focal cartilage lesion on the femoral condyle, ✿ moderate knee pain (>4 on a 10 point VAS).	✿ aged 18-50 yrs, ✿ one or two isolated cartilage defects of the knee grade III or IV according to the Outerbridge classification, ✿ located either on the medial or lateral femoral condyle, trochlea or patella, ✿ defect size between 2 and 10 cm^2.
Exclusion criteria	NR	NR	✿ pts. with multiple lesions or kissing lesions, ✿ clinically relevant compartment malalignment (>5 degrees), ✿ pts. who underwent ligament treatments in the affected knee within two 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.	✿ pts. with >2 defects, 2 corresponding defects or bilateral defects, ✿ osteoarthritis, ✿ bone lesions deeper than 0.7 cm, ✿ axis deviation of more than ±5° in the frontal plane, ✿ unresolved knee instability, ✿ rheumatoid arthritis, ✿ infectious diseases, ✿ endocrine, metabolic or autoimmune diseases, ✿ previous subtotal or total meniscus resection or mosaicplasty, ✿ treatment with cartilage specific medication (e.g., hyaluronic acid), ✿ chondropathia patellae, patella dysplasia or patella instability, ✿ concomitant lesions of anterior cruciate ligament, meniscus or axial malalignement.
Prior surgery, n (%)	27 (52.9) vs. 23 (46.9)	1 (2.2*) vs. 0 (0)	NR[13]	10 (58.8*) | 8 (47.1*) vs. 6 (46.2*)
Postoperative treatment(s)	Early isometric and isotonic exercises and electrical neuromuscular stimulation (n/a)	Postoperative rehabilitation protocol (all pts.): weightbear as tolerated (WBAT), after 15 days formal standard physical therapy	Physiotherapy/rehabilitation (all pts.)	Staged rehabilitation program (all pts.)

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

Author, year [Reference]	Kon, 2018 [47]	Pipino, 2018 [46]	Shive, 2015 [3] (Stanish, 2013[7] [5])[8]	Volz, 2017 [7] (Anders, 2013[7] [4])[9]
Age of patients, mean, yrs (SD/range)	34.0 (± 10.9) vs. 35.2 (± 10.2)	54.5 (±9.5/26–72) vs. 56.6 (±7.6/44–70)	35.1 (±9.6) vs. 37.2 (±10.6)[12]	34 (±11.0) | 39 (±9.0) vs. 40 (±6.0)
Female sex, n (%)	15 (29.4) vs. 18 (36.7)	17 (37.0) vs. 12 (52.2)	18 (43.9*) vs. 14 (35.9*)[12]	5 (29.4*) | 2 (11.8*) vs. 3 (23.1*)
Follow-up (months)	24	24	60	60
Loss to follow-up, n (%)	10 (n/a)	2 (4.3*) vs. 0 (0)	12 months: 0 (0) vs. 2 (5) 60 months: 8 (20.0) vs. 13 (33.3)[14]	1 (5.9*) | 3 (17.6*) vs. 4 (30.8*)
BMI, mean, kg/m² (SD/range)	25.6 (± 3.3) vs. 25.2 (± 3.2)	NR	27.0 (±3.3) vs. 25.2 (±3.0)[12]	27.4 (±4.4) | 27.6 (±4.0) vs. 25.0 (±2.9)
Defect size, mean, cm² (SD)	3.4 (± 1.5) vs. 3.5 (± 1.6)	2.7* (n/a) vs. 2.6* (n/a)	2.3 (±1.4) vs. 1.9 (±1.4)[12]	3.8 (±2.1) | 3.9 (±1.1) vs. 2.9 (±0.8)
Clinical classification, n (%)	NR	Outerbridge III: 10 (23) vs. 6 (39) Outerbridge IV: 36 (78) vs. 17 (61)	NR	Grade III (Outerbridge): NR Grade IV (Outerbridge): NR
Primary endpoint(s)	IKDC subjective knee evaluation form 2000 score after 24 months	NR	Degree of lesion fill & repair cartilage T2 relaxation time (both via MRI)	Clinical evaluation as well as MRI evaluation at one, two and five years follow-up
Outcomes				
Efficacy				
Mobility/joint functionality, scales:				
KOOS[15] (sport/rec), mean (SD)	NR	NR	NR	NR
IKDC [16], mean (SD) *Higher scores indicate better function.*	**Subjective IKDC:** **Baseline:** 43.2 (±16.6) vs. 41.1 (±15.9) **12 months**: 60.7 (±17.3) vs. 61.8 (±18.0) *Change after 12 months:* +17.5* vs. +20.7* **24 months**: 66.7 (±21.0) vs. 63.6 (±18.2), n.s., p=n/a *Change after 24 months:* +23.5* vs. +22.5*	NR	NR	NR

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

[15] The KOOS holds 42 items in five separately scored subscales; Pain, other Symptoms, Function in daily living (ADL), Function in Sport and Recreation (Sport/Rec), and knee-related Quality of Life (QOL). Scores are transformed to a 0–100 scale, 0 representing extreme problems and 100 representing no problems.

[16] The IKDC (International Knee Documentation Committee) scoring system includes ten items investigating symptoms, function and return to sporting activities. It combines objective clinician and subjective patient measures. Scores range from 0 points (lowest level of function or highest level of symptoms) to 100 points (highest level of function and lowest level of symptoms).

Author, year [Reference]	Kon, 2018 [47]	Pipino, 2018 [46]	Shive, 2015 [3] (Stanish, 2013[7] [5])[8]	Volz, 2017 [7] (Anders, 2013[7] [4])[9]
WOMAC[17] stiffness subscale, mean (%/SD) *Lower scores indicate better function.*	NR	**Baseline:** 5.6 (3.1) vs. 5.1 (2.1), p=1.000, n.s. **Change after 6 months:** -4.9* (87.6) (p<0.0001) vs. -2.8* (55.6) p<0.0001, **s.s.** **Change after 12 months:** -5.3* (94.2) (p<0.0001) vs. -1.9* (37.6) (p=0.0024[18]), **s.s.** **Change after 24 months:** -5.4* (97.2) (p<0.0001) vs. -1.9* (37.6) (p= 0.0004), **s.s.**	**Baseline[19]:** 10.5 (±4.4) vs. 9.4 (±4.9), n.s. **Change after 12 months[12]:** -5.9 (±0.7) vs. -6.6 (±0.71), n.s. **Change after 60 months:** -5.6 (±0.7) vs. -6.7 (±0.6), n.s.	NR
WOMAC[17] physical function subscale, mean (%/SD) *Lower scores indicate better function.*	NR	**Baseline:** 38.1 (8.1) vs. 41.7 (5.7), p=0.3394, n.s. **Change after 6 months:** -33.2* (87.1) (p<0.0001) vs. -19.4* (46.6) (p<0.0001), **s.s.** **Change after 12 months:** -35.1* (92.1) (p<0.0001) vs. -10.6* (25.5) (p<0.0001), **s.s.** **Change after 24 months:** -36.0* (94.4) (p<0.0001) vs. -6.3* (15.2) (p=0.044), **s.s.**	**Baseline[19]:** 80.3 (±38.5) vs. 75.9 (±38), n.s. **Change after 12 months[12]:** -55.9 (±4.24) vs. -60.6 (±4.4), n.s. **Change after 60 months:** -56.5 (±4.6) vs. -62.1 (±3.4), n.s.	NR
Modified Cincinnati Knee total core[20], mean (SD) *Higher scores indicate better function.*	NR	NR	NR	**Baseline[21]**: 45 (±19) | 48 (±15) vs. 38 (±19) **12 months:** 82 (±15) (p< 0.001) | 67 (±26) (p=0.028) vs. 72 (±18) (p<0.001), **s.s.** *Change after 12 months:* +37* | +19* vs. +34* **24 months**: n/a | 85 (±18) vs. 74 (±26) *Change after 24 months:* n/a | +37* vs. +36* **60 months**: n/a | n/a vs. n/a stable or improving in both AMIC groups, whereas a **significant** decrease was observed in the MFx group (p = 0.002 AMIC glued, p =0.01 AMIC sutured).

17 The WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) scoring system includes pain, stiffness and physical function, measured on a visual analogue scale (VAS). The scores for each subscale are summed up, with a possible score range of 0-8 for stiffness, 0-68 for physical function and 0-20 for pain. Higher scores indicate worse stiffness, functional limitations and pain.

18 According to the study, no statistical difference.

19 Scores had a maximum value of 50 for Pain, 20 for Stiffness, and 170 for Function.

20 The Modified Cincinnati Score is divided into three parts: knee function (6-30 points), clinical pathology (0-20 points), highest activity level without pain (0-50 points). The total score is calculated as the sum of all questions responses, with 100 representing the best/excellent knee function, and 0 representing the worst/poor knee function.

Author, year [Reference]	Kon, 2018 [47]	Pipino, 2018 [46]	Shive, 2015 [3] (Stanish, 2013[7] [5])[8]	Volz, 2017 [7] (Anders, 2013[7] [4])[9]
Lysholm score[22], mean (SD)	NR	NR	NR	NR
Short Form Health Survey (**SF-36**, SF-12, SF-8)[23], mean (SD) Subscale: physical functioning (PF), physical role (PR), vitality (VI) *Higher scores indicate better function.*	NR	NR	***SF-36 v2 physical component***: **Baseline**: n/a **Change after 12 months**[12]: +13.0 (±1.5) vs. +14.8 (±1.5), n.s. **Change after 60 months**: +13.1 (±1.6) vs. +14.5 (±1.4), n.s.	NR
(Modified) ICRS macroscopic score[24], mean (SD)	NR	NR	NR	**Baseline**: 54 (±19) | 46 (±20) vs. 57 (±22) **12 months**: 16 (±15) (p<0.001) | 15 (±13) (p<0.001) vs. 15 (±17) (p<0.001), s.s. *Change after 12 months:* -38.0* | -31.0* vs. -42.0* **60 months**: n/a | n/a vs. n/a both AMIC groups still reported very low pain, whereas pain increased non-significantly in the MFx group.
Quality of life (QoL), scales:				
KOOS[15] (QoL), mean (SD)	NR	NR	NR	NR
EQ-5D	NR	NR	NR	NR

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

[22] The Lysholm score consists of eight items that measure: pain (25 points), instability (25 points), locking (15 points), swelling (10 points), limp (5 points), stair climbing (10 points), squatting (5 points), and need for support (5 points). The total score is the sum of each response to the eight questions, and may range from 0-100. Higher scores indicate a better outcome with fewer symptoms or disability.

[23] 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. Each scale is directly transformed into a 0-100 scale. A score of 0 is equivalent to maximum disability and a score of 100 is equivalent to no disability. Only the subscale scores for the physical and mental component were presented.

[24] The (modified) ICRS (International Cartilage Repair Society) macroscopic score consists of ratings by patient (pain, functional status of knee) and surgeon (functional status knee, classification crepitation). However, due to lacking scoring instruction, the interpretation of reported scores was not possible.

Author, year [Reference]	Kon, 2018 [47]	Pipino, 2018 [46]	Shive, 2015 [3] (Stanish, 2013[7] [5])[8]	Volz, 2017 [7] (Anders, 2013[7] [4])[9]
Short Form Health Survey (**SF-36**, SF-12, SF-8)[23], mean (SD) Subscale: emotional role (ER), **psychological well-being** (PS) *Higher scores indicate better QoL.*	NR	NR	**Baseline:** n/a **Change after 12 months**[12]: +3.5 (±1.7) vs. +0.8 (±1.6), n.s. **Change after 60 months:** +2.7 (±1.3) vs. -0.17 (±1.8), n.s.	NR
Pain, scales:				
KOOS[15] (pain), mean (SD)	NR	NR	NR	NR
VAS[25], mean (SD) *Lower scores indicate less pain.*	**Baseline:** 50.1 (±26.7) vs. 53.1 (±22.7), p=n/a **12 months**: 23.8 (±20.8) vs. 29.2 (±23.2), p=n/a *Change after 12 months:* -26.3* vs. -23.9* **24 months**: 26.5 (±27.5) vs. 23.2 (±20.9), p=n/a *Change after 24 months:* -23.6* vs. -29.9*	NR	NR	NR
WOMAC[17] pain subscale, mean (%/SD) *Lower scores indicate less pain.*	NR	**Baseline:** 12.6 (6.1) vs. 7.9 (4.7), p=0.0153, **s.s.** **Change after 6 months:** -11.3* (90.0) (p<0.0001) vs. -5.2* (65.4) (p<0.0001), **s.s.** **Change after 12 months:** -11.6* (92.4) (p<0.0001) vs. -1.5* (19.2) (p=0.3154) **Change after 24 months:** -12.1* (96.4) (p<0.0001) vs. -0.1* (1.6), (p=0.9446)	**Baseline**[19]**:** 22.4 (±10.3) vs. 22.9 (±9.1), n.s. **Change after 12 months**[12]: -16.2 (±1.2) vs. -16.9 (±1.2), n.s. **Change after 60 months**: -15.4 (±1.5) vs. -16.6 (±1.2), n.s.	NR
Short Form Health Survey (SF-36, SF-12, SF-8)[23], mean (SD) Subscale: physical pain (PA)	NR	NR	NR	NR

[25] The visual analogue scale (VAS) for pain intensity is most commonly anchored by "no pain" (score of 0) and "pain as bad as it could be" or "worst imaginable pain" (score of 100 [100-mm scale]).

Author, year [Reference]	Kon, 2018 [47]	Pipino, 2018 [46]	Shive, 2015 [3] (Stanish, 2013[7] [5])[8]	Volz, 2017 [7] (Anders, 2013[7] [4])[9]
Necessity of total joint replacement, n (%)	NR	**At 12 months:** total knee arthroplasty: 1 (n/a)	NR	NR
Activities of daily living, scales:				
KOOS[15] (ADL) score/ Return to activities, mean (SD)	NR	NR	NR	NR
Tegner Activity Score (TAS)[26], mean (range) *Higher scores indicate improved ADL.*	**Baseline:** 3.0 (0.0-7.0) vs. 3.0 (0.0-9.0) **12 months:** 4.0 (2.0-7.0) vs. 4.0 (1.0-9.0) *Change after 12 months:* +1.0* vs. +1.0* **24 months:** 4.0 (1.0-9.0) vs. 4.0 (2.0-8.0) *Change after 24 months:* +1.0* vs. +1.0*	NR	NR	NR
Complete defect filling (MRI/MRT imaging), n (%)				**At 12 months:** 35-50% of the pts. had a defect filling of two-thirds or more. **At 24 months:** defect filling was more complete in the AMIC groups, where at least 60% of the pts. had a defect filling of more than two-thirds compared to only 25% of the pts. in the MFx group. **At 60 months:** defect filling was the lowest in the MFx group, versus both AMIC groups.
MOCART score[27] *Higher scores indicate more complete defect filling.*	**Complete filling of the defect (%)**[28]: **6 months**: 53.3 vs. 39.5 **12 months**: 40.8 vs. 55.6 **24 months**: 49.0 vs. 65.9 n.s. difference in the MRI scores between groups	NR	NR	NR

[26] The Tegner Activity Score is a one-item score that graded activity based on work and sports activities on a scale of 0 to 10. Zero represents disability because of knee problems and 10 represents national or international level soccer.

[27] Lower MOCART scores indicate more positive/normal MRI diagnostic findings of the cartilage repair.

[28] Scores were calculated on the sample that remained at follow-up only.

Author, year [Reference]	Kon, 2018 [47]	Pipino, 2018 [46]	Shive, 2015 [3] (Stanish, 2013[7] [5])[8]	Volz, 2017 [7] (Anders, 2013[7] [4])[9]
Safety				
Complications/ adverse events, n (%)	13 (21.0*) vs. 4 (6.5*)[29]	NR	**12 months** (41 vs. 37 pts.)[12]: 40 (98.0)[30] vs. 36 (92.0)[31], n.s. **60 months** (34 vs. 26 pts.): 13 (19.0) vs. 18 (27.0)[32]; p=n/a	13 adverse events in 9 pts.
Severe adverse events, n(%)	3 (4.8*) vs. 1 (1.6*)[33] Joint adhesions: 2 vs. 0 Persistent pain: 1 vs. 0 Loose body: 0 vs. 1	NR	**12 months** (41 vs. 37 pts)[12]: 5 (12.2*)[30] vs. 1 (2.7*)[31] **60 months** (34 vs. 26 pts.): 0 (0) vs. 1 (3.8*)[34]	0 (0.0) vs. 0 (0.0)
Procedure-related adverse event, n (%)	8 (12.9*) vs. 3 (4.8*)[35] Inflammation: 3 vs. 0 Joint adhesions: 1 vs. 0 Persistent pain: 1 vs. 0 Loose body: 0 vs. 0 Joint instability: 0 vs. 1	NR	**12 months** (41 vs. 37 pts.)[12]: 38 (93.0) vs. 30 (77.0)[36]; p=n/a **60 months** (34 vs. 26 pts.): 2 (6.0*) vs. 2 (8.0*)[36]; p=n/a	0 (0.0) vs. 0 (0.0)
Device-related adverse events, n (%)	Failures: 2 (3.2*) vs. 0 (0.0)	NR	**12 months** (41 vs. 37 pts.)[12]: 9 (22.0)[37] vs. 0 (0.0) **60 months** (34 vs. 26 pts.): 1 (3.0*)[36] vs. 0 (0.0)	NR
Re-operation rate, n (%)	NR	NR	**60 months** (34 vs. 26 pts.): 0 (0) vs. 1 (3.8*)[34]	**12 months:** 0 (0.0) | 1 (5.9*) vs. 1 (7.7*)
Procedure-related mortality, n (%)	NR	NR	0 vs. 0	NR

Abbreviations: *AMIC autologous matrix-induced chondrogenesis; ADL Activities of daily living; EQ-5D EuroQual-5D; ICRS International Cartilage Repair Society; IKDC International Knee Documentation Committee; KOOS Knee Injury and Osteoarthritis Outcome Score; n number; n/a data not available; NR not reported; n.s. not significant; MFx microfracture; MOCART Magnetic Resonance Observation of Cartilage Repair Tissue; MRI magnetic resonance imaging; pts. patients; RCT randomised controlled trial; s.s. statistically significant; TAS Tegner Activity Score; VAS Visual Analogue Pain Scale; WOMAC Western Ontario and McMaster Universities Osteoarthrisits Index; yrs years; * Own calculations.*

[29] Safety was evaluated focusing on number and type of adverse events after surgery in all patients randomised and treated (124 patients); safety population: 62 vs. 62 pts.

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

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

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

[33] Reported severe adverse events were related to the treatment.

[34] Severe adverse event was not related to the study treatment or index knee but required surgery and radiotherapy.

[35] Reported adverse events were minor early post-operation symptoms.

[36] Kind of complications not stated.

[37] Kind of complications not clearly stated.

*Table A-2: Autologous matrix-induced chondrogenesis in combination with MFx (AMIC) for cartilage repair of **knee joints** Results from non-randomised controlled studies*

Author, year [Reference]	Sharma, 2013[38] [6]
Country	Germany, Italy, Netherlands
Sponsor	Arthritis Foundation, NIH
Intervention/Product	AMIC (/n/a[39]): Miniarthrotomy, single-step cartilage repair + MFx
Comparator	Miniarthrotomic MFx alone
Study design	Multi-centre controlled trial (CT)[40]
Number of pts, n	18 (15 vs. 3)
Location of lesion, n (%)	Medial femoral condyle defect (NR)
Inclusion criteria	✿ aged 18-50 yrs, ✿ standing radiograph showing a Kellgren score of 0–2, ✿ diagnostic arthroscopy/MRI identification of a medial femoral condyle defect, ✿ stable and asymptomatic contralateral knee.
Exclusion criteria	✿ 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).
Prior surgery, n (%)	None (exclusion criterion)

[38] Study already included in initial report DSD98 2016.

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

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

Author, year [Reference]	Sharma, 2013[38] [6]
Postoperative treatment(s)	Physiotherapy/rehabilitation (all pts.)
Age of patients, mean, yrs (SD/range)	(20-59) vs. (40-49)[41]
Female sex, n (%)	NR
Follow-up (months)	6
Loss to follow-up, n (%)	0 vs. 0
BMI, mean, kg/m² (SD/range)	(20-30) vs. (20-30)[41]
Defect size, mean, cm² (range)	(1-3) vs. (2-3)[41]
Clinical classification, n (%)	NR
Primary endpoint(s)	NR
Outcomes	
Efficacy	
Mobility/joint functionality, scales:	
KOOS[15] (sports/rec), mean (SD)	NR
IKDC score[16], mean (SD) *Higher scores indicate better function.*	**Baseline:** n/a, n.n.; **Change after 3 months:** n/a, n.s.; **Change after 6 months:** n/a, n.s.
WOMAC[17] stiffness subscale, mean (%/SD)	NR
WOMAC[17] physical function subscale, mean (%/SD)	NR
Modified Cincinnati Knee Score[20], mean (SD)	NR
Lysholm score[22], mean (SD)	NR
Short Form Health Survey (SF-36, SF-12, SF-8)[23], mean (SD) Subscales: physical functioning (PF), physical role (PR), vitality (VI)	NR
(Modified) ICRS macrosopic score[24], mean (SD)	NR
Quality of life (QoL), scales:	
KOOS[15] (QoL), mean (SD)	NR
EQ-5D	NR
Short Form Health Survey (SF-36, SF-12, SF-8)[23], mean (SD) Subscales: emotional role (ER), psychological well-being (PS)	NR

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

Author, year [Reference]	Sharma, 2013[38] [6]
Pain, scales:	
KOOS[15] (pain), mean (SD)	NR
VAS[25], mean (SD) *Lower scores indicate less pain.*	***Severity:*** **Baseline:** 54.3 (±16.4) vs. 54.0 (±21.0), p=n/a. *Change after 3 months:* -29.0 (±n/a) vs. -34.7 (±n/a), p=n/a *Change after 6 months:* -32.1 (±n/a) vs. -15.3 (±n/a), p=n/a ***Frequency:*** **Baseline:** 77.0 (±20.3) vs. 84.3 (±24.5), p=n/a. *Change after 3 months:* -41.0 (±n/a) vs. -62.6 (±n/a), p=n/a *Change after 6 months:* -52.9 (±n/a) vs. -41.0 (±n/a), p=n/a
WOMAC[17] pain subscale, mean (%/SD)	NR
Short Form Health Survey (SF-36, SF-12, SF-8)[23], mean (SD) Subscale: physical pain (PA)	NR
Necessity of total joint replacement, n (%)	NR
Activities of daily living, scales:	
KOOS[15] (ADL) score/Return to activities, mean (SD)	NR
Tegner Activity Score (TAS)[26]	NR
Complete defect filling (MRI/MRT imaging), n (%)	
MOCART score[27]	NR
Safety	
Complications/adverse events, n (%)	NR
Severe adverse events, n (%)	NR
Procedure-related adverse events, n (%)	1 (7.0)[42] vs. 0 (0.0), p=n/a
Device-related adverse events, n (%)	n/a vs. 0 (0.0)
Re-operation rate, n (%)	NR
Procedure-related mortality, n (%)	0 (0.0) vs. 0 (0.0)

Abbreviations: *AMIC autologous matrix-induced chondrogenesis; ADL Activities of daily living; EQ-5D EuroQual-5D; ICRS International Cartilage Repair Society; IKDC International Knee Documentation Committee; KOOS Knee Injury and Osteoarthritis Outcome Score; n number; n/a data not available; NR not reported; n.s. not significant; MFx microfracture; MOCART Magnetic Resonance Observation of Cartilage Repair Tissue; MRI magnetic resonance imaging; pts. patients; RCT randomised controlled trial; s.s. statistically significant; TAS Tegner Activity Score; VAS Visual Analogue Pain Scale; WOMAC Western Ontario and McMaster Universities Osteoarthrisits Index; yrs years;*

* *Own calculations.*

[42] Mild haemarthrosis in one patient.

*Table A-3: Matrix-induced autologous chondrocyte implantation (MACI) for cartilage repair of **knee joints**. Results from randomised controlled trials*

Author, year [Reference]	Bartlett, 2005 [22]	Basad, 2010 [48]	Brittberg[43], 2018 [9] (Saris, 2014 [8])
Country	England	Germany	7 European countries (n/a)
Sponsor	n/a[44]	NR	Vericel Cooperation, Genzyme (Sanofi company), previous sponsor of the SUMMIT Extension study
Intervention/Product	MACI (Verigen, Leverkusen, Germany): Membrane of a porcine type I/type III collagen bilayer seeded with chondrocytes	MACI™ (Genzyme Biosurgery, Cambridge, MA): Third generation ACI product – chondrocytes seeded onto a type I/III collagen scaffold (secured into the lesion with fibrin glue) + miniarthrotomy	MACI (ACI-Matix, Matricel GmbH): Autologous chondrocytes isolated, cultured and seeded onto a purified, resorbable, porcine-derived collagen type I/III membrane
Comparator	ACI-C[45]	MFx	MFx
Study design	Single-centre, prospective, randomised controlled trial (RCT)	Prospective, randomised controlled trial (RCT)	Prospective, randomised, open-label, parallel-group, multi-centre study (RCT)
Number of pts., n	91 (47 vs. 44)	60 (40 vs. 20)	Original SUMMIT trial: 144 Extension study: 128 (65 vs. 63)
Location of lesion, n (%)	Chondral lesions: Medial femoral condyle: 25 (47.2) vs. 25 (42.4) Lateral femoral condyle: 6 (11.3) vs. 5 (8.5) Patella: 16 (30.2) vs. 20 (33.9) Trochlea: 6 (11.3) vs. 9 (15.2)	Chondral lesions: Condylar: 29 (73.0) vs. 16 (80.0) Patellar-trochlear: 11 (28.0) vs. 4 (20.0)	Cartilage defects: Medial femoral condyle: 48 (74.0) vs. 44 (70.0) Lateral femoral condyle: 13 (20.0) vs. 15 (24.0) Trochlea: 4 (6.0) vs. 4 (6.0)
Inclusion criteria	✿ aged 15-50 years, ✿ isolated osteochondral defect >1 cm², ✿ ability to follow the rehabilitation programme.	✿ aged 18-50 years, ✿ post-traumatic, single, isolated, symptomatic chondral defects (4-10 cm²) of the femoral condyle or patella.	✿ aged 18-55 years, ✿ ≥1 symptomatic cartilage defects, ✿ moderate to severe KOOS pain value (<55) at baseline, ✿ Outerbridge grade III/IV focal cartilage defects on the medial femoral condyle (MFC), lateral femoral condyle (LFC), and/or trochlea ≥ 3 cm².
Exclusion criteria	✿ osteoarthritis, ✿ inflammatory joint disease.	✿ resence of chronic inflammatory arthritis, ✿ instability of the knee joint, ✿ prior or planned meniscectomy (>30% of the meniscus), ✿ BMI > 30,	✿ any knee joint surgery within 6 months before screening, ✿ modified Outerbridge III/IV on the patella or tibia, ✿ symptomatic musculoskeletal condition in the lower limbs that could impede efficacy measures in the target knee,

[43] Brittberg 2018, the SUMMIT extension study (NCT01251588), is a three year follow-up of the original SUMMIT clinical trial (NCT00719576; Saris 2014), entailing up to five years of observation after surgery. Study results after two years were published in Saris 2014 (assessing 70 vs. 67 pts.) and results after two and five years follow-up were presented in Brittberg 2018 (assessing 65 vs. 63 pts.). Therefore, only the data from the latest publication are presented.

[44] One or more of the authors have received or will receive benefits for personal or professional use from a commercial party related directly or indirectly to the subject of this article.

[45] ACI-C includes the use of a cover manufactured from porcine-derived type I/type III collagen (Matricel, Herzogenrath, Germany). Compared to MACI, the implantation of the chondrocytes takes place via a suspension.

Author, year [Reference]	Bartlett, 2005 [22]	Basad, 2010 [48]	Brittberg[43], 2018 [9] (Saris, 2014 [8])
Exclusion criteria *(continuation)*	✿	✿ varus or valgus abnormality, ✿ osteonecrosis, ✿ osteoarthritis, ✿ chondrocalcinosis, ✿ pts. with osteochondral defects.	✿ total meniscectomy, meniscal allograft, bucket-handle tear or displaced tear requiring >50% removal of the meniscus in the target knee, ✿ malalignment requiring osteotomy to correct tibial-femoral or patella-femoral alignment, ✿ Kellgren-Lawrence grade 3 or 4 osteoarthritis, ✿ inflammatory disease or other condition affecting the joints, or septic arthritis within 1 year before screening[46].
Prior surgery, n (%)	2.1 (NR) vs. 2.3 (NR)	NR	n/a[47]
Postoperative treatment(s)	First postoperative days: weight-bearing days with aid of crutches, after 2-3 days: discharge from hospital with light-weight cylinder cast, after 10 days: cast is removed and beginning of supervised regime of physiotherapy.	IG: dorsal plaster cast (10° flexion) for 2 days post-operatively, continuous passive motion and physiotherapy, followed by 8 weeks of partial weight-bearing (10 kg) on crutches. CG: 6 weeks of partial weight-bearing (10 kg) on crutches, CPM and physiotherapy. From 6 weeks post-operatively, gradual progression to full weight-bearing. IG & CG: anti-thrombotic prophylaxis with low-molecular heparin certoparin-natrium (Monoembolex s.c. 1/day) for entire weight-bearing period.	4-phase standardised rehabilitation program: physical therapy[48]
Age of patients, mean, yrs (SD/range)	33.4 (17-47) vs. 33.7 (15-49)	33.0 (NR) vs. 37.5 (NR)	35 (18-54) vs. 34 (18-54)
Female sex, n (%)	37 (40.7*)	15 (38.0) vs. 3 (15.0)	60 (38.0)
Follow-up (months)	24	24	60
Loss to follow-up, n (%)	0 (0.0) vs. 0 (0.0)	12 months: 1 (2.5) vs. 3 (15.0) 24 months: 6 (15.0) vs. 2 (10.0)	0 (0.0) vs. 4 (6.3*)
BMI, mean, kg/m² (SD/range)	NR	25.3 (20-34) vs. 27.3 (24-35)	26.2 (±4.3) vs. 26.4 (±4.0)[49]
Defect size, mean, cm² (SD/range)	6.1 (1.0-22) vs. 6.0 (1.5-16)	NR	5.1 (±3.0) vs. 4.9 (±2.0)
Clinical classification, n (%)	NR	NR	Outerbridge grade III: 19 (29.0) vs. 12 (19.0) Outerbridge grade IV: 46 (71.0) vs. 51 (81.0)

[46] Exclusion criteria were extracted from the original SUMMIT study (Saris 2014), as the extension study did not report any criteria.

[47] Major exclusion criteria included any knee joint surgery within six months before screening.

[48] Postoperative treatment was extracted from the original SUMMIT study (Saris 2014), as the extension study did not report it.

[49] Extracted from Saris 2014.

Author, year [Reference]	Bartlett, 2005 [22]	Basad, 2010 [48]	Brittberg[43], 2018 [9] (Saris, 2014 [8])
Primary endpoint(s)	NR	NR	Change from baseline to week 156 (year 3) in KOOS pain and function (sports and recreational activities) scores[50]
Outcomes			
Efficacy			
Mobility/joint functionality, scales:			
KOOS[15, 51] (sports, rec), mean (SD) *Higher scores indicate better function.*	NR	NR	**Baseline vs. 24 months:** IG: 15.4 (±14.8) vs. 60.5 (±26.5) CG: 11.9 (±16.2) vs. 48.9 (±30.6) *Change after 24 months:* +45.1* vs. + 37.0* **Baseline vs. 60 months:** IG: 15.4 (±14.8) vs. 61.9 (±30.9) CG: 11.9 (±16.2) vs. 50.3 (±32.3) *Change after 60 months:* +46.5* vs. +38.4* **s.s.** improvement IG vs. CG, p=0.0122
IKDC score[16], mean (SD) *Higher scores indicate better function.*	NR	NR	**Baseline vs. 24 months:** IG: 33.1 (±13.5) vs. 65.3 (±18.1) CG: 29.3 (±12.0) vs. 60.1 (±22.7) *Change after 24 months*: +32.2* vs. +30.8* **Baseline vs. 60 months:** IG: 33.1 (±13.5) vs. 68.5 (±21.2) CG: 29.3 (±12.0) vs. 61.8 (±21.5) *Change after 60 months*: +35.4* vs. +32.5* n.s. differences between IG and CG, p=0.113
WOMAC[17] stiffness sub-scale, mean (%/SD)	NR	NR	NR
WOMAC[17] physical function subscale, mean (%/SD)	NR	NR	NR
Modified Cincinnati Knee total score[20], mean (SD) *Higher scores indicate better function.*	**Baseline vs. 12 months**: IG: 44.5 (NR) vs. 64.1 (NR) [**s.s.** improvement +19.6* (p=0.002)] CG: 41.4 (NR) vs. 59.0 (NR) [**s.s.** improvement +17.5* (p=0.01)] *Change after 12 months*: +19.6* vs. +17.5*, n.s., p=0.32	NR	**Baseline vs. 24 months:** IG: 3.0 (±1.2) vs. 6.3 (±1.9) CG: 3.0 (±1.2) vs. 5.5 (±2.3) *Change after 24 months*: +3.3* vs. +2.5* **Baseline vs. 60 months:** IG: 3.0 (±1.2) vs. 6.6 (±2.1) CG: 3.0 (±1.2) vs. 5.8 (±2.2) *Change after 60 months*: +3.6* vs. +2.8* **s.s.** better improvement for IG, p=0.035

[50] Primary endpoint of the extension study Brittberg 2018.

[51] A responder was defined as having at least a ten-point improvement in both the KOOS pain and function subscales.

Author, year [Reference]	Bartlett, 2005 [22]	Basad, 2010 [48]	Brittberg[43], 2018 [9] (Saris, 2014 [8])
Lysholm score[22], mean (SD) *Higher scores indicate better function.*	NR	**Baseline vs. 12 months:** IG: 52.0 (±26.0) vs. 92.0 (±11.0) CG: 55.0 (±25.0) vs. 82.0 (±22.0) *Change after 12 months*: +40.0* vs. +27.0* **Baseline vs. 24 months:** IG: 52.0 (±26.0) vs. 92.0 (±9.0), s.s., p<0.0001 CG: 55.0 (±25.0) vs. 69.0 (±26.0), s.s., p<0.0001 *Changer after 24 months*: +40.0* vs. +14.0* **s.s.** better improvements for IG vs. CG, p=0.005	NR
Short Form Health Survey (SF-36, **SF-12**, SF-8)[23], mean (SD) Subscales: physical functioning (PF), physical role (PR), vitality (VI) *Higher scores indicate better function.*	NR	NR	**Baseline vs. 24 months:** IG: -1.7 (±0.8) vs. -0.35 (±0.09) CG: -2.0 (±0.8) vs. -0.79 (±1.1) *Change after 24 months*: +1.4* vs. +1.2*, p=n/a **Baseline vs. 60 months:** IG: -1.7 (±0.8) vs. -0.2 (±0.9) CG: -2.0 (±0.8) vs. -0.7 (±1.1) *Change after 60 months*: +1.5* vs. +1.3* **s.s.** better improvement for IG, p=0.025
(Modified) ICRS macroscopic score[24], n (%)	**Diagnostic at 12 months**: (18 vs. 24 pts.): Excellent: 4 (22.2) vs. 4 (16.7) Good: 8 (44.4) vs. 15 (62.5) Fair: 5 (27.8) vs. 5 (20.8) Poor: 1 (5.6) vs. 0 (0.0)	Baseline vs. 24 months (subjective score): ✿ **s.s.** for both treatment groups, p<0.0001 ✿ -**s.s.** better improvement in IG for month 24, p=0.03 Baseline vs. 24 months (objective score): ✿ **s.s.** for both treatment groups, p<0.0001 ✿ **s.s**. better improvement in IG for month 24, p=0.02	NR
Quality of life (QoL), scales:			
KOOS[15] (QoL), mean (SD) *Higher scores indicate better QoL.*	NR	NR	**Baseline vs. 24 months:** IG: 19.9 (±14.6) vs. 55.4 (±22.3) CG: 17.1 (±13.2) vs. 47.8 (±26.8) *Change after 24 months*: +35.5* vs. +30.7*, p=n/a **Baseline vs. 60 months:** IG: 19.9 (±14.6) vs. 59.8 (±24.6) CG: 17.1 (±13.2) vs. 52.4 (±26.6) *Change after 60 months*: +39.9* vs. +35.3*, p=n/a
EQ-5D[52], mean (SD) *Higher scores indicate better QoL.*	NR	NR	**Baseline vs. 24 months:** IG: 60.3 (±21.1) vs. 76.5 (±15.2) CG: 54.7 (±21.7) vs. 74.1 (±18.5) *Change after 24 months*: +16.2* vs. +19.4*, p=n/a

[52] The EQ-5D consists of a descriptive system and the EQ VAS and includes five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The five dimensions were rated via the VAS scale numbered from 0 to 100: 100 meaning the best health imaginable and 0 meaning the worst health.

Author, year [Reference]	Bartlett, 2005 [22]	Basad, 2010 [48]	Brittberg[43], 2018 [9] (Saris, 2014 [8])
EQ-5D[52], mean (SD) *Higher scores indicate better QoL.* *(continuation)*			**Baseline vs. 60 months:** IG: 60.3 (±21.1) vs. 80.4 (±13.7) CG: 54.7 (±21.7) vs. 73.8 (±19.1) *Change after 60 months*: +20.1* vs. +19.1* **s.s.** better improvement for IG, p=0.043
Short Form Health Survey (SF-36, **SF-12**, SF-8)[23], mean (SD) Subscales: emotional role (ER), psychological well-being (PS) *Higher scores indicate better QoL.*	NR	NR	**Baseline vs. 24 months:** IG: 0.04 (±1.2) vs. 0.4 (±0.9) CG: -0.07 (±1.3) vs. 0.5 (±0.9) *Change after 24 months*: +0.4* vs. +0.6*, p= n/a **Basline vs. 60 months:** IG: 0.04 (±1.2) vs. 0.4 (±0.9) CG: -0.07 (±1.3) vs. 0.5 (±1.0) *Change after 60 months*: +0.4* vs. +0.5*, n.s., p=0.740
Pain, scales:			
KOOS[15] (pain), mean (SD) *Higher scores indicate less pain.*	NR	NR	**Baseline vs. 24 months:** IG: 37.1 (±13.1) vs. 82.2 (±15.8) CG: 35.2 (±12.3) vs. 71.8 (±23.9) *Change after 24 months*: +45.1* vs. +36.6*, p=n/a **Baseline vs. 60 months:** IG: 37.1 (±13.1) vs. 82.2 (±20.1) CG: 35.2 (±12.3) vs. 74.8 (±21.7) *Change after 60 months*: +45.1* vs. +39.6*, p=n/a
VAS[25], mean (SD) *Lower scores indicate less pain.*	**Baseline vs. postoperative follow-up (n/a):** IG: 6.0 vs. 4.1, **s.s.** p=0.003 CG: 6.0 vs. 4.3, **s.s.**, p=0.001 *Change after n/a:* -1.9* vs. -1.7* n.s. difference between IG and CG	NR	NR
WOMAC[17] pain subscale, mean (%/SD)	NR	NR	NR
Short Form Health Survey (SF-36, SF-12, SF-8)[23], mean (SD) Subscale: physical pain (PA)	NR	NR	NR
Necessity of total joint replacement, n (%)	NR	NR	NR

Author, year [Reference]	Bartlett, 2005 [22]	Basad, 2010 [48]	Brittberg[43], 2018 [9] (Saris, 2014 [8])
Activities of daily living, scales:			
KOOS[15] (ADL) score/Return to activities, mean (SD) *Higher scores indicate improved ADL.*	NR	NR	**Baseline vs. 24 months:** IG: 43.6 (±18.6) vs. 87.3 (±16.2) CG: 42.6 (±18.2) vs. 77.0 (±23.6) *Change after 24 months:* +43.7* vs. 34.4*, p=n/a **Baseline vs. 60 months:** IG: 43.6 (±18.6) vs. 86.4 (±17.6) CG: 42.6 (±18.2) vs. 80.0 (±21.2) *Change after 60 months:* +42.8* vs. +37.4*, **s.s.** better improvements for IG, p=0.007
Tegner Activity Score (TAS)[26], median *Higher scores indicate improved ADL.*	NR	**Baseline vs. 12 and 24 months:** IG: 2 vs. 4, s.s., p<0.0001 CG: 2 vs. 3, s.s., p<0.0001 **s.s.** better improvement for IG in month 24, p=0.04	NR
Complete defect filling (MRI/MRT imaging), n (%)	NR	NR	NR
MOCART score[27]	NR	NR	NR
Safety			
Complications/ adverse events, n (%)	N.s. general complications in any of the pts.	Slight swelling and inflammation of the knee after partial weight-bearing (during early rehabilitation time period – 12 week): NR	**Total:** 55 (76.4) vs. 60 (83.3)[53,54]: ✿ Arthralgia: 37 (51.4) vs. 46 (63.9) ✿ Headache: 13 (18.1) vs. 21 (29.2) ✿ Nasopharyngitis: 10 (13.9) vs. 7 (9.7) ✿ Back pain: 8 (11.1) vs. 7 (9.7) ✿ Joint swelling: 7 (9.7) vs. 4 (5.6) ✿ Joint effusion: 5 (6.9) vs. 4 (5.6) ✿ Influenza: 4 (5.6) vs. 5 (6.9) ✿ Pyrexia: 4 (5.6) vs. 2 (2.8) ✿ Cartilage injury: 3 (4.2) vs. 9 (12.5) ✿ Procedural pain: 3 (4.2) vs. 4 (5.6) ✿ Ligament sprain: 2 (2.8) vs. 4 (5.6) ✿ Abdominal pain: 0 (0.0) vs. 5 (6.9)
Severe adverse events, n (%)	0 (0.0) vs. 0 (0.0)	0 (0.0) vs. 0 (0.0)	**Total:** n/a (15.3) vs. n/a (26.4)[53]**:** Most common: treatment failure, cartilage injury, arthralgia

[53] AEs were extracted from the original SUMMIT study (*72 vs. 72 pts*), as the extension study did not report any AEs, but reported that the frequency of AEs was consistent with the previous publication.

[54] Reported adverse events reported were treatment-emergent.

Author, year [Reference]	Bartlett, 2005 [22]	Basad, 2010 [48]	Brittberg[43], 2018 [9] (Saris, 2014 [8])
Procedure-related adverse events, n (%)	NR	NR	**Total:** n/a (34.7) vs. n/a (38.9)[53,55] Most common adverse events: • Discontinuation due to treatment failure: 2* (1.4), • Discontinuation due to arthralgia: 2* (1.4), • Discontinuation due to joint swelling: 2* (1.4)
Device-related AEs, n (%)	**Total:** 6 (12.5*) vs. 4 (9.0*) **At 6 months:** Symptomatic hypertrophy: 1 (2.1*) vs. 0 (0.0) **At 9 months:** Painful catching: 0 (0.0) vs. 1 (2.3*) **At 12 months:** Symptomatic hypertrophy: 2 (4.3*) vs. 3 (6.8*) Superficial wound infection: 1 (2.1*) vs. 0 (0.0) Graft failure: 2 (4.3*) vs. 0 (0.0)	NR	NR
Re-operation rate, n (%)	Need for manipulation of the knee because of a restricted range of flexion: 3 (6.4*) vs. 3 (6.8*)	In IG 1 pt. (2.5*) persistent pain after 12 months due to persistent subchondral oedema → retrograde bone grafting → pain relief	n/a (8.3) vs. n/a (9.7), n.s., p=0.427[53]
Procedure-related mortality, n (%)	NR	NR	**At 24 months:** 0 (0.0) vs. 0 (0.0)

Abbreviations: *AMIC autologous matrix-induced chondrogenesis; ADL Activities of daily living; EQ-5D EuroQual-5D; ICRS International Cartilage Repair Society; IKDC International Knee Documentation Committee; KOOS Knee Injury and Osteoarthritis Outcome Score; n number; n/a data not available; NR not reported; n.s. not significant; MFx microfracture; MOCART Magnetic Resonance Observation of Cartilage Repair Tissue; MRI magnetic resonance imaging; pts. patients; RCT randomised controlled trial; s.s. statistically significant; TAS Tegner Activity Score; VAS Visual Analogue Pain Scale; WOMAC Western Ontario and McMaster Universities Osteoarthrisits Index; yrs years;*

* *Own calculations.*

[55] Adverse events reported were treatment-emergent and related to the procedure.

Table A-4: Matrix-induced autologous chondrocyte implantation (MACI) for cartilage repair of knee joints: Results from randomised controlled trials continued

Author, year [Reference]	Crawford, 2012 [49]	Zeifang, 2010 [23]
Country	USA	Germany
Sponsor	Histogenics Corporation, Waltham, Massachusetts	Ministry of Science, Research and Arts, Baden-Württemberg, Germany
Intervention/Product	MACI (NeoCart, Histogenics, Waltham, Massachusetts): Bovine type-I collagen matrix scaffold with autogenous chondrocytes	MACI (BioSeed-C, BioTissue Technologies Freiburg, Germany): 20 Mio. autologous chondrocytes embedded in fibrin and combined with the rectangular resorbable scaffold of poyglactin 910 and poly-p-dioxanon
Comparator	MFx	Two-step ACI[56]
Study design	Phase-II prospective, randomised clinical trial (RCT)	Prospective randomised controlled trial (RCT)
Number of pts, n	30[57] (21 vs. 9)	21 (11 vs. 10)
Location of lesion, n (%)	Cartilage lesion of the femoral condyle: Medial or lateral femoral condyle (NR)	Cartilage defects: Medial femoral condyle: 18 (85.7)
Inclusion criteria	**For initial enrolment:** ✿ aged 18-55 yrs, ✿ knee pain indicative of an articular cartilage injury, ✿ medical ability to undergo arthroscopic MFx or biopsy and subsequent arthrotomy for NeoCart implantation, ✿ availability of informed consent. **For arthroscopy:** ✿ ≥1 treatable lesion(s) located on either medial or lateral femoral condyle that would be a candidate for MFx, ✿ symptomatic ICRS grade-III cartilage lesion of femoral condyle, ✿ lesions with max. linear dimension ≥1 cm and ≤3 cm to healthy cartilage border, ✿ lesions with total areas less than area of NeoCart (7-8 cm²).	✿ aged 16-50 yrs, ✿ isolated cartilage defects between 2.5 and 6 cm² detected by MRI and verified with arthroscopy, ✿ localised at the medial or lateral femoral condyle.

[56] In this study, the autologous chondrocyte implantation with periosteal flap (ACI-P, first generation) was used as the control intervention.

[57] 30 pts for randomisation. 49 pts for initial enrolment and 35 pts before arthroscopy.

Author, year [Reference]	Crawford, 2012 [49]	Zeifang, 2010 [23]
Exclusion criteria	**For initial enrolment:** ✿ any previous surgical treatment of lesion other than debridement, ✿ BMI>35 kg/m², ✿ joint space narrowing of >1/3 compared with normal knee or <3 mm of joint space measured on radiographs, ✿ osteophytes, sclerosis, or degenerative conditions in treatment knee noted on radiographs, ✿ malalignment >3° outside mechanical axis of other knee, or need for surgery to correct malalignment, ✿ other symptomatic pathology of contralateral knee, ✿ surgery on contralateral knee within 8 weeks prior to scheduled arthroscopy, ✿ any form of inflammatory arthritis, ankylosing spondylitis, synovioma, hemangioma, pigmented villonodular synovitis, or neoplasms in knee, ✿ chemotherapy, ✿ pt. unable to undergo MRI, ✿ pregnancy or intends to become pregnant during year following initial enrollment, ✿ known history of allergy to bovine products or to collagen or more than a minimal reaction to an intradermal collagen injection challenge, ✿ history of autoimmune disease, ✿ evidence of HIV or chonric hepatitis-B or C viral infection, ✿ known allergy to gentamicin, ✿ current drug or alcohol abuse, ✿ pt. deemed by investigator as unlikely to comply with protocol. **For arthroscopy:** ✿ subchondral bone loss, ✿ pt. requiring a concomitant procedure other than medial or lateral partial meniscectomy, ✿ removal of loose bodies, ✿ debridement of articular cartilage lesions other than that being treated and synovectomy, ✿ untreated anterior cruciate ligament and/or posterior cruciate ligament deficiency or ligamentous instability in involved knee, ✿ meniscus with rim <50% of normal thickness, ✿ ICRS grade-III or IV kissing lesion, ✿ more than slight anterior knee pain referable to patellofemoral joint and ICRS grade-III (B), III(C), or IV trochlear groove or patellar lesion.	✿ extended cartilage erosion, ✿ restricted mobility, ✿ corresponding cartilage defects <grade II according to Outerbridge, ✿ extended meniscal defect (meniscus resection >1/3), ✿ untreated cruciate or collateral ligament laxity, ✿ untreated varus/valgus alignment >5°, ✿ obesity, ✿ inflammation, ✿ procedures in the respective knee (e.g. MFx or osteochondral autograft) <1 year ago, ✿ hyaluronan injection <6 months ago, ✿ corticosteroid injection <3 months ago.
Prior surgery, n (%)	None (exclusion criterion)	2.1 (1.2) vs. 1.9 (0.7)

Author, year [Reference]	Crawford, 2012 [49]	Zeifang, 2010 [23]
Postoperative treatment(s)	Standardised rehabilitation protocol	Day after surgery: ✿ 6 weeks continuous passive motion and only partial weight-bearing, ✿ 2 weeks restricted range of motion to 90° of flexion, until week 12 no sports allowed
Age of patients, mean, yrs (SD/range)	41.0 (±9.0) vs. 39.0 (±10.0)	29.1 (±7.5) vs. 29.5 (±11.0)
Female sex, n (%)	2 (10.0) vs. 3 (33.0)	5 (45.5*) vs. 0 (0.0)
Follow-up (months)	24	24
Loss to follow-up, n (%)	12 months: 0 (0.0) vs. 0 (0.0) 24 months: 2 (9.5*) vs. 0 (0.0)	12 months: 4 (19.1) vs. n/a (n/a) 24 months: 10 (47.6) vs. n/a (n/a)
BMI, mean, kg/m² (SD/%)	29.0 (±3.0) vs. 25.0 (±4.0)	19.6 kg/m²: 1 (4.8) 20.0-25.0 kg/m²: 10 (47.6) >25≤30 kg/m²: 9 (42.9) 34.4 kg/m²: 1 (4.8)
Defect size, mean, cm² (SD)	2.9 (±1.4) vs. 2.5 (±1.4)	4.3 (±1.1) vs. 4.1 (±0.9)
Clinical classification, n (%)	ICRS grade-III cartilage lesion of the femoral condyle (all pts.)	Outerbridge grade IV (all pts.)
Primary endpoint(s)	NR	Postoperative change in subjective knee function assessed by the IKDC score at 12 months
Outcomes		
Efficacy		
Mobility/joint functionality, scales		
KOOS[15] (sports/rec) *Higher scores indicate better function.*	**At 12 months[58]:** More improvements in IG vs. CG **At 24 months:** **s.s.** improvement in IG vs. CG, p<0.05	NR
IKDC score[16], mean (SD) *Higher scores indicate better function.*	**At 12 months[58]:** More improvements in IG vs. CG **Baseline vs. 24 months:** **s.s.** difference in IG vs. CG by +11.59 (95% CI 1.353-21.82, p=0.028)	**Baseline vs. 12 months:** IG: 51.1 (±22.8) vs. 72.0 (±22.7) CG: 52.0 (±13.5) vs. 76.6 (±18.9) *Change after 12 months:* +20.9 (±20.9) vs. +24.6 (±19.3), n.s., p=0.5573 **Baseline vs. 24 months:** IG: 51.1 (±22.8) vs. 70.1 (±28.6) CG: 52.0 (±13.5) vs. 77.1 (±22.7) *Change after 24 months:* +19.0 (±26.8) vs. +25.2 (±23.2), n.s., p=0.4994
WOMAC[17] stiffness subscale, mean (%/SD)	NR	NR

[58] A responder was defined as having at least a 12-point improvement in the pain score of the KOOS and a 20-point improvement in the IKDC subjective score.

Author, year [Reference]	Crawford, 2012 [49]	Zeifang, 2010 [23]
WOMAC[17] physical function subscale, mean (%/SD)	NR	NR
Modified Cincinnati Knee total score[20], mean (SD)	NR	NR
Lysholm score[22], mean (SD) *Higher scores indicate better function.*	NR	**Baseline vs. 12 months:** IG: 71.4 (±23.8) vs. 76.3 (±27.5) CG: 61.3 (±14.3) vs. 86.3 (±17.0), s.s., p=0.0137 *Change after 12 months:* +4.9 (±19.0) vs. +25.0 (±22.8), **s.s.** better improvement for CG vs. IG, p=0.0449 **Baseline vs. 24 months:** IG: 71.4 (±23.8) vs. 72.5 (±28.0) CG: 61.3 (±14.3) vs. 84.0 (±21.9), s.s., p=0.0273 *Change after 24 months:* +1.2 (±22.3) vs. +22.7 (±25.9), **s.s.** better improvements for CG vs. IG, p=0.0487
Short Form Health Survey (**SF-36**, SF-12, SF-8)[23, 59], mean (SD) Subscales: physical functioning (PF), physical role (PR), vitality (VI) *Higher scores indicate better function.*	NR	**Change after 12/24 months for PR:** IG: n/a, **s.s.**, p=0.0156/p=0.0156 **Change after 12/24 months for PF:** CG: n/a, **s.s.**, p=0.0059/p=0.0156 **Change after 24 months for PF:** IG: n/a, **s.s.**, p=0.0020 N.s. difference between IG vs. CG for 12 and 24 months
ICRS macroscopic score[24], n (%)	NR	NR
Quality of life (QoL), scales		
KOOS[15] (QoL), mean (SD) *Higher scores indicate better QoL.*	**At 24 months[58]:** **s.s.** improvement in IG vs. CG, p<0.05	NR
EQ-5D	NR	NR
Short Form Health Survey (**SF-36**, SF-12, SF-8)[23,59], mean (SD) Subscales: emotional role (ER), psychological well-being (PS) *Higher scores indicate better QoL.*	NR	N.s. difference between IG vs. CG for 12 and 24 months
Pain, scales:		
KOOS[15] (pain), mean (SD) *Higher scores indicate less pain.*	**At 12 months[58]:** more improvements in IG than in CG **Baseline vs. 24 months:** **s.s.** difference in IG vs. CG +12.06 (95% CI 2.388-21.74, p=0.016)	NR

[59] There were no significant differences between the study groups regarding the postoperative change of the eight sub-categories at 12 and 24 months (data not shown).

Author, year [Reference]	Crawford, 2012 [49]	Zeifang, 2010 [23]
VAS[25], mean (SD) *Lower scores indicate less pain.*	**At 12 months:** more improvements in IG than in CG, p=n/a **At 24 months:** **s.s**. improvements in IG vs. CG, p<0.05	NR
WOMAC[17] pain subscale, mean (SD)	NR	NR
Short Form Health Survey (**SF-36**, SF-12, SF-8)[23,59], mean (SD) Subscale: physical pain (PA) *Higher scores indicate less pain.*	NR	*Change after 12 months:* IG n/a, **s.s**., p=0.0391 N.s. difference between IG vs. CG for 12 and 24 months
Necessity of total joint replacement, n (%)	1 (4.8*)[60] vs. 0 (0.0)	NR
Activities of daily living		
KOOS[15] (ADL) score/Return to activities	NR	NR
Tegner Activity Score (TAS)[26], mean (SD) *Higher scores indicate improved ADL.*	NR	**Baseline vs. 12 months:** IG: 4.1 (±2.8) vs. 4.2 (±2.0), n.s., p=0.9141 CG: 3.7 (±1.9) vs. 4.6 (±2.0), n.s., p=0.2500 *Change after 12 months:* +0.1 (±2.1) vs. +0.9 (±2.5), n.s., p=0.4063 **Baseline vs. 24 months:** IG: 4.1 (±2.8) vs. 4.7 (±2.9), n.s., p=0.7832 CG: 3.7 (±1.9) vs. 5.3 (±1.9), n.s., p=0.0625 *Change after 24 months:* +0.6 (±2.7) vs. +1.7 (±2.0), n.s., p=0.1043
Complete defect filling (MRI/MRT imaging), n (%)	NR	**At 6 months:** 4/8 pts. (50.0*) vs. 1/9 pts. (11.1*)
MOCART score[27], mean (SD) *Higher scores indicate more complete defect filling.*	NR	**At 6 months:** 7.0 (±2.7) vs. 10.3 (±1.6), **s.s**. better improvements for IG, p=0.0123 **At 12 months:** 6.3 (±3.5) vs. 8.4 (±2.2), n.s. difference, p=0.2065 **At 24 months:** 6.3 (±3.0) vs. 6.8 (±4.7), n.s. difference, p=0.6926
Safety		
Complications/adverse events, n (%)	**Total:** 62 AEs in 21 pts. (295.2*) vs. 24 AEs in 9 pts. (266.7*) Most common: postoperative pain, stiffness, swelling, back pain, arm pain, peri-incisional numbness Other adverse events: ❁ repeat arthroscopic biopsy due to loss of autologous cartilage tissue implant because of a contamination: 1 (n/a)	**At 6 months:** ❁ Osteochondral lesion: 1 (9.0*) vs. n/a ❁ Effusion: 5 (45.5*) vs. 6 (60.0*) **At 12 months:** ❁ Effusion: 5 (45.5*) vs. 5 (50.0*) ❁ Development of an osseous spur: n/a vs. 1 (9.0*)

[60] Also reported as a severe adverse event.

Author, year [Reference]	Crawford, 2012 [49]	Zeifang, 2010 [23]
Complications/adverse events, n (%) *(continuation)*	✿ arthroscopic MFx of a lesion in the ipsilateral knee: 1 (n/a) ✿ arthroscopic anterior cruciate ligament (ACL) reconstruction of the contralateral knee: 1 (n/a)	
Severe adverse events, n (%)	**IG**: 1 (4.8*): ✿ Case of septic arthritis in the contralateral knee after meniscectomy ✿ Following total knee arthroplasty **CG**: 1 (11.1*): Cancer of gynecologic origin[61]	Inability to work due to persistent problems in IG: 1 (9.0*)
Procedure-related adverse events, n (%)	0 (0.0) vs. 0 (0.0)	NR
Device-related adverse events, n (%)	NR	**Total:** 4 (36.4*) vs. 14 (140*) **At 6 months:** ✿ Transplant delamination after 6 months: 0 (0.0) vs. 1 (10.0*)[62] ✿ Transplant hypertrophy: 1 (10.0*) vs. 7 (63.6*) **At 12 months:** ✿ Transplant hypertrophy: 3 (27.3*) vs. 6 (60.0*)
Re-operation rate, n (%)	**IG:** ✿ Total knee arthroplasty: 1 (4.8*)[63] ✿ Arthroscopic MFx of a lesion in the ipsilateral knee[63] ✿ Arthroscopic anterior cruciate ligament (ACL) reconstruction of the contralateral knee[63]	✿ Revision arthroscopy: 3 (27.3*) vs. 1 (10.0*), n.s., p=0.5865
Procedure-related mortality, n (%)	NR	NR

Abbreviations: *AMIC autologous matrix-induced chondrogenesis; ADL Activities of daily living; EQ-5D EuroQual-5D; ICRS International Cartilage Repair Society; IKDC International Knee Documentation Committee; KOOS Knee Injury and Osteoarthritis Outcome Score; n number; n/a data not available; NR not reported; n.s. not significant; MFx microfracture; MOCART Magnetic Resonance Observation of Cartilage Repair Tissue; MRI magnetic resonance imaging; pts. patients; RCT randomised controlled trial; s.s. statistically significant; TAS Tegner Activity Score; VAS Visual Analogue Pain Scale; WOMAC Western Ontario and McMaster Universities Osteoarthrisits Index; yrs years;*

**Own calculations.*

[61] None of the severe adverse events were considered to be related to the treatment of the cartilage defect.

[62] It was not clear whether it was an osteochondritis dissecans lesion or maybe a partial ossification and delamination of the graft that was mistaken for an osteochondritis dissecans lesion.

[63] See AEs (general).

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 [53] and in the Guidelines of EUnetHTA [10, 51].

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Table A-5: Risk of bias – study level (non–randomised controlled studies) [11]

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 [6]	Serious[64]	Serious[65]	Low	Moderate[66]	Moderate[67]	Serious[68]	Moderate[69]	Serious	-

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

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

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

[67] Values for IKDC Score were not reported (only summarised in a figure of the publication).

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

[69] No study protocol available.

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Table A-6: Risk of bias – study level (randomised studies), see [51]

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Incomplete outcome data addressed	Free of selective outcome reporting	Free of other bias	Risk of bias – study level
			Patient	Treating physician				
Kon, 2018 [47]	Yes	Yes	No (not possible)[70]	No (not possible)[70]	No[71]	Unclear[72]	No[73,74]	High
Pipino, 2018 [46]	Unclear[75]	Unclear[76]	No (not possible)[77]	No (not possible)[77]	Yes	Unclear[72]	No[73]	High
Shive, 2014 [3] (Stanish, 2013 [5])[78]	Yes[79] (Yes)	Unclear (Yes)	No (not possible)[80] (No [not possible])[80]	No (not possible)[80] (No [not possible])[80]	No[81] (No[81])	Yes (Yes)	No[73,74,82] (No[73,74])	High (High)
Volz, 2017 [7] (Anders, 2013 [4])	Yes (Yes)	Yes (Yes)	No (not possible)[83] (No [not possible])	No (not possible)[83] (No [not possible])	No[84] (No[81])	No[85] (No[86])	No[73,74] (No[73,87])	High (High)

[70] No information about the blinding of patients and study personnel. A blinded radiologist carried out the postoperative MRI assessments. A blinded statistician carried out the analysis. An external independent agency (Contract Research Organization, CRO) was involved to ensure data correctness and objectiveness of the study results.

[71] No statistical analyses of outcomes between groups for defect regeneration; missing confidence intervals and p-values.

[72] Insufficient information; no study protocol available.

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

[74] Possible conflict of interests of the authors.

[75] Insufficient information; matched pair study.

[76] Insufficient information; no description of allocation concealment.

[77] No information about the blinding of patients and study personnel.

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

[79] Assuming that the same randomisation method hold for the extension study.

[80] Investigators and patients were not blinded because of differences in incision size related to treatment. However, the independent third party carrying out the analyses of primary endpoints was unaware of patient treatment.

[81] Missing confidence intervals and p-values.

[82] 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.

[83] No blinding of patients and study personnel, due to the comparison of a total arthroscopic procedure (MFx) to an open procedure (AMIC).

[84] No statistical analyses of outcomes between groups for 60 months follow-up; missing confidence intervals and p-values partially missing.

[85] Unclear approach for assessing Modified ICRS; no study protocol available.

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

[87] Data from interim analysis of an open-label trial.

MACI

Table A-7: Risk of bias – study level (randomised studies), see [51]

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Incomplete outcome data addressed	Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating physician				
Bartlett, 2005 [22]	Yes	Yes	No (not possible)	No (not possible)	No[100]	Unclear[101]	No[97, 88]	High
Basad, 2010 [48]	Yes	No[89]	No (not possible)[90]	No (not possible)[90]	No[91]	Yes	Unclear[97,92]	High
Brittberg, 2018 [9] (Saris, 2014 [8])	Yes[93] (Yes)	Unclear[93] (Yes)[94]	No (not possible)[95] (No [not possible])[95]	No (not possible)[95] (No [not possible])[95]	No[96] (No[96])	Yes (Yes)	No[88,97] (No)[88,97]	High
Crawford, 2012 [49]	Yes[98]	Yes	No (not possible)	No (not possible)[99]	No[100]	Unclear[101]	No[88,97]	High
Zeifang, 2010 [23]	Yes	Yes	No (not possible)	No (not possible)[102]	No[100]	Yes	No[97,88]	High

[88] Possible conflict of interests of the authors.

[89] Pts. were allocated consecutive numbers in the order of their study entry.

[90] In the discussion of the study it is reported that blinding is practically impossible in some studies.

[91] Partially missing statistical analyses of outcomes between groups; missing confidence intervals.

[92] For pt. criteria no information about the cartilage defect size and the clinical classification was reported.
Moreover, no information about potential conflicts of interest and about the sponsor of the study was reported.

[93] Assuming that the same randomisation method hold for the extension study.

[94] Randomisation using an interactive voice response system.

[95] Given that the surgical techniques for MACI (two surgeries) and MFx (one surgery) are different, the study could not be blinded;
however, histological and MRI evaluations were assessor blinded.

[96] Missing confidence intervals and p-values partially missing.

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

[98] A permuted block design, generated by a statistician independent of the study, was utilised to minimise the opportunity for guessing the next treatment assignment.

[99] IKDC objective data reported by one physician (no author) blinded to the treatment or by clinicians (no authors) blinded to all patient-reported subjective data scores.

[100] Partially missing statistical analyses of outcomes between groups; missing confidence intervals and partially missing p-values.

[101] Insufficient information; no study protocol available.

[102] An independent musculoskeletal radiologist blinded to the treatment groups assessed the postoperative MRI scans.
However, the biostatistician who performed the statistical analysis was not blinded to the treatment groups.

GRADE evidence profiles

AMIC

Table A-8: Evidence profile: efficacy and safety of AMIC compared to MFx for cartilage repair in the knee

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AMIC	MFx or ACI	Relative	Absolute	
Mobility/joint functionality: improvement from baseline (follow-up: mean 24 months; assessed with: IKDC; Scale from: 0 to 100)											
1	randomised trials	serious [a]	not serious [b]	not serious	not serious	None	51	49	-	MD **1 point higher** [d]	⊕⊕⊕◯ MODERATE
Mobility/joint functionality: improvement from baseline (follow-up: mean 60 months; assessed with: WOMAC stiffness; Scale from: 0 to 8)											
1	randomised trials	serious [a]	not serious [b]	not serous	not serious	None	46	23	-	MD **3.5 points higher** [d]	⊕⊕⊕◯ MODERATE
Mobility/joint functionality: reduction from baseline (follow-up: mean 12 months; assessed with: WOMAC stiffness; Scale from: 0 to 20)											
1	randomised trials	serious [a]	not serious [b]	not serous	not serious	None	41	39	-	MD **1.1 points lower** [d]	⊕⊕⊕◯ MODERATE
Mobility/joint functionality: improvement from baseline (follow-up: mean 24 months; assessed with: WOMAC physical function; Scale from: 0 to 68)											
1	randomised trials	serious [a]	not serious [b]	not serous	not serious	None	46	23	-	MD **29.7 points higher** [d]	⊕⊕⊕◯ MODERATE
Mobility/joint functionality: reduction from baseline (follow-up: mean 60 months; assessed with: WOMAC physical function; Scale from: 0 to 170)											
1	randomised trials	serious [a]	not serious [b]	not serous	not serous	None	41	39	-	MD **5.6 points lower** [d]	⊕⊕⊕◯ MODERATE
Mobility/joint functionality: reduction from baseline (follow-up: mean 12 months; assessed with: Modified Cincinnati Knee Rating System; Scale from: 0 to 100)											
1	randomised trials	serious [a]	not serious [b]	not serious	serious [f]	None	34	13	-	MD **6 points higher** [d]	⊕⊕◯◯ LOW
Mobility/joint functionality: reduction from baseline (follow-up: mean 60 months; assessed with: SF-36; Scale from: 0 to 100)											
1	randomised trials	serious [a]	not serious [b]	not serious	not serious	None	41	39	-	MD **1.4 points higher** [d]	⊕⊕⊕◯ MODERATE
Quality of life: improvement from baseline (follow-up: mean 60 months; assessed with: SF-36; Scale from: 0 to 100)											
1	randomised trials	serious [a]	not serious [b]	not serious	not serious	None	41	39	-	MD **2.9 points higher** [d]	⊕⊕⊕◯ MODERATE
Pain: reduction from baseline (follow-up: mean 24 months; assessed with: VAS; Scale from: 0 to 100)											
1	randomised trials	serious [a]	not serious [b]	not serious	not serious	None	51	49	-	MD **6.3 points higher** [d]	⊕⊕⊕◯ MODERATE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AMIC	MFx or ACI	Relative	Absolute	
Pain: improvements from baseline (follow-up: mean 24 months; assessed with: WOMAC pain; Scale from: 0 to 20)											
1	randomised trials	serious [a]	not serious	not serous	not serous	None	46	23	-	MD **12.0 points higher** [d]	⊕⊕⊕◯ MODERATE
Pain: improvements from baseline (follow-up: mean 60 months; assessed with: WOMAC pain; Scale from: 0 to 50)											
1	randomised trials	serious [a]	not serious	not serious	not serious	None	41	39	-	MD **1.2 points lower** [d]	⊕⊕⊕◯ MODERATE
Necessity of total joint replacement (assessed with: in % of pts.)											
1	randomised trials	serious [a]	not serious [b]	not serious	not serious	None	At 12 months: 1 total knee arthroplasty (study group n/a).				⊕⊕⊕◯ MODERATE
Safety: Severe adverse events (follow-up: range 24 months to 60 months; assessed with: in % of pts.)											
3	randomised trials	serious [a]	serious [g]	not serious	serious [h]	None	8/126 (6.3%)	3/101 (3.0%)	**RR 2.1** [d]	**33 more per 1,000**	⊕◯◯◯ VERY LOW
Safety: Procedure-related adverse events (follow-up: range 24 months to 60 months; assessed with: in % of pts.)											
3	randomised trials	serious [a]	serious [g]	not serious	serious [h]	None	48/126 (38.1%)	35/101 (34.7%)	**RR 1.1** [d]	**35 more per 1,000**	⊕◯◯◯ VERY LOW
Safety: Device-related adverse events (follow-up: range 24 months to 60 months; assessed with: in % of pts.)											
2	randomised trials	serious [a]	not serious	not serious	not serious	None	12/92 (13.0%)	0/88 (0.0%)	not estimable	-	⊕⊕⊕◯ MODERATE
Safety: Re-operation rate (follow-up: range 12 months to 60 months; assessed with: in % of pts.)											
2	randomised trials	serious [a]	not serious	not serious	serious [h]	None	1/75 (1.3%)	2/52 (3.8%)	**RR 0.34** [d]	**25 fewer per 1,000**	⊕⊕◯◯ LOW

Abbreviations: *CI confidence interval; MD mean difference; RR risk ratio*

Comments

[a] *There was a serious risk of bias due to possible confounding, missing data, and the use of un-blinded patient-reported outcome measures.*

[b] *Heterogeneity in reported cases across studies.*

[d] *Based on self-calculated mean difference between study groups/relative risk.*

[e] *Different age of pts. between studies.*

[f] *Low incidence/pts. numbers.*

[g] *Heterogeneity in reported cases across studies.*

[h] *Low incidence/pts. numbers in one study.*

Nomenclature for GRADE table:

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

Inconsistency: NA: 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)

MACI

Table A-9: Evidence profile: efficacy and safety of MACI compared to MFx or ACI for cartilage repair in the knee

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MACI	MFx or ACI	Relative	Absolute	
Mobility/joint functionality: improvement from baseline (follow-up: mean 60 months; assessed with: KOOS sport/rec; Scale from: 0 to 100)											
2	randomised trials	serious [a]	serious [b]	serious [c]	serious [d]	None	86	72	-	MD **8.1 points higher** [f,g]	⊕◯◯◯ VERY LOW
Mobility/joint functionality: reduction from baseline (follow-up: mean 24 months; assessed with: IKDC; Scale from: 0 to 100)											
3	randomised trials	serious [a]	serious [b]	serious [c]	serious [h]	None	97	82	-	MD **2.4 points higher** [f]	⊕◯◯◯ VERY LOW
Mobility/joint functionality: improvement from baseline (follow-up: range 12 months to 60 months; assessed with: Modified Cincinnati Knee Scoring System; Scale from: 0 to 100)											
2	randomised trials	serious [a]	serious [b]	not serious	not serious	None	112	107	-	MD **1.5 points higher** [f]	⊕⊕◯◯ LOW
Mobility/joint functionality: improvement from baseline (follow-up: mean 24 months; assessed with: Lysholm scoring scale; Scale from: 0 to 100)											
2	randomised trials	serious [a]	serious [b]	not serious	serious [d]	None	51	30	-	MD **2.3 points higher** [f]	⊕◯◯◯ VERY LOW
Mobility/joint functionality: improvement from baseline (follow-up: mean 2 months; assessed with: SF-36; Scale from: 0 to 100)											
1 [o]	randomised trials	serious [a]	not serious [i]	not serious	serious [d]	None	At 12/24 months n.s. difference between study groups.				⊕⊕◯◯ LOW
Quality of life: improvement from baseline (follow-up: mean 60 months; assessed with: KOOS QoL; Scale from: 0 to 100)											
2	randomised trials	serious [a]	serious [b]	serious [c]	serious [d]	None	86	72	-	MD **4.6 points higher** [f,g]	⊕◯◯◯ VERY LOW
Quality of life: improvement from baseline (follow-up: mean 60 months; assessed with: EQ-5D; Scale from: 0 to 100)											
1	randomised trials	serious [a]	not serious [i]	not serious	not serious	None	65	63	-	MD **1 point higher** [f]	⊕⊕⊕◯ MODERATE
Quality of life: reduction from baseline (follow-up: mean 24 months; assessed with: SF-36; Scale from: 0 to 100)											
1 [o]	randomised trials	serious [a]	not serious [i]	not serious	serious [d]	None	At 12/24 months n.s. difference between study groups.				⊕⊕◯◯ LOW
Pain: improvement from baseline (follow-up: mean 60 months; assessed with: KOOS pain; Scale from: 0 to 100)											
2	randomised trials	serious [a]	serious [b]	serious [c]	serious [d]	None	86	72	-	MD **5.5 points higher** [f,g]	⊕◯◯◯ VERY LOW
Pain: improvement from baseline (follow-up: N/A; assessed with: VAS; Scale from: 0 to 100)											
2	randomised trials	serious [a]	serious [b]	serious [c]	serious [d]	None	68	53	-	MD **0.2 points higher** [f,j]	⊕◯◯◯ VERY LOW

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MACI	MFx or ACI	Relative	Absolute	
Pain: (follow-up: mean 24 months; assessed with: SF-12, SF-36)											
1	randomised trials	serious [a]	not serious [i]	not serious	serious [k]	None	n.s. difference between IG vs. CG for 12 and 24 months.				⊕⊕◯◯ LOW
Necessity of total joint replacement (assessed with: in % of pts.)											
1	randomised trials	serious [a]	not serious [i]	not serious	serious [k]	None	1/21 (4.8%)	0/9 (0.0%)	not estimable	-	⊕⊕◯◯ LOW
Safety: Severe adverse events (follow-up: range 24 months to 60 months)											
5	randomised trials	serious [a]	serious [b]	serious [c]	serious [h]	None	2/184 (1.1%)	1/146 (0.7%)	**RR 1.57** [f]	**4 more per 1,000**	⊕◯◯◯ VERY LOW
Safety: Procedure-related adverse events											
1 [l]	randomised trials	serious [a]	not serious [i]	not serious	serious [k]	None	0/21 (0.0%)	0/9 (0.0%)	not estimable	-	⊕⊕◯◯ LOW
Safety: Device-related adverse events (follow-up: range 6 months to 24 months)											
2[p]	randomised trials	serious [a]	serious [b]	serious [c]	serious [d]	None	10/58 (17.2%)	18/54 (33.3%)	**RR 0.52** [f]	**160 fewer per 1,000** [m]	⊕◯◯◯ VERY LOW
Safety: Re-operation rate (follow-up: mean 24 months)											
5	randomised trials	serious [a]	serious [b]	serious [c]	serious [h]	None	8/184 (4.3%)	4/146 (2.7%)	**RR 1.59** [f]	**16 more per 1,000** [n]	⊕◯◯◯ VERY LOW

Abbreviations: *CI confidence interval; RR risk ratio*

Comments:

[a] *There was a serious risk of bias due to possible confounding, missing data, and the use of un-blinded patient-reported outcome measures.*

[b] *Heterogeneity in reported cases across studies.*

[c] *Different defect size in pts. between studies.*

[d] *Low incidence/pts. numbers in one study.*

[f] *Based on self-calculated mean difference between study groups/relative risk.*

[g] *Absolute effect based on one study (Brittberg 2018).*

[h] *Low incidence/pts. numbers in two studies.*

[i] *N/A (only one trial).*

[i] *Absolute effect based on one study (Bartlett 2005).*

[k] *Low incidence/pts. numbers.*

[l] *Absolute numbers for adverse events given only in one study.*

[m] *Absolute effect based on three studies.*

[n] *Absolute effect based on four studies.*

[o] *In one RCT [9], negative scores of the SF-12, which were not translated on a 0-100 score, were reported. Thus, the reported negative values could not be interpreted and this study could not be graded for this outcome.*

[p] *For device-related adverse events only the studies with ACI as the comparator were considered.*

Nomenclature for GRADE table:

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

Inconsistency: NA: 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)

Applicability table

Table A-10: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	All studies included patients with (osteo)chondral defects in the knee. The patients had defects grades 3-4 of the Outerbridge Classification (stated in four studies) or grade-III of the ICRS classification (stated in one study). Across all studies, male patients were included more frequently. The mean age of patients was 35.9 years in the AMIC studies and 34.5 years in the MACI studies. One of the AMIC studies included patients with a slightly higher age (55.6 years), which is likely to have influenced the effects of the intervention. The studies included a total of 187 patients with the AMIC intervention vs. 127 with MFx and 184 patients with the MACI intervention vs. 92 with MFx or 54 with ACI. The inclusion criteria and the population in the studies seem to be in accordance with the intended patient population for the technology. There was no study that included patients with (osteo)chondral defects in the talus.
Intervention	The implantations of the scaffolds, either single-step or two-step, were either performed by miniarthrotomy or by an arthroscopy. In all studies, it was stated that patients received postoperative physiotherapy or rehabilitation. *AMIC studies*: Patients in the included studies received Chondro-Gide®, MaioRegen™, JointRep™ or BST-CarGel®. In one study, it was not stated which product was used; however, based on the compounds, it could have been GelrinC®. *MACI studies*: Patients in the included studies received NeoCart®, BioSeed®-C, ACI-Maix™ or MACI™. In one study, it was not stated which product was used.
Comparators	*AMIC studies*: In all studies, the control groups received microfracture alone. To date, there are no published studies in which the single-step scaffold-assisted treatment of cartilage defects in combination with microfracture has been compared with autologous chondrocyte implantation (ACI). *MACI studies*: In three studies the control groups received microfracture and in two studies the control groups received autologous chondrocyte implantation (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 (AMIC) or the two-step scaffold-based cartilage repair (MACI). The most reported outcomes for the assessment of the efficacy were mobility/joint functionality, pain and quality of life. For the assessment of safety, severe complications, procedure-, and/or device-related adverse events, as well as re-operation rates, were recorded. However, the presented data in the studies is limited, especially due to small study samples, partly short time horizons for follow-up, various scoring systems for efficacy outcomes between studies and obviously different approaches to the reporting/recording of complications (becoming apparent in a high variability in complication rates between studies).
Setting	*AMIC studies*: With two exceptions, the studies were carried out in Europe: Germany, Italy, and the Netherlands. Two studies were multi-centre studies carried out in (1) Canada, Spain and South Korea, and in (2) 9 European countries and South Africa. *MACI studies:* With one exception, the studies were carried out in Europe: Germany, England as well as 7 European countries (not specified). The latter was a multi-centre study. One study was carried out in the USA. 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. No applicability issues are expected from the geographical setting.

List of ongoing randomised controlled trials

Table A-11: List of ongoing randomised controlled trials

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT01656902[103]	Pts. with localised articular cartilage defect of the femoral condyle or the trochlea of the knee	NOVOCART® 3D plus (MACI)	Microfracture	Subjective IKDC score baseline vs. 36 months follow-up	May 2019	Tetec – Tissue Engineering Technologies – AG
EUCTR2011-005798-22-DE[103]	Pts. with localised, full-thickness cartilage defects of the femoral condyle (medial, lateral or trochlea)	NOVOCART® 3D plus (MACI)	Microfracture	Safety and Effectiveness	NR	TETEC – Tissue Engineering Technologies – AG
NCT02659215 FastTRACK	Pts. with symptomatic lesion of the femoral condyle (medial and/or lateral) or femoral trochlea images confirmed	Hyalofast® (AMIC)	Microfracture	% change in Knee injury and Osteoarthritis Outcome (KOOS) Pain Score for 2-year follow-up	December 2020	Anika Therapeutics, Inc.
NCT01957722	Pts. with isolated articular cartilage lesions on the femoral condyle	NOVOCART® 3D (AMIC)	Microfracture	Pain and function change from baseline to 24 months with KOOS score	July 2019	Aesculap Biologics, LLC
NCT03307668	Pts. with diagnosed isolated knee cartilage defects in condyles of femur by arthroscopy	CaReS®-1S (AMIC)	Microfracture	Difference of Magnetic resonance observation of cartilage repair tissue (MOCART) score between two groups after 12 months	December 2019	Arthro-Anda Tianjin Biologic Technology Co., Ltd.
NCT01222559	Pts. with isolated ICRS grade III or IV single defect chondral lesions on femoral condyles	co.don chondrosphere® (AMIC)	Microfracture	Change of overall KOOS after 24 months	September 2017	co.don AG
EUCTR2017-002601-35-CZ	Pts. with symptomatic knee articular cartilage defects	Chondrograft® (AMIC)	Microfracture	Effectiveness and Safety	NR	PrimeCell Advanced Therapy a.s.

[103] These studies may be connected and may represent the same results.

Literature search strategies

Search strategy for Cochrane

Search date: 07/12/2018	
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* (Word variations have been searched)
#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	(Matri* NEAR (Chondrogenes* OR Chondrocyte*)) (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	MeSH descriptor: [Transplantation, Autologous] explode all trees
#28	(Matri*) (Word variations have been searched)
#29	(#27 AND #28) (Word variations have been searched)
#30	(Matri* NEAR (autologous chondrocyte* NEAR (implant* or transplant*))) (Word variations have been searched)
#31	(MACI):ti,ab,kw (Word variations have been searched)
#32	(MACT):ti,ab,kw (Word variations have been searched)
#33	Chondro-Gide (Word variations have been searched)
#34	Chondrotissue (Word variations have been searched)
#35	Chondro-Tissue (Word variations have been searched)
#36	Hyalofast (Word variations have been searched)
#37	MaioRegen (Word variations have been searched)
#38	(CaRes-1S) (Word variations have been searched)
#39	(Gelrin*) (Word variations have been searched)
#40	(BST-Car*) (Word variations have been searched)

#41	(Novocart*) (Word variations have been searched)
#42	(MeRG)
#43	(Chondrofiller*) (Word variations have been searched)
#44	(JointRep*) (Word variations have been searched)
#45	(Spherox*) (Word variations have been searched)
#46	(BioSeed*) (Word variations have been searched)
#47	#21 or #22 or #23 or #24 or #25 or #26 or #29 #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR 39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 (Word variations have been searched)
#48	#20 and #47 in Trials
#31	(MACI):ti,ab,kw (Word variations have been searched)
#32	(MACT):ti,ab,kw (Word variations have been searched)
#33	Chondro-Gide (Word variations have been searched)
#34	Chondrotissue (Word variations have been searched)
#35	Chondro-Tissue (Word variations have been searched)
#36	Hyalofast (Word variations have been searched)
#37	MaioRegen (Word variations have been searched)
#38	(CaRes-1S) (Word variations have been searched)
#39	(Gelrin*) (Word variations have been searched)
#40	(BST-Car*) (Word variations have been searched)
#41	(Novocart*) (Word variations have been searched)
#42	(MeRG)
#43	(Chondrofiller*) (Word variations have been searched)
#44	(JointRep*) (Word variations have been searched)
#45	(Spherox*) (Word variations have been searched)
#46	(BioSeed*) (Word variations have been searched)
#47	#21 or #22 or #23 or #24 or #25 or #26 or #29 #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR 39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 (Word variations have been searched)
#48	#20 and #47 in Trials
Total: 165 Hits	

Search strategy for CRD

Search Date: 10/12/2018	
#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	(BST-Car*)
#14	(Gelrin*)
#15	(Novocart*)
#16	(MeRG)

#17	(Chondrofiller*)
#18	(JointRep*)
#19	(Spherox*)
#20	(BioSeed*)
#21	MeSH DESCRIPTOR Transplantation, Autologous EXPLODE ALL TREES
#22	(Matri*)
#23	#21 AND #22
#24	(Matri* NEAR (autologous OR chondrocyte* OR implant* OR transplant*))
#25	(MACI)
#26	(MACT)
#27	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #23 OR #24 OR #25 OR #26
Total: 25 Hits	

Search strategy for Embase

No.	Query Results	Results	Date
#57.	#54 OR #56	102	7 Dec 2018
#56.	#53 AND #55	96	7 Dec 2018
#55.	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti	2,328,003	7 Dec 2018
#54.	#18 AND #52 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)	26	7 Dec 2018
#53.	#18 AND #52	598	7 Dec 2018
#52.	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51	2,331	7 Dec 2018
#51.	bioseed*	80	7 Dec 2018
#50.	'spherox*'	7	7 Dec 2018
#49.	'joint rep*':dn,df	9	7 Dec 2018
#48.	chondrofiller*	3	7 Dec 2018
#47.	merg:ti,ab	140	7 Dec 2018
#46.	novocart*	39	7 Dec 2018
#45.	'gelrin*'	10	7 Dec 2018
#44.	'bstcar*'	7	7 Dec 2018
#43.	'bst car*'	50	7 Dec 2018
#42.	cares:df	1	7 Dec 2018
#41.	cares:dn	32	7 Dec 2018
#40.	maioregen*	27	7 Dec 2018
#39.	hyalofast*	11	7 Dec 2018
#38.	'chondro tissue*'	3	7 Dec 2018
#37.	chondrotissue*	20	7 Dec 2018
#36.	'chondrogide*'	29	7 Dec 2018
#35.	'chondro-gide*'	77	7 Dec 2018
#34.	mact:ti,ab	222	7 Dec 2018
#33.	maci:ti,ab	298	7 Dec 2018
#32.	(('matri*-induc*' OR 'matri*-appli*' OR 'matri*-associat*' OR 'matri*-assist*') NEAR/5 ('autologous chondrocyte*' OR implant* OR transplant*)):ti,ab,de	563	7 Dec 2018

#31.	#29 AND #30	790	7 Dec 2018
#30.	matri*:ti,ab,de	517,666	7 Dec 2018
#29.	'autotransplantation'/exp	30,282	7 Dec 2018
#28.	'ocd regeneration'	2	7 Dec 2018
#27.	'osteochondral regeneration':ti,ab,de	118	7 Dec 2018
#26.	amic:ti,ab	312	7 Dec 2018
#25.	(('matri*-induc*' OR 'matri*-appli*' OR 'matri*-associat*' OR 'matri*-assist*') NEAR/5 (chondrogenes* OR chondrocyte*)):ti,ab,de	491	7 Dec 2018
#24.	(autologous NEAR/5 chondrogenes*):ti,ab,de	146	7 Dec 2018
#23.	#19 AND #22	9	7 Dec 2018
#22.	#20 OR #21	2,613	7 Dec 2018
#21.	'collagen'/exp/dd_dt,dd_ad	2,613	7 Dec 2018
#20.	'collagen'/exp/dm_dt,dm_th	2,200	7 Dec 2018
#19.	'chondrogenesis'/exp	9,461	7 Dec 2018
#18.	#12 OR #17	34,253	7 Dec 2018
#17.	#13 OR #14 OR #15 OR #16	20,292	7 Dec 2018
#16.	(osteochondr* NEAR/5 (damage* OR disorder* OR defect* OR lesion* OR disease*)):ti,ab,de	6,718	7 Dec 2018
#15.	ocd:ti,ab	12,197	7 Dec 2018
#14.	'osteochondritis dissecans':ti,ab,de	3,062	7 Dec 2018
#13.	'osteochondritis dissecans'/exp	2,541	7 Dec 2018
#12.	#4 AND #11	16,356	7 Dec 2018
#11.	#5 OR #6 OR #7 OR #8 OR #9 OR #10	284,302	7 Dec 2018
#10.	'ankle injury'/exp	12,986	7 Dec 2018
#9.	'knee injury'/exp	30,570	7 Dec 2018
#8.	ankle*:ti,ab,de	87,803	7 Dec 2018
#7.	'ankle'/exp	31,394	7 Dec 2018
#6.	knee*:ti,ab,de	213,273	7 Dec 2018
#5.	'knee'/exp	63,468	7 Dec 2018
#4.	#1 OR #2 OR #3	67,853	7 Dec 2018
#3.	'articular cartilage'/mj	11,920	7 Dec 2018
#2.	(cartilage NEAR/5 (damage* OR disorder* OR	24,645	7 Dec 2018
#1.	'chondropathy'/exp/mj	39,431	7 Dec 2018

Search strategy for Medline via OVID

Database: Ovid MEDLINE(R) <1946 to November Week 5 2018>, Ovid MEDLINE(R) Epub Ahead of Print <December 06, 2018>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 06, 2018>, Ovid MEDLINE(R) Daily Update <December 06, 2018>	
Search Strategy:	
1	exp Cartilage Diseases/ (12449)
2	(cartilage adj5 (damage* or disorder* or defect* or lesion* or disease*)).mp. (16307)
3	exp *Cartilage, Articular/ab, in, pa, ph, pp [Abnormalities, Injuries, Pathology, Physiology, Physiopathology] (7539)
4	1 or 2 or 3 (28870)
5	exp Knee Joint/ (55377)
6	Knee*.mp. (154628)
7	exp Ankle Joint/ (14535)
8	Ankle*.mp. (61360)
9	exp Knee Injuries/ (23319)

10	exp Ankle Injuries/ (9262)
11	5 or 6 or 7 or 8 or 9 or 10 (205925)
12	4 and 11 (9203)
13	exp Osteochondritis Dissecans/ (1518)
14	osteochondritis dissecans.mp. (2255)
15	OCD.mp. (8547)
16	(osteochondr* adj5 (damage* or disorder* or defect* or lesion* or disease*)).mp. (4829)
17	13 or 14 or 15 or 16 (14337)
18	12 or 17 (22175)
19	exp Chondrogenesis/ (4544)
20	exp *Collagen/ad, tu [Administration & Dosage, Therapeutic Use] (2867)
21	19 and 20 (12)
22	(autologous adj10 chondrogenes*).mp. (115)
23	((Matri*-Induc* or Matri*-appli* or Matri*-associat* or Matri*-assist*) adj10 (Chondrogenes* or Chondrocyte*)).mp. (378)
24	AMIC.mp. (255)
25	osteochondral regeneration*.mp. (100)
26	OCD regeneration.mp. (2)
27	exp Transplantation, Autologous/ (47796)
28	Matri*.mp. (441072)
29	27 and 28 (1025)
30	((Matri*-induc* or Matri*-appli* or Matri*-associat* or Matri*-assist*) adj5 autologous chondrocyte* adj5 (implant* or transplant*)).mp. (245)
31	MACI.ti,ab. (203)
32	MACT.ti,ab. (168)
33	Chondro?Gide*.mp. (9)
34	Chondrotissue*.mp. (5)
35	Chondro-Tissue*.mp. (1)
36	Hyalofast*.mp. (1)
37	MaioRegen*.ti,ab. (10)
38	CaRes-1S.mp. (3)
39	BST-Car*.mp. (17)
40	Gelrin*.mp. (2)
41	Novocart*.mp. (16)
42	MeRG.mp. (92)
43	Chondro?filler*.mp. (1)
44	JointRep*.mp. (1)
45	Spherox*.mp. (3)
46	BioSeed*.mp. (22)
47	21 or 22 or 23 or 24 or 25 or 26 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 (1895)
48	18 and 47 (466)
49	limit 48 to clinical trial, all (40)
50	((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.) (3757380)
51	48 and 50 (92)
52	49 or 51 (111)
53	remove duplicates from 52 (111)
Search date: 07/12/2018	

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Health Technology Assessment