APPENDIX 2

SECTION A

Appendix A1: Outcome measures

Publication data:

First author, publication date, main country, international, number of involved centers, registration status

Demographic data:

Trial arms, treatments, number of knees at randomization, total knees at randomization, procedure type (open, arthro, mini open), number of non-weightbearing postoperative weeks, total males in the whole trial population, mean age per trial arm, age standard deviation per trial arm, age minimum and maximum per trial arm, osteochondritis dissecans: yes/no per trial population, chondromalacia patellae, tibial plateau lesions, trochlea lesions, single lesions versus multiple lesions, defect size: mean, minimum, maximum per trial arm, mean symptoms duration in years, concomitant knee surgery, prior cartilage operation, prior knee operation, follow-up mean, knees at short – intermediate – long term, last follow-up sample size per trial arm, total number of analysed knees, intention-to-treat versus per-protocol

Clinical and functional outcome measures:

At short, intermediate and long term,

Mean, standard deviation, variance, median, interquartile 1 and 3, minimum, maximum, confidence interval for

KOOS, Lysholm, Tegner, IKDC, modified Cincinnati, WOMAC, HSS

Safety outcomes:

Infection, symptomatic cartilage loosening, neuroapraxia of the saphenous nerve, deep vein thrombosis or pulmonary embolism, persistent pain conservatively treated, limitation of the range of motion conservatively treated, reoperation such as arthroscopy, adesiolysis, meniscectomy, debridement, drainage of hematoma, reoperation such as open or arthroscopic cartilage revision, reoperation as total knee arthroplasty, reoperation such as open surgery different than cartilage revision, total number of reoperations, development of arthritis, failure definition and absolute number per trial group, total failures, total patient number with complications.

The outcome measures for postoperative MRI, 2nd look surgery, and conflicts of interest are shown in Appendix 2, section C.

Appendix A2: Demographic Data

STUDY	TREATMENT ARM	KNEES□	OVERALL MALES	MEAN AGE years	OVERALL OCD	OVERALL AFFECTED SITES	OVERALL NUMBER OF LESIONS TREATED FOR INDEX KNEE	DEFECT SIZE*- mean cm^2	MEAN SYMPTOMS DURATION years	OVERALL CONCOMITANT SURGERY	OVERALL PRIOR MF AND CARTILAGE DEBRIDEMENT	OVERALL PRIOR NON-CARTILAGE KNEE SURGERY	MATERIALS AND TECHNIQUES	OVERALL NWB WEEKS
Horas et al. 2003[1]	ACI1	20	23	31.4	no	FC	1	3.86	n.a.	no	yes	yes	Periost	2
	OCT	20		35.4				3.63	n.a.				0.1 mm plugs	
Schneider et al. 2003[2]	ACI3	10	n.a.	37.2	yes	FC, P, T	2	5.78	n.a.	n.a.	n.a.	yes	CaRes	n.a.
	ACI1	10		38.8				6.63	n.a.				Periost	
Dozin et al. 2005[3]	ACI1	22	27	29.61	no	FC, P	1	n.a.	n.a.	no	yes	n.a.	Periost	2
	OCT	22		27.89				n.a.	n.a.				n.a.	
Gooding et al. 2006[4]	ACI2	35	n.a.	30.54	yes	FC, P, T	1	n.a.	7.09	no	yes	yes	Porcine type I-III collagen membrane	0
	ACI1	33		30.52				n.a.	7.09				Periost	
Basad et al. 2010[5]	ACI3	40	42	33	no	FC, P, T	1	n.a.	2.2	yes	no[Ø]	n.a.	MACItm	6
	MF	20		37.5				n.a.	2.5				Steadman[40]	
Vanlauwe et al. 2011[6-8]	ACI1	51	76	33.9	yes	FC	1	2.6*	1.97	yes	yes	yes	Periost	2
	MF	61		33.9				2.4*	1.57				Steadman[40]	
Gudas et al. 2012[9,10]	OCT	30	36	24.6	yes	FC	1	2.8	1.7	no	no	no	5.5mm plugs	4
	MF	30		24.3				2.77	1.7				Steadman[40]	
Lim et al. 2012[11]	MF	30	39	32.9	no	FC	1	2.77	n.a.	no	no	no	0.5mm tapered awls	0
	OCT	22		30.4				2.75	n.a.				4,6,8 mm plugs	
	ACI1	18		25.1				2.84	n.a.				Periost	
Shive et al. 2015[12,13]	AMIC	41	48	35.1	no	FC	1	2.32*	1.25	no[Ø]	yes[Ø]	yes[Ø]	BSTCar-gel	6
	MF	39		37.2				1.95*	2.17				Steadman[40]	
Clavé et al. 2016[14]	ACI3	30	40	29.2	yes[Ø]	FC	1	3.9*	n.a.	no[Ø]	no[Ø]	yes[Ø]	Cartipatch	4
	OCT	25		28.3				4.7*	n.a.				Plugs	
Knutsen et al. 2016[15-17]	ACI1	40	48	33.3	yes	FC	1	5.1	3	no	yes	yes	Periost	n.a.
	MF	40		31.1				4.5	3				Steadman[40]	
Volz et al. 2017[18,19]	AMIC	34	37	36.5	yes	FC, P, T	2	3.85*	n.a.	no	no	yes	Chondrogide	0
	MF	13		40				2.9*	n.a.				Steadman[40]	

Brittberg et al. 2018[20,21]	ACI3	72	93	34.8	yes	FC, T	2	5.8*	5.8	yes	yes	yes	Porcine type I-III collagen membrane	0
	MF	72		32.9				5.3*	3.7				Steadman[40]	
Kane et al. 2018[22,23]	ACI3	21	25	41	no	FC	2	2.87*	3	yes	yes	n.a.	Neocart	0
	MF	9		39				2.52*	2				n.a.	
Solheim et al. 2018[24]	OCT	20	28	31	no	FC, T	2	3.4	4.3	no	n.a.	n.a.	n.a.	0
	MF	20		35				3.6	4.8				Steadman[40]	
Barié et al. 2020[25,26]	ACI3	11	16	29.1	yes	FC, P, T	1	4.3	2	yes	yes	yes	Bioseed-C	0
	ACI1	10		29.5				4.1	2.7				Periost	
Glasbrenner et al. 2020[27]	AMIC	15	15	49.7	no	FC	1	1.7	n.a.	no	yes	yes	Chondrotissue	6
	MF	15		36.7				1.7	n.a.				Arthroscopic awl	
Ibarra et al. 2021[28]	ACI3	24	31	33.7	no	FC, P, T	1	1.9	n.a.	yes	no	yes	Neoveil	0
	MF	24		35.8				1.7	n.a.				Steadman[40]	
Hoburg et al. 2022[29-31]	spheroids	52	61	36	yes	FC, P, T	1	2.7*	n.a.	no	yes	yes	Co.don	0
	MF	50		37				2.4*	n.a.				Steadman[40]	

Legend:

ACI1: autologous chondrocyte implantation with periosteal membrane.
ACI2: autologous chondrocyte implantation with collagen membrane.
ACI3: autologous chondrocyte implantation with scaffold.
AMIC: autologous matrix-induced chondrogenesis.
FC: femoral condyles.
MF: microfracture.
n.a.: not available.
NWB: non-weight bearing.
OCD: osteochondritis dissecans.
OCT: osteochondral transplantation.
P: patella.
Spheroids: chondrospheres (Co.don, produced according to the self-aggregation technique).
T: trochlea.

Data are presented for each trial arm in the following columns: knee, mean age, defect size, mean symptoms duration, materials and techniques.
In the remaining columns data are presented for the overall trial population.

When multiple publications are available for the same trial, we have written the author and date of publication of the most recent one and in apex the references of all available publications.

□: number of randomized knees.
*: post-debridement mean defect size. Pre-debridement mean defect size where not indicated.
Ø: information verified with the trial author, by email.

Appendix A3: Summary of Trials' Demographic Data

	TRIALS	N. OF KNEES (%)	OCD INCLUDED / TRIAL N.*	N. TREATED LESIONS*	CONCOMITANT SURGERY*	OVERALL PRIOR MF AND CARTILAGE DEBRIDEMENT*	OVERALL PRIOR NON-CARTILAGE KNEE SURGERY*
MF	13	421 (36.6)	6/13	1: 9/13 2: 4/13	Yes: 5/13 No: 8/13	Yes: 7/13 No: 5/13 N.a.: 1/13	Yes: 8/13 No: 2/13 N.a.: 3/13
AMIC	3	90 (7.8)	1/3	1: 2/3 2: 1/3	No	Yes: 2/3 No: 1/3 N.a.: 0/3	Yes
OCT	6	139 (12)	2/6	1: 5/6 2: 1/6	Yes: 1/6 No: 5/6	Yes: 2/6 No: 3/6 N.a.: 1/6	Yes: 2/6 No: 2/6 N.a.: 2/6
ACI1	8	204 (17.7)	5/8	1: 7/8 2: 1/8	Yes: 2/8 No: 5/8 N.a.: 1/8	Yes: 6/8 No: 1/8 N.a.: 1/8	Yes: 6/8 No: 1/8 N.a.: 1/8
ACI2	1	35 (3)	1/1	1	No	Yes	Yes
ACI3	7	208 (18.1)	4/7	1: 4/7 2: 3/7	Yes: 5/7 No: 1/7 N.a.: 1/7	Yes: 3/7 No: 3/7 N.a.: 1/7	Yes: 5/7 N.a.: 2/7
SPHEROIDS	1	52 (4.5)	1/1	1	No	Yes	Yes
OVERALL	19	1149	10/19	1: 14/19 2: 5/19	Yes: 6/19 No: 12/19 N.a.: 1/19	Yes: 11/19 No: 6/19 N.a.: 2/19	Yes: 13/19 No: 2/19 N.a.: 4/19

Legend:

ACI1: autologous chondrocyte implantation with periosteal membrane.
ACI2: autologous chondrocyte implantation with collagen membrane.
ACI3: autologous chondrocyte implantation with scaffold.
AMIC: autologous matrix-induced chondrogenesis.
MF: microfracture.
N.: number.
n.a.: not available.
OCD: osteochondritis dissecans.
OCT: osteochondral transplantation.

Spheroids: chondrospheres (Co.don, produced according to the self-aggregation technique).
*: according the eligibility criteria.

Appendix A4: Adverse Events Conservatively Treated

STUDY	ARMS	MEAN FOLLOW-UP months	INFECTION	NEUROAPRAXIA SAPHENUS N.	DVT/PE	CONSERVATIVELY TREATED PERSISTENT SYMPTOMS, EFFUSION	CONSERVATIVELY TREATED ROM LIMITATION
Horas et al. 2003[1]	ACI1	24	0	2	n.a.	2	1
	OCT	24	1	2	n.a.	0	3
Schneider et al. 2003[2]	ACI3	6	n.a.	n.a.	0	n.a.	n.a.
	ACI1	6	n.a.	n.a.	1	n.a.	n.a.
Dozin et al. 2005[3]	ACI1	36	n.a.	n.a.	n.a.	n.a.	n.a.
	OCT	36	n.a.	n.a.	n.a.	n.a.	n.a.
Gooding et al. 2006[4]	ACI2	24	0	n.a.	1	n.a.	n.a.
	ACI1	24	2	n.a.	0	n.a.	n.a.
Basad et al. 2010[5]	ACI3	24	0	n.a.	0	0	n.a.
	MF	24	0	n.a.	0	0	n.a.
Vanlauwe et al. 2011[6-8]	ACI1	60	n.a.	n.a.	1	n.a.	n.a.
	MF	60	n.a.	n.a.	0	n.a.	n.a.
Gudas et al. 2012[9,10]	OCT	124.8	2	n.a.	n.a.	n.a.	n.a.
	MF	124.8	0	n.a.	n.a.	n.a.	n.a.
Lim et al. 2012[11]	MF	80.4	n.a.	n.a.	n.a.	n.a.	n.a.
	OCT	69.6	n.a.	n.a.	n.a.	n.a.	n.a.
	ACI1	62.4	n.a.	n.a.	n.a.	n.a.	n.a.
Shive et al. 2015[12,13]	AMIC	60	n.a.	n.a.	1	n.a.	n.a.
	MF	60	n.a.	n.a.	0	n.a.	n.a.
Clavé et al. 2016[14]	ACI3	24	1	n.a.	n.a.	n.a.	n.a.
	OCT	24	0	n.a.	n.a.	n.a.	n.a.
Knutsen et al. 2016[15-17]	ACI1	180	0	n.a.	0	n.a.	n.a.
	MF	180	0	n.a.	0	n.a.	n.a.
Volz et al. 2017[18,19]	AMIC	60	n.a.	n.a.	n.a.	n.a.	n.a.
	MF	60	n.a.	n.a.	n.a.	n.a.	n.a.
Brittberg et al. 2018*[20,21]	ACI3	60	n.a.	n.a.	n.a.	n.a.	n.a.
	MF	60	n.a.	n.a.	n.a.	n.a.	n.a.
Kane et al. 2018[,22,23]	ACI3	60	n.a.	n.a.	n.a.	n.a.	n.a.
	MF	60	n.a.	n.a.	n.a.	n.a.	n.a.
Solheim et	OCT	192	2	n.a.	1	n.a.	n.a.

al. 2018[24]	MF	192	0	n.a.	0	n.a.	n.a.
Barié et al. 2020[25,26]	ACI3	115.2	0	0	n.a.	5	n.a.
	ACI1	103.2	0	0	n.a.	5	n.a.
Glasbrenner et al. 2020[27]	AMIC	27	1	n.a.	n.a.	3	3
	MF	27	n.a.	n.a.	n.a.	1	0
Ibarra et al. 2021[28]	ACI3	74	n.a.	n.a.	n.a.	13	n.a.
	MF	71	1	n.a.	n.a.	17	n.a.
Hoburg et al. 2022[29-31]	spheroids	60	n.a.	n.a.	0	n.a.	n.a.
	MF	60	n.a.	n.a.	1	n.a.	n.a.

Legend:

ACI1: autologous chondrocyte implantation, 1st generation.
ACI2: autologous chondrocyte implantation, 2nd generation.
ACI3: autologous chondrocyte implantation, 3rd generation.
AMIC: autologous matrix-induced chondrogenesis.
MF: microfracture.
n.a.: not available.
OCT: osteochondral transplantation.
Spheroids: chondrospheres (Co.don, produced according to the self-aggregation technique).

When multiple publications are available for the same trial, we have written the author and date of publication of the most recent one and in apex the references of all available publications.
Data describes patients affected by the considered adverse events for each trial arm.
Data on donor site morbidity in case of OCT is never mentioned apart from one study (Gudas et al. 2005) reporting its absence.

*: data reported as safety events, not *per* patients.

Appendix A5: Adverse Events Surgically Treated

STUDY	ARMS	MEAN FOLLOW-UP months	ARTHROSCOPY FOR OTHER KNEE SURGERY THAN CARTILAGE REVISION	SYMPTOMATIC CARTILAGE LOOSENING	SYMPTOMATIC CARTILAGE HYPERTROPHY	REOPERATION FOR CARTILAGE REVISION	CONVERSION TO TKA	ARTHRITIS *	OPEN KNEE SURGERY FOR OTHER THAN CARTILAGE REVISION	FAILURES	FAILURE definition
Horas et al. 2003[1]	ACI1	24	6	0	n.a.	0	0	n.a.	1	1	Intraoperative finding of thinned fibrocartilage in the treated defect
	OCT	24	7	0	n.a.	2	0	n.a.	0	0	
Schneider et al. 2003[2]	ACI3	6	1	n.a.	n.a.	0	0	n.a.	0	n.a.	n.a.
	ACI1	6	1	n.a.	n.a.	0	0	n.a.	0	n.a.	
Dozin et al. 2005[3]	ACI1	36	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	1	Lysholm<60
	OCT	36	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0	
Gooding et al. 2006[4]	ACI2	24	8	n.a.	2	n.a.	n.a.	n.a.	n.a.	0	n.a.
	ACI1	24	10	n.a.	13	n.a.	n.a.	n.a.	n.a.	2	
Basad et al. 2010[5]	ACI3	24	n.a.	n.a.	n.a.	1	n.a.	n.a.	n.a.	0	n.a.
	MF	24	n.a.	n.a.	n.a.	1	n.a.	n.a.	n.a.	1	
Valauwe et al. 2011[6-8]	ACI1	60	n.a.	7	n.a.	n.a.	n.a.	n.a.	n.a.	7	Persistent or recurrent symptoms, requiring cartilage revision surgery
	MF	60	n.a.	1	n.a.	n.a.	n.a.	n.a.	n.a.	10	
Gudas et al. 2012[9,10]	OCT	124.8	0	n.a.	n.a.	4	0	7	5	4	Persistent or recurrent symptoms, requiring cartilage revision surgery
	MF	124.8	1	n.a.	n.a.	10	0	14	3	11	
Lim et al. 2012[11]	MF	80.4	3	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	OCT	69.6	1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	
	ACI1	62.4	2	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	
Shive et al. 2015[12,13]	AMIC	60	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	MF	60	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	
Clavé et al. 2016[14]	ACI3	24	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	OCT	24	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	
Knutsen et al. 2016[15-17]	ACI1	180	10	0	10	8	6	10	4	17	Lack of healing requiring reoperation
	MF	180	4	0	0	8	3	7	4	13	
Volz et al. 2017[18,19]	AMIC	60	n.a.	n.a.	n.a.	0	1	n.a.	n.a.	n.a.	n.a.
	MF	60	n.a.	n.a.	n.a.	1	0	n.a.	n.a.	n.a.	
Brittberg et al. 2018[20,21]	ACI3	60	n.a.	n.a.	n.a.	0	n.a.	n.a.	n.a.	1	n.a.
	MF	60	n.a.	n.a.	n.a.	2	n.a.	n.a.	n.a.	3	
Kane et al. 2018*[22,23]	ACI3	60	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	MF	60	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	
Solheim et al. 2018[24]	OCT	192	n.a.	n.a.	n.a.	n.a.	1	n.a.	n.a.	n.a.	n.a.
	MF	192	n.a.	n.a.	n.a.	n.a.	3	n.a.	n.a.	n.a.	
Barié et al.	ACI3	115.2	n.a.	1	0	3	n.a.	3	0	n.a.	Cartilage revision surgery

2020[25,26]	ACI1	103.2	n.a.	1	1	2	n.a.	1	0	n.a.	
Glasbrenner et al. 2020[27]	AMIC	27	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	MF	27	n.a.	1	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	
Ibarra et al. 2021[28]	ACI3	74	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0	Reoperation
	MF	71	n.a.	2	n.a.	n.a.	n.a.	n.a.	n.a.	2	
Hoburg et al. 2022[29-31]	spheroids	60	n.a.	n.a.	0	n.a.	n.a.	n.a.	n.a.	0	Cartilage injury and persistent pain requiring reoperation
	MF	60	n.a.	n.a.	0	n.a.	n.a.	n.a.	n.a.	4	

Legend:

ACI1: autologous chondrocyte implantation, 1st generation.
ACI2: autologous chondrocyte implantation, 2nd generation.
ACI3: autologous chondrocyte implantation, 3rd generation.
AMIC: autologous matrix-induced chondrogenesis.
MF: microfracture.
n.a.: not available.
OCT: osteochondral transplantation.
Spheroids: chondrospheres (Co.don, produced according to the self-aggregation technique).

When multiple publications are available for the same trial, we have written the author and date of publication of the most recent one and in apex the references of all available publications.
Data describes patients affected by the considered adverse events for each trial arm.

*: knee osteoarthritis conservatively and surgically treated.

Appendix A6: Follow-Up Duration

STUDY	ARMS	MEAN FOLLOW-UP months
Horas et al. 2003[1]	ACI1	24
	OCT	24
Schneider et al. 2003[2]	ACI3	6
	ACI1	6
Dozin et al. 2005[3]	ACI1	36
	OCT	36
Gooding et al. 2006[4]	ACI2	24
	ACI1	24
Basad et al. 2010[5]	ACI3	24
	MF	24
Vanlauwe et al. 2011[6-8]	ACI1	60
	MF	60
Gudas et al. 2012[9,10]	OCT	124.8
	MF	124.8
Lim et al. 2012[11]	MF	80.4
	OCT	69.6
	ACI1	62.4
Shive et al. 2015[12,13]	AMIC	60
	MF	60
Clavé et al. 2016[14]	ACI3	24
	OCT	24
Knutsen et al. 2016[15-17]	ACI1	180
	MF	180
Volz et al. 2017[18,19]	AMIC	60
	MF	60
Brittberg et al. 2018*[20,21]	ACI3	60
	MF	60
Kane et al. 2018[22,23]	ACI3	60
	MF	60
Solheim et	OCT	192

al. 2018[24]	MF	192
Barié et al. 2020[25,26]	ACI3	115.2
	ACI1	103.2
Glasbrenner et al. 2020[27]	AMIC	27
	MF	27
Ibarra et al. 2021[28]	ACI3	74
	MF	71
Hoburg et al. 2022[29-31]	spheroids	60
	MF	60
MEAN FOLLOW-UP PER TRIAL ARM	MF: 79.6 AMIC: 49 OCT:78.4 ACI1: 61.9 ACI2: 24 ACI3: 51.9 SPHEROIDS: 60	
MEAN FOLLOW-UP	57.8	

When multiple publications are available for the same trial, we have written the author and date of publication of the most recent one and in apex the references of all available publications.

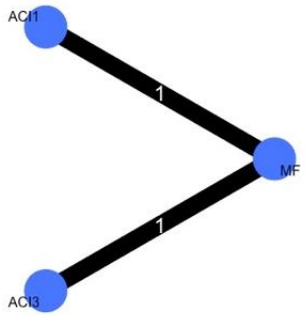
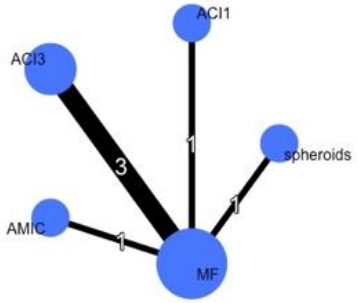
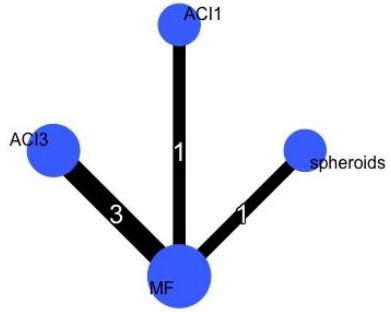
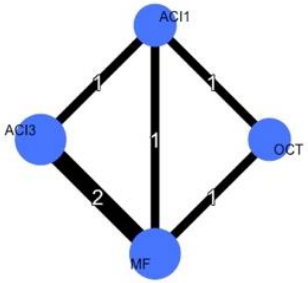
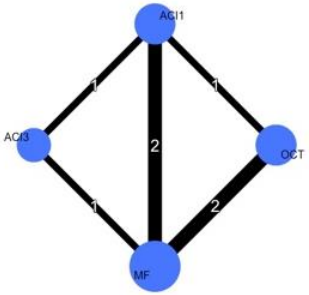
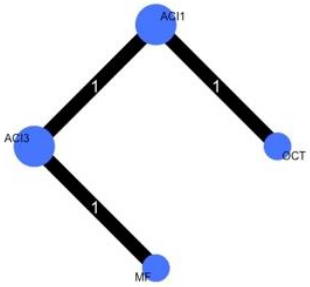
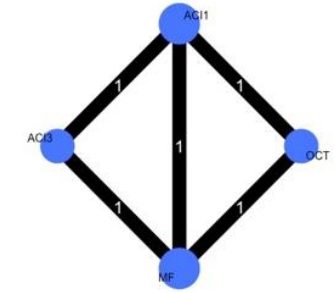
Appendix A7: Functional scores

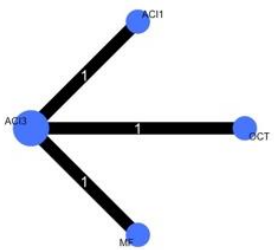
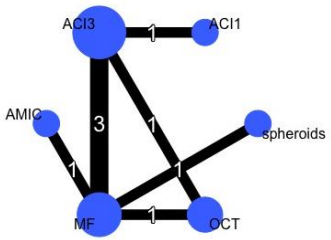
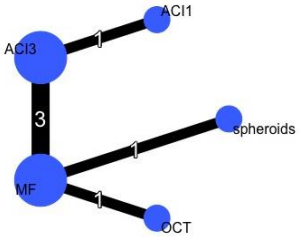
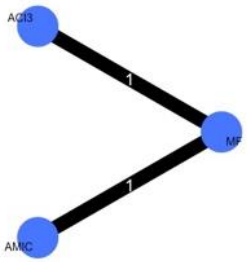
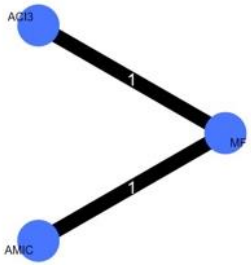
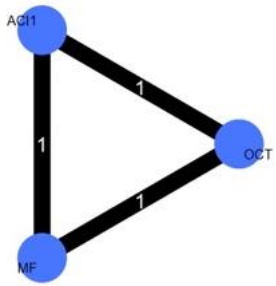
	KOOS	LYSHOLM	TEGNER	IKDC	HSS	MODIFIED CINCINNATI	WOMAC
Horas et al. 2003[1]		X	X				
Schneider et al. 2003[2]				X			
Dozin et al. 2005[3]		X					
Gooding et al. 2006[4]						X	
Basad et al. 2010[5]		X	X				
Vanlauwe et al. 2011[6-8]	X						
Gudas et al. 2012[9,10]				X	X		
Lim et al. 2012[11]		X	X		X		
Shive et al. 2015[12,13]							X
Clavé et al. 2016[14]				X			
Knutsen et al. 2016[15-17]		X					
Volz et al. 2017[18,19]						X	
Brittberg et al. 2018[20,21]	X			X		X	
Kane et al. 2018[22,23]	X			X			
Solheim et al. 2018[24]	X						
Barié et al. 2020[25,26]		X	X	X			
Glasbrenner et al. 2020[27]	X			X			
Ibarra et al. 2021[28]	X	X	X	X			
Hoburg et al. 2022[29-31]	X			X			
OVERALL	7/19 (36.8%)	7/19 (36.8%)	5/19 (26.3%)	9/19 (47.3%)	2/19 (10.5%)	3/19 (15.8%)	1/19 (5.2%)

When multiple publications are available for the same trial, we have written the author and date of publication of the most recent one and in apex the references of all available publications.

SECTION B

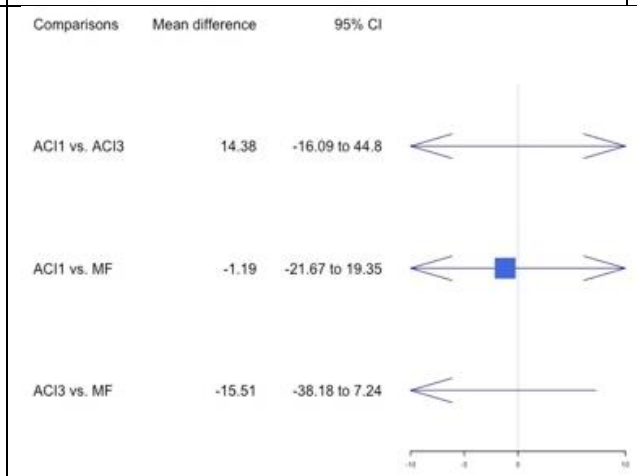
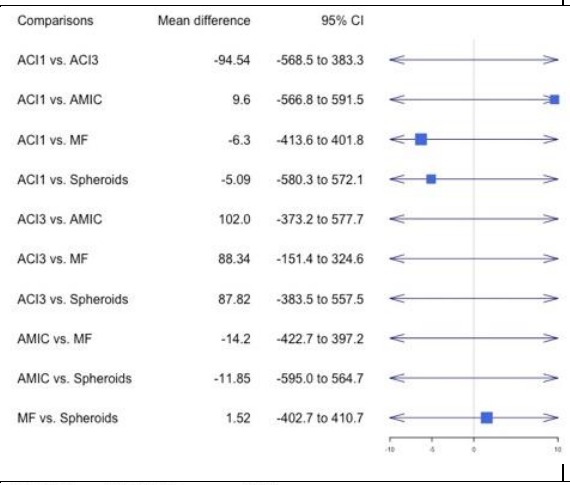
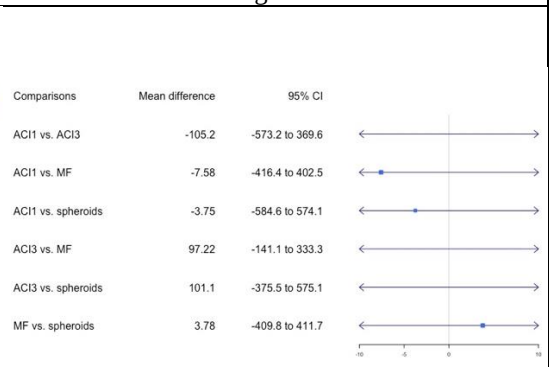
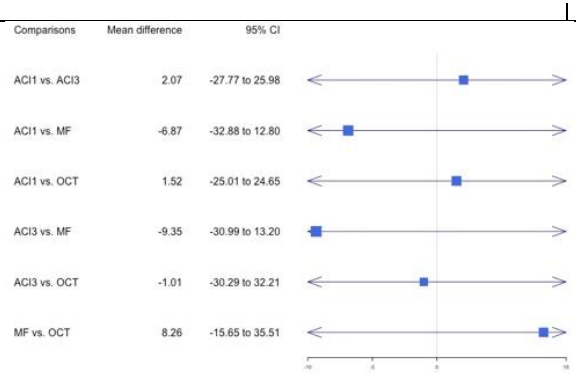
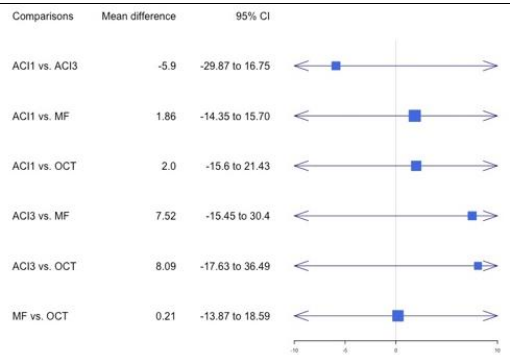
Appendix B1: Net-plots for the clinical scores

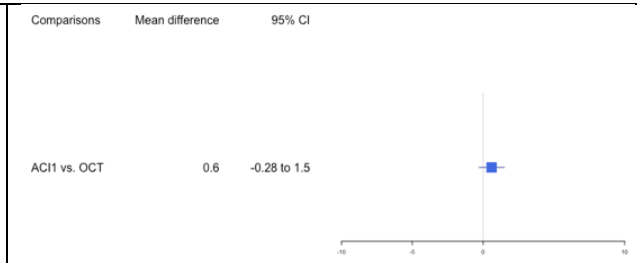
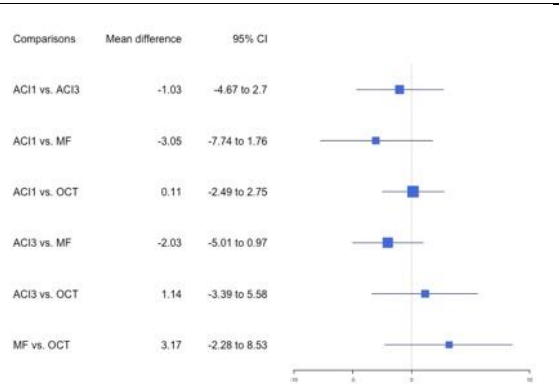
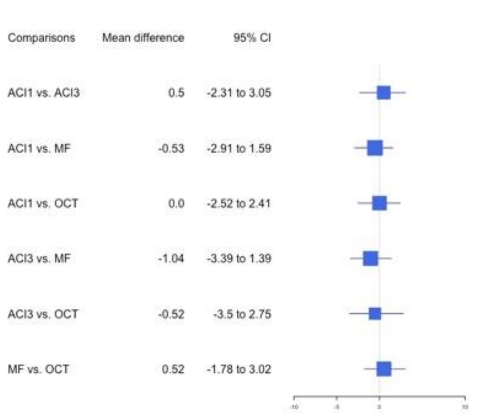
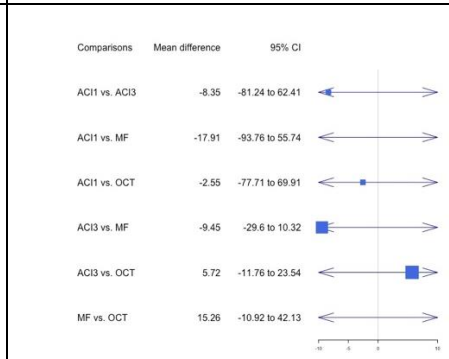
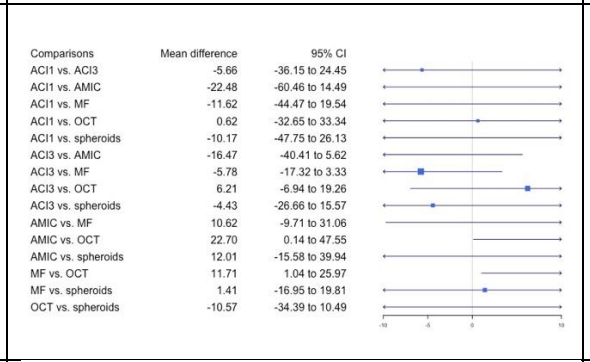
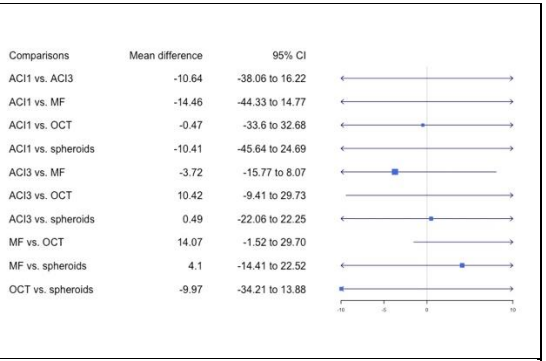
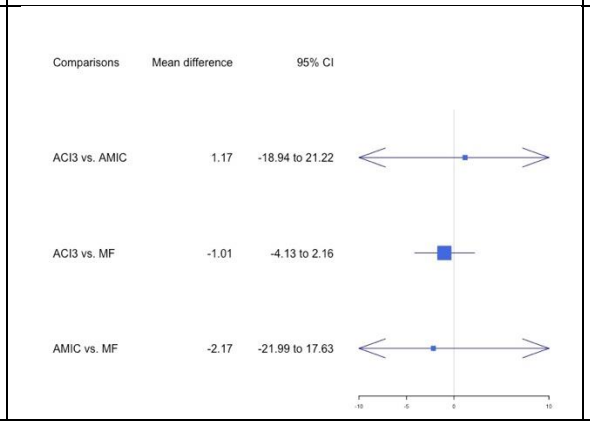
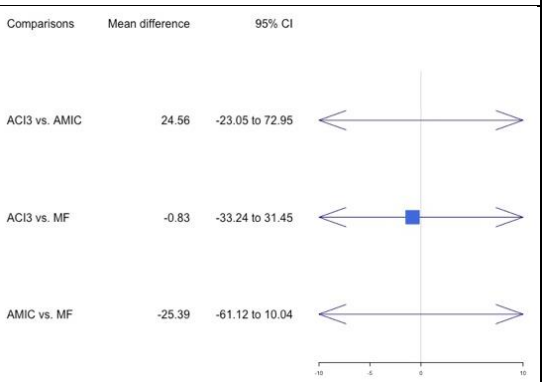
	Short-term	Mid-term	Long-term
KOOS			
Lysholm			
Tegner			

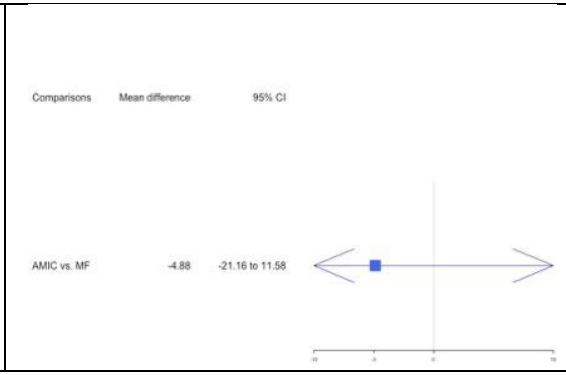
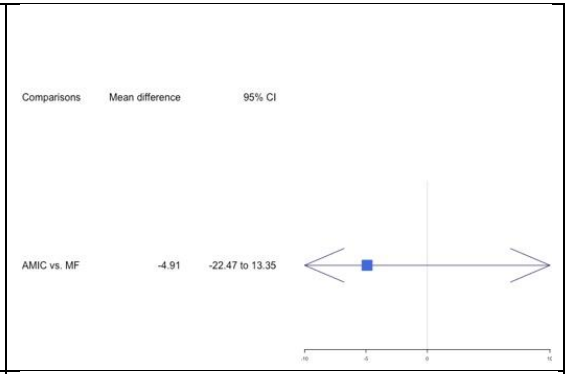
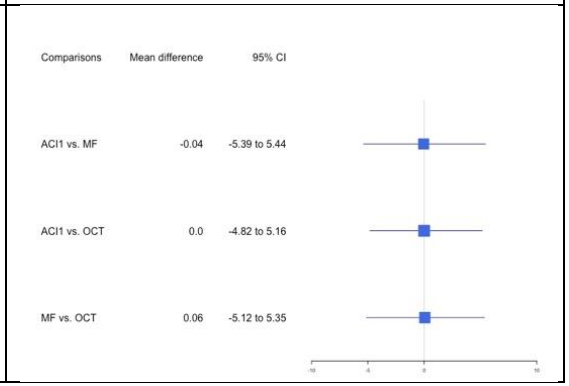
IKDC			
Cincinnati			
WOMAC			
HSS			

Network diagrams showing the direct comparisons (lines) among treatments (nodes). The size of the nodes is proportional to the sample size of each treatment. The thickness of the lines is proportional to the number of available studies, indicated by the white number.

Appendix B2: Forest plots for the clinical scores

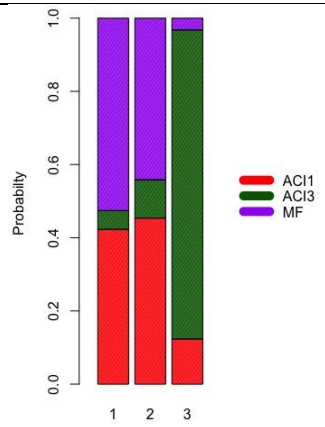
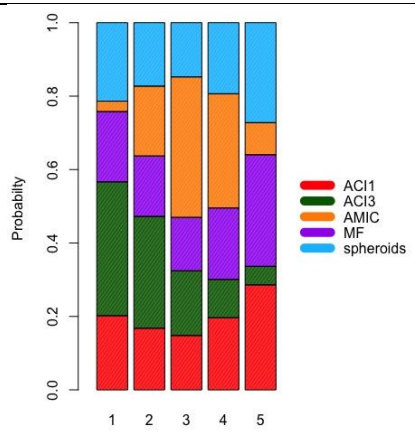
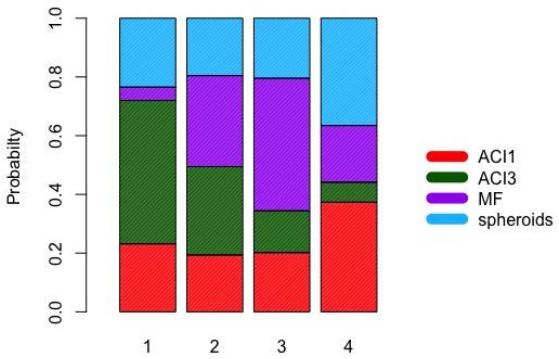
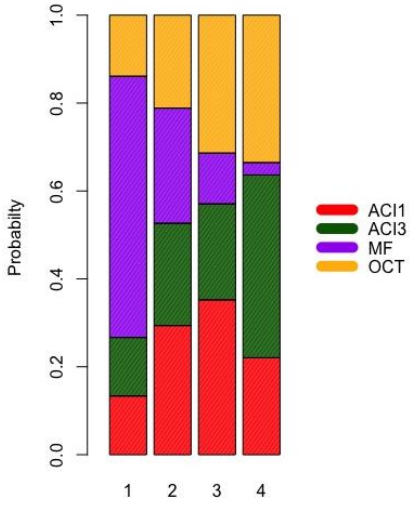
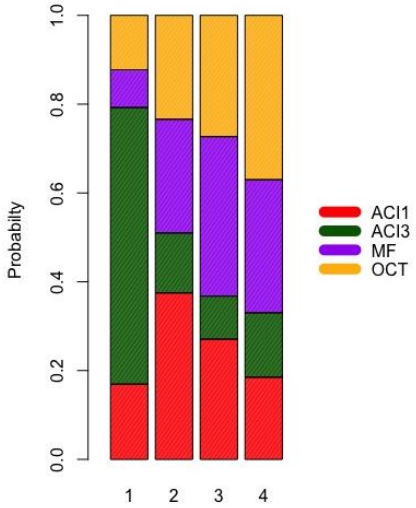
	Short-term	Mid-term	Long-term
KOOS			
Lysholm			

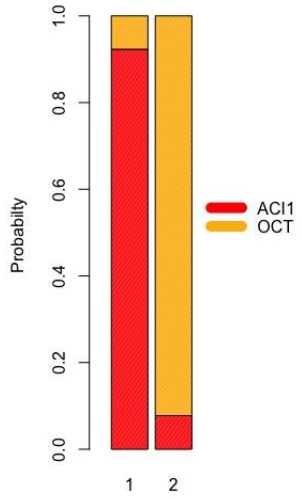
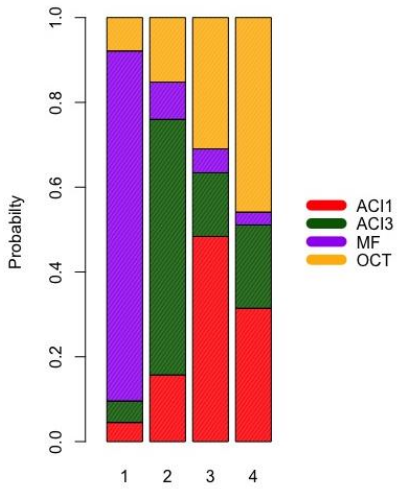
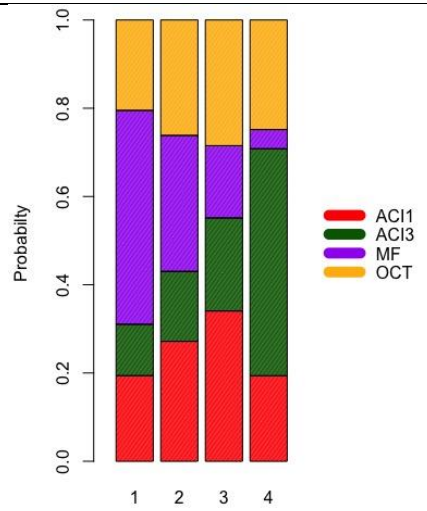
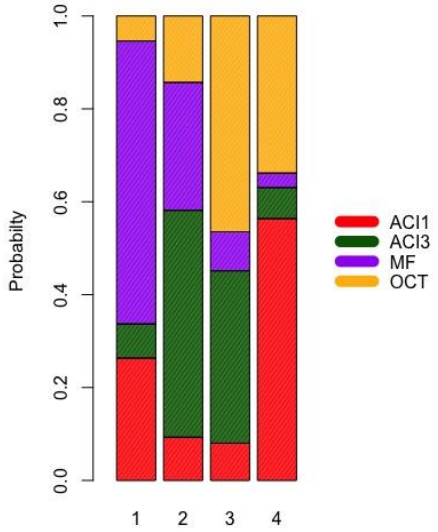
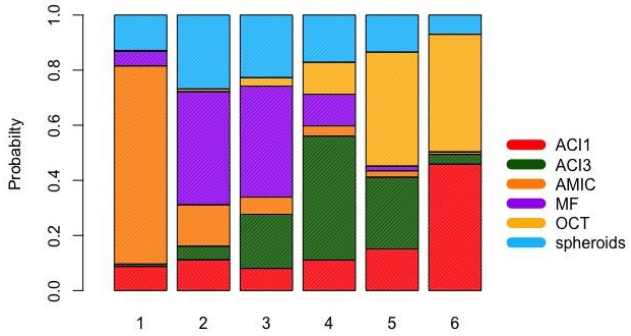
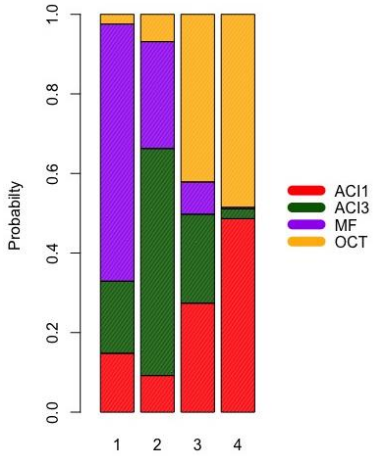
Tegner			
IKDC			
Cincinnati			

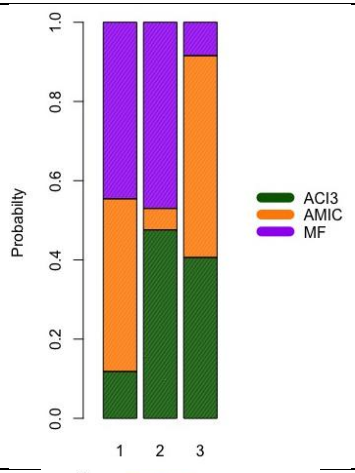
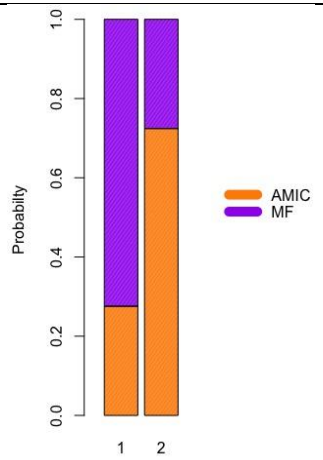
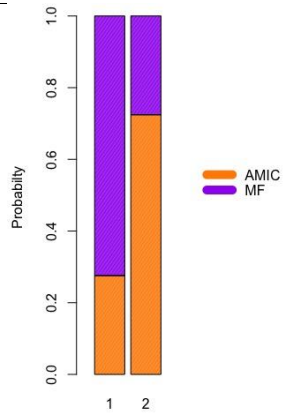
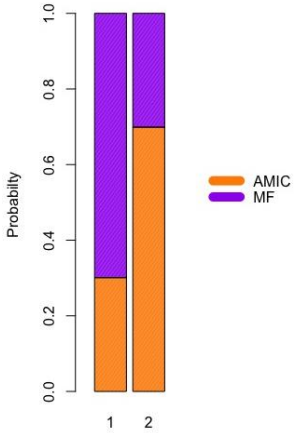
WOMAC			
HSS			

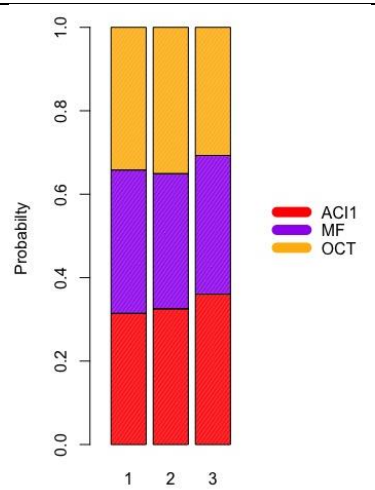
There were no available studies using Lysholm at short-term.
In forest plots, no difference for the mean differences corresponds to 0.
The I2 for KOOS: at short-term 25%, mid-term 8%, long-term 10%.
The I2 for Lysholm: at mid-term 16%, long-term 15%.
The I2 for Tegner: at short-term 50%, mid-term 17%, long-term 18%.
The I2 for IKDC: at short-term 16%, mid-term 2%, long-term 2%.
The I2 for Cincinnati: at mid-term 22%, long-term 25%.
The I2 for WOMAC: at mid-term 49%, long-term 50%.
The I2 for HSS: at long-term 30%.

Appendix B3: Rankogram for the clinical scores

	Short-term	Mid-term	Long-term
KOOS			
Lysholm			

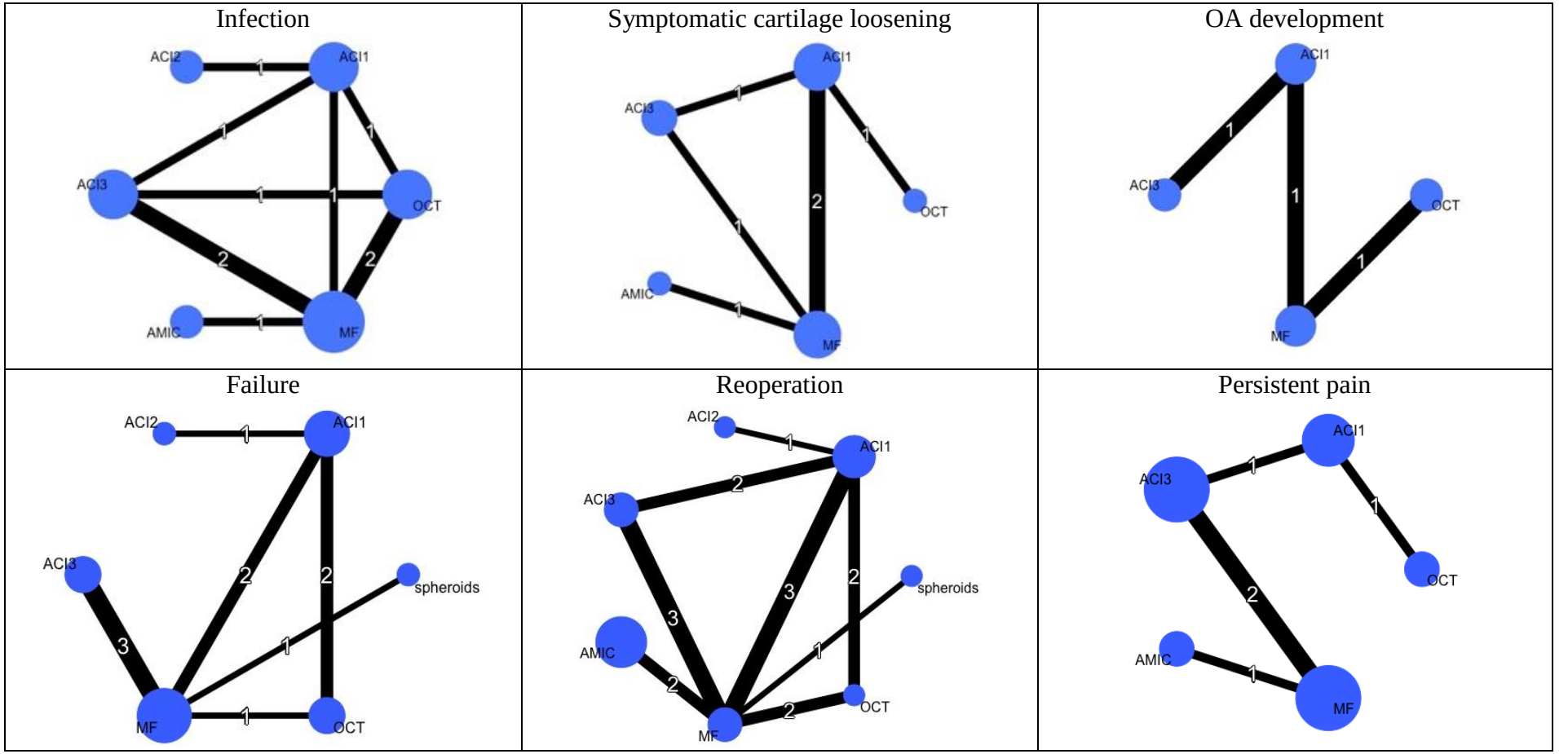
Tegner	 Probabilty 0.0 0.2 0.4 0.6 0.8 1.0 1 2 ACI1 OCT	 Probabilty 0.0 0.2 0.4 0.6 0.8 1.0 1 2 3 4 ACI1 ACI3 MF OCT	 Probabilty 0.0 0.2 0.4 0.6 0.8 1.0 1 2 3 4 ACI1 ACI3 MF OCT
IKDC	 Probabilty 0.0 0.2 0.4 0.6 0.8 1.0 1 2 3 4 ACI1 ACI3 MF OCT	 Probabilty 0.0 0.2 0.4 0.6 0.8 1.0 1 2 3 4 5 6 ACI1 ACI3 AMIC MF OCT spheroids	 Probabilty 0.0 0.2 0.4 0.6 0.8 1.0 1 2 3 4 ACI1 ACI3 MF OCT

Cincinnati			
WOMAC			

HSS		

The ranking diagrams were generated for each outcome using the surface under the cumulative ranking curve (SUCRA) and mean ranks.

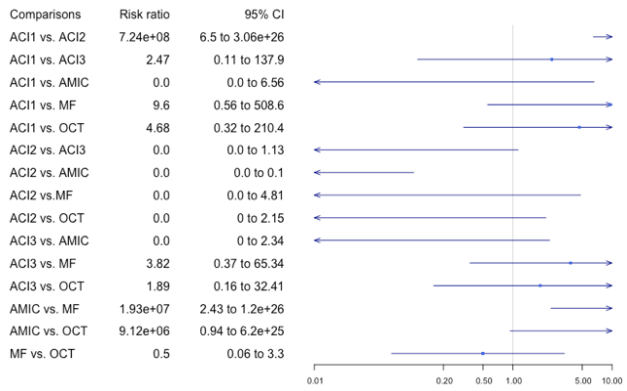
Appendix B4: Net-plots for the adverse events



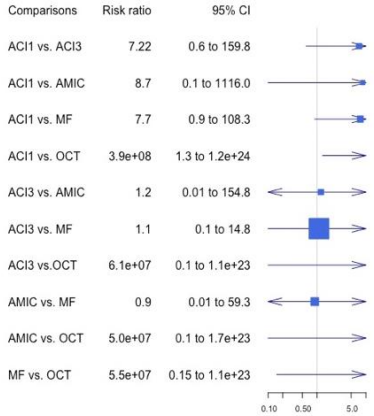
Network diagrams showing the direct comparisons (lines) among treatments (nodes). The size of the nodes is proportional to the sample size of each treatment. The thickness of the lines is proportional to the number of available studies, indicated by the white number.

Appendix B5: Forest plots for the adverse events

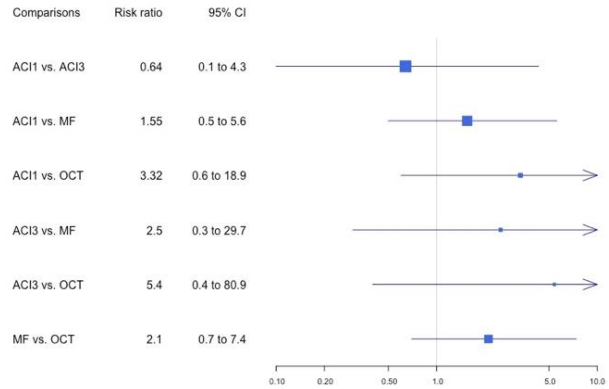
Infection



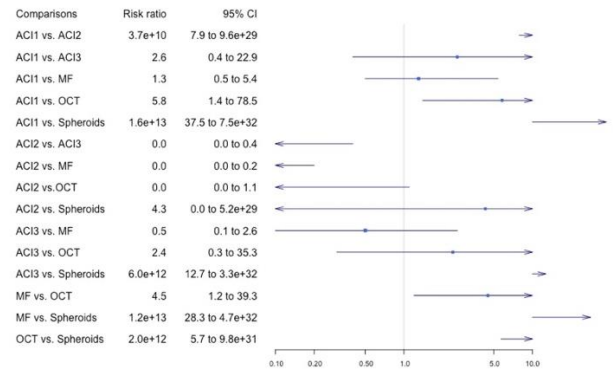
Symptomatic cartilage loosening



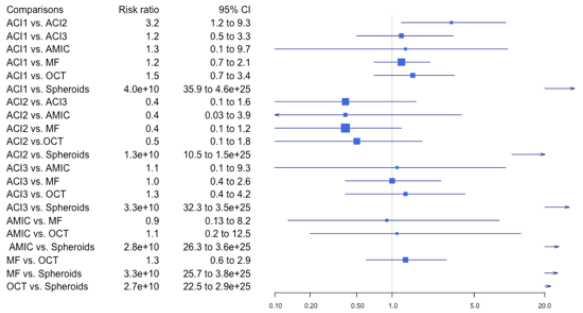
OA development



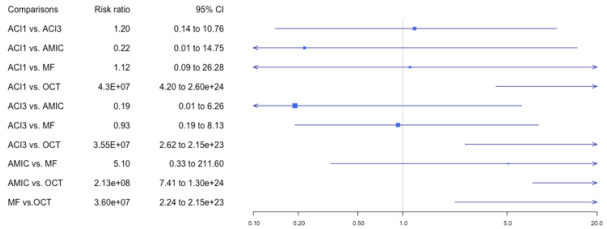
Failure



Reoperation

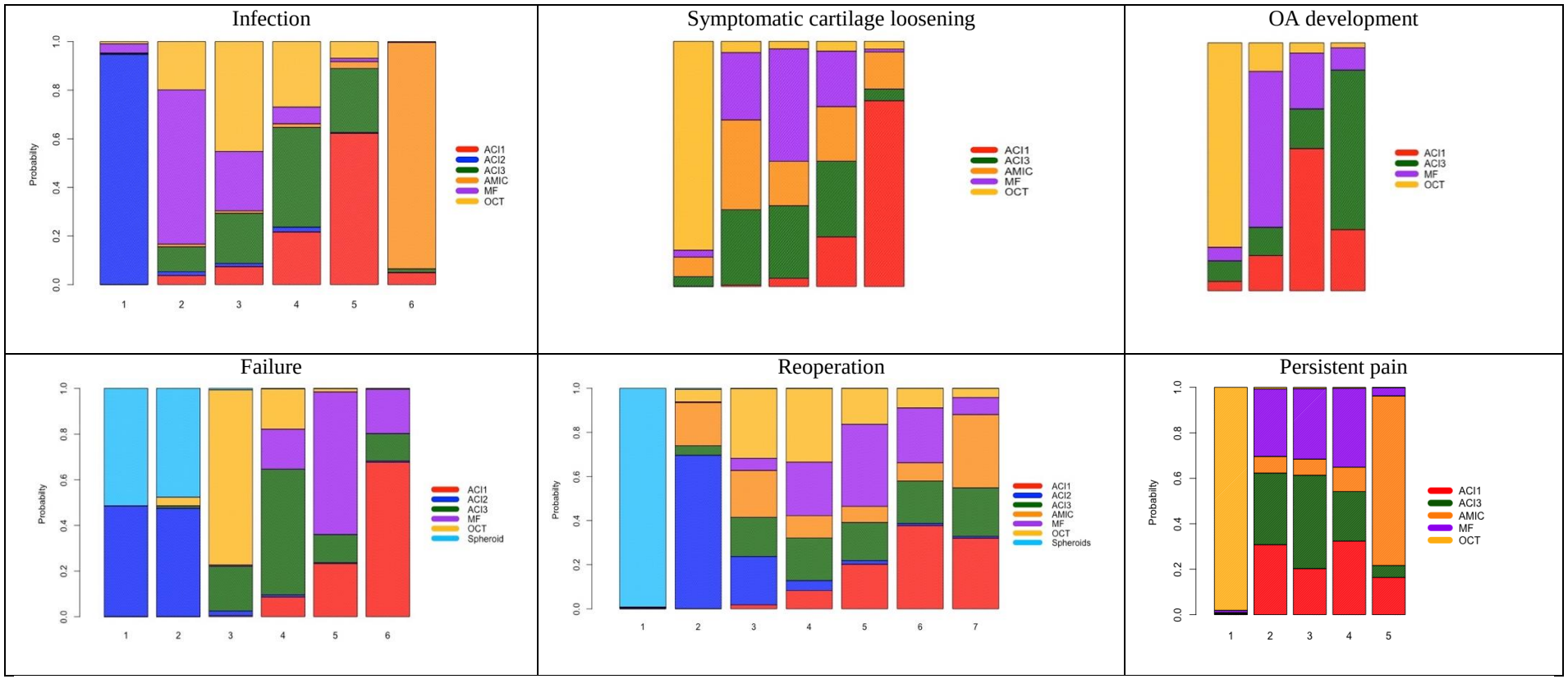


Persistent Pain



In forest plots, no difference for the relative risk corresponds to 1.
The I2 for: infection was 23%, symptomatic cartilage loosening was 29%, for osteoarthritis development was 17%, for failure, reoperation and persistent pain was 0%.

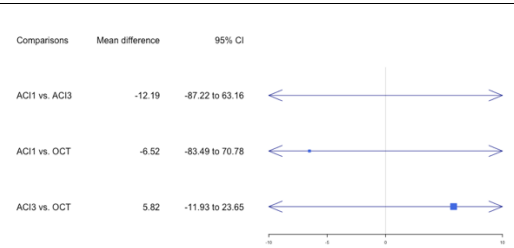
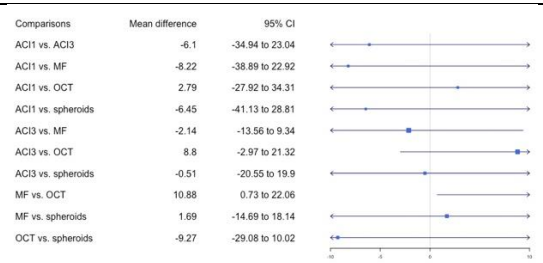
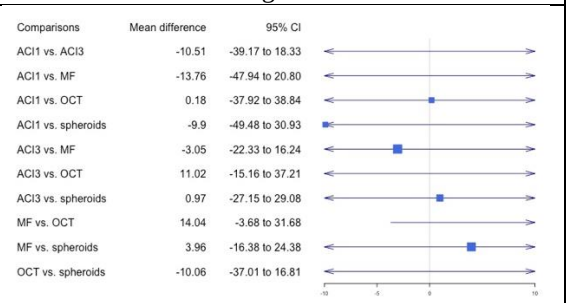
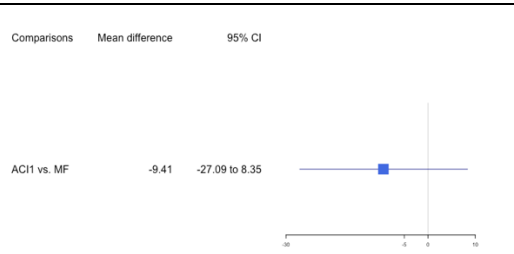
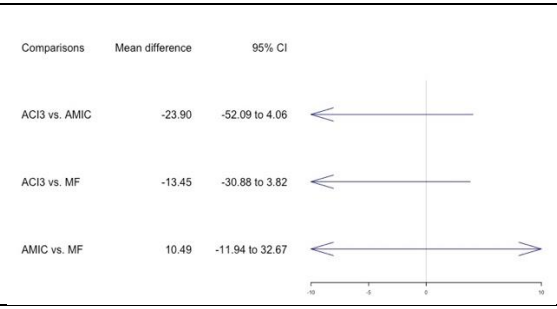
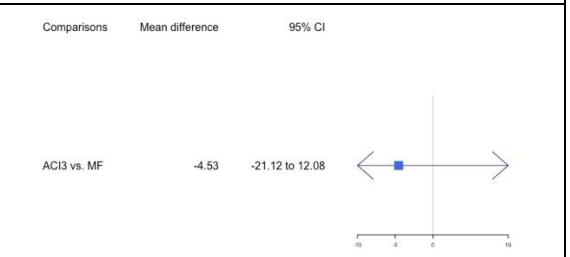
Appendix B6: Rankogram for the adverse events

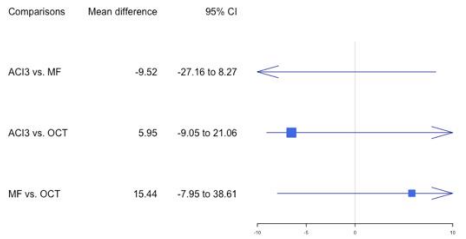
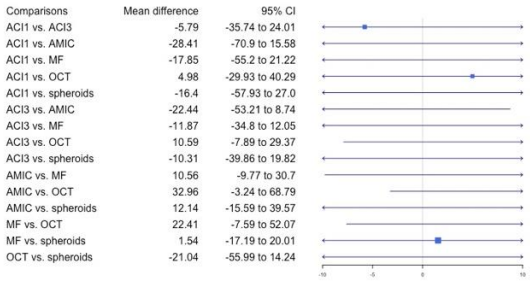
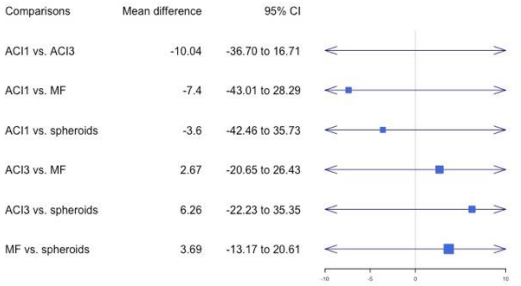
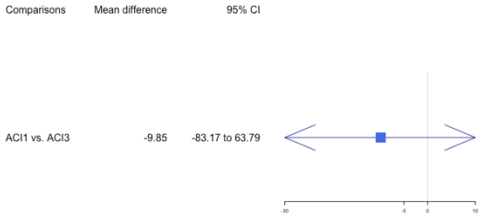
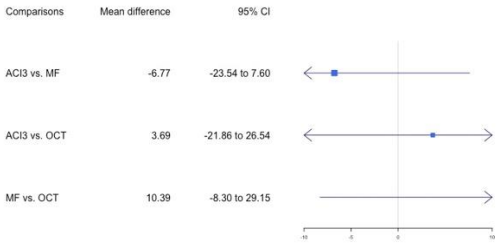
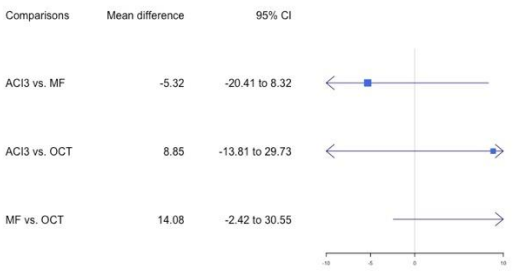


The ranking diagrams were generated for each outcome using the surface under the cumulative ranking curve (SUCRA) and mean ranks.

Appendix B7: Forest plots of the subgroup analysis, for the clinical scores

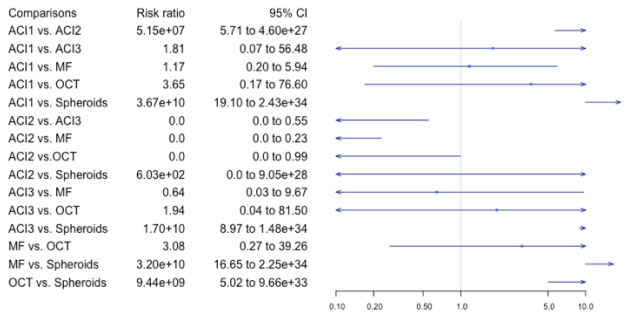
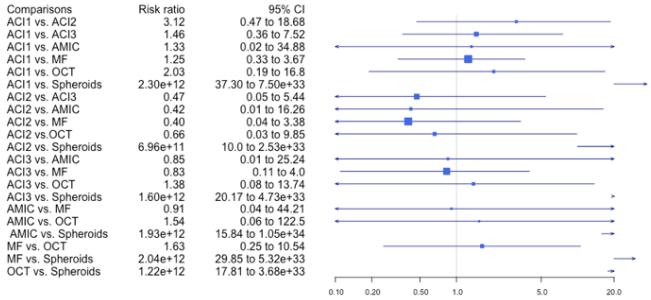
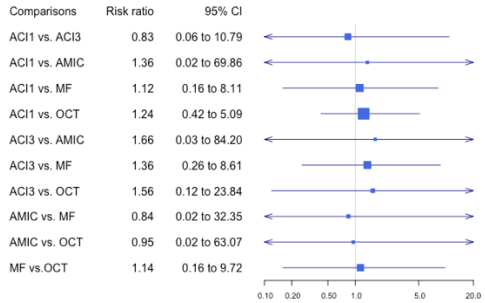
IKDC

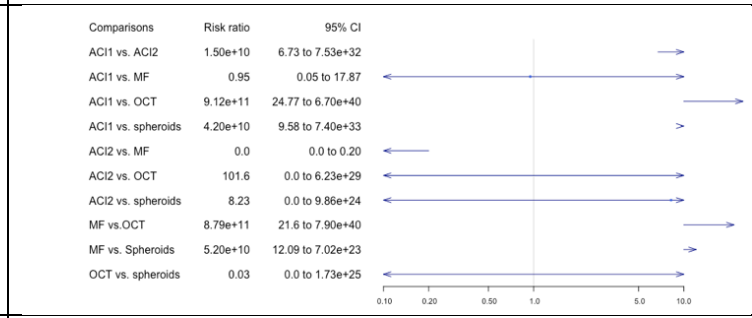
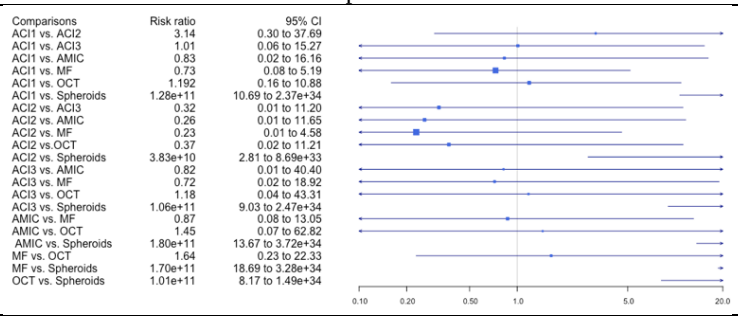
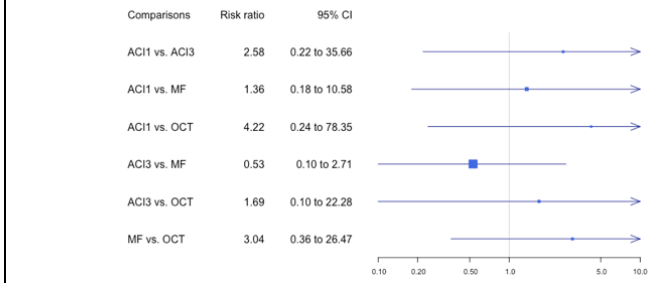
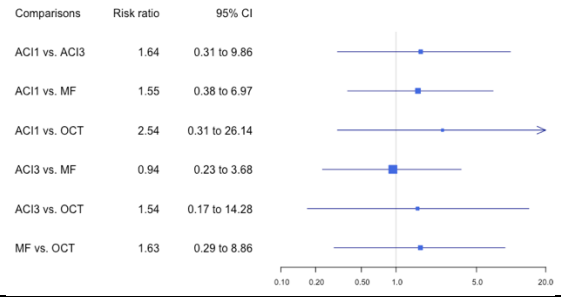
	Short-term	Mid-term	Long-term
OCD included			
OCD excluded			

	Short-term	Mid-term	Long-term
Prior surgery included			
Prior surgery excluded			

In forest plots, no difference for the mean differences corresponds to 0.

Appendix B8: Forest plots of the subgroup analysis, for the adverse events

	Failure	Reoperation
OCD included		
OCD excluded	null	

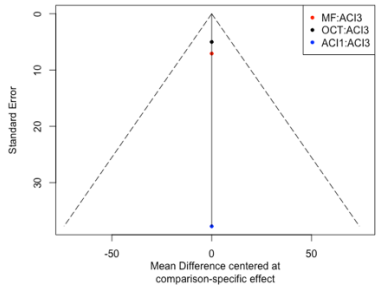
	Failure	Reoperation
Prior surgery included		
Prior surgery excluded		

In forest plots, no difference for the relative risk corresponds to 1.

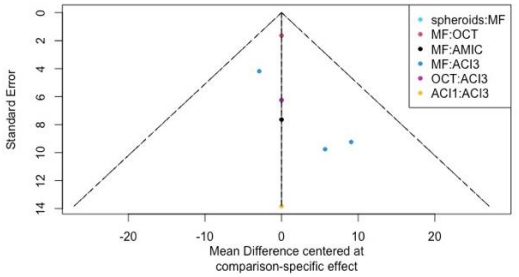
Appendix B9: Funnel plots

For primary outcomes

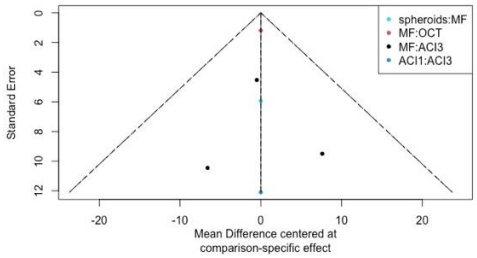
Funnel plot IKDC short term



Funnel plot IKDC mid term

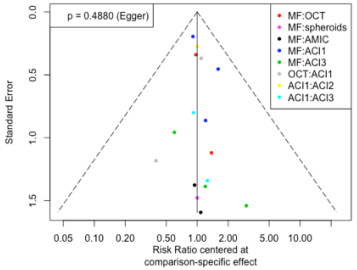


Funnel plot IKDC long term

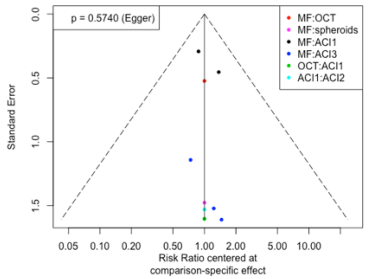


For secondary outcomes

Funnel plot reoperation rate

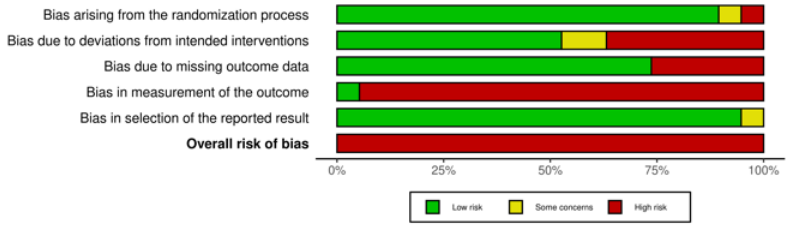


Funnel plot failure rate



SECTION C

Appendix C1: Risk of bias assessment

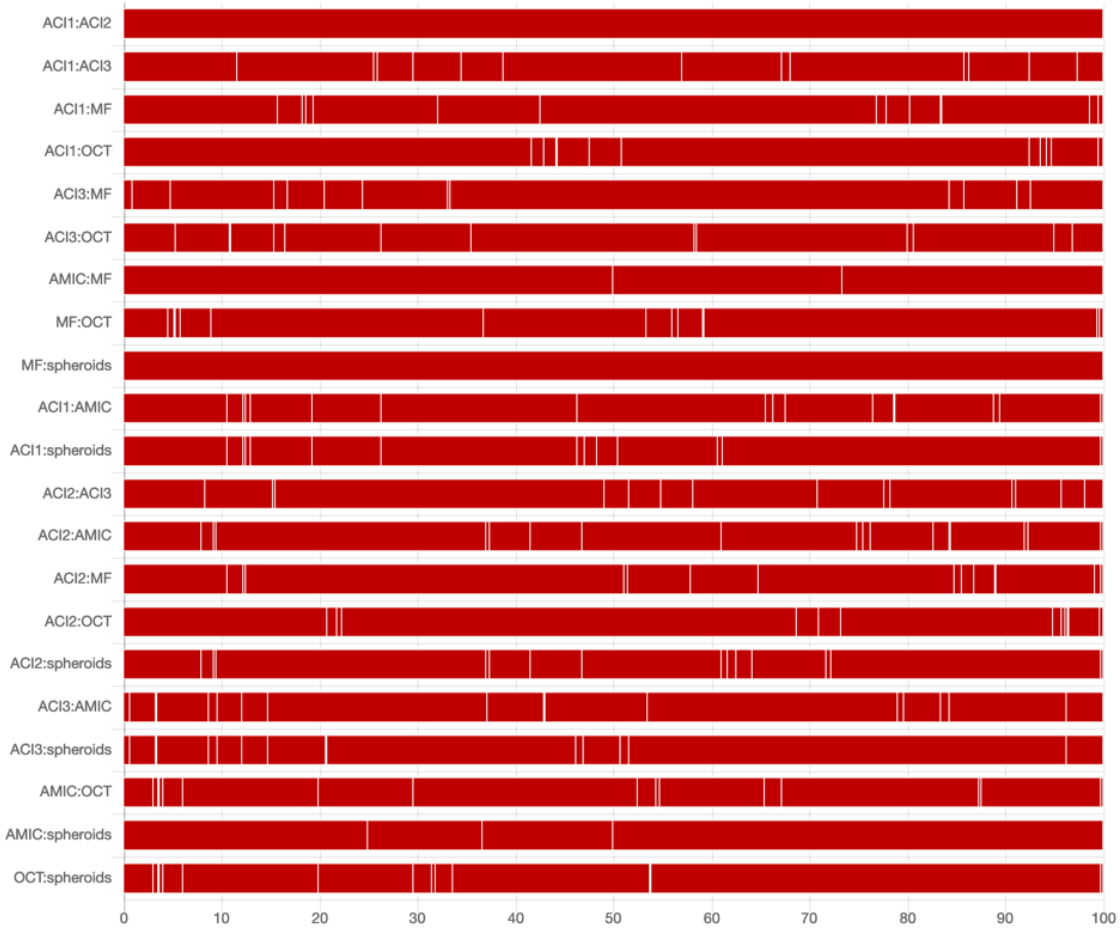


	H (%)	S (%)	L (%)
D1	1/19 (5.2)	1/19 (5.2)	17/19 (89.5)
D2	7/19 (36.8)	2/19 (10.5)	10/19 (52.6)
D3	5/19 (26.3)	0	14/19 (73.7)
D4	18/19 (94.7)	0	1/19 (5.2)
D5	0	1/19 (5.2)	18/19 (94.7)

Legend:
D1: bias arising from the randomization process
D2: bias due to deviations from intended intervention
D3: bias due to missing outcome data
D4: bias in measurement of the outcome
D5: bias in selection of the reported result

L: low risk of bias
H: high risk of bias
S: some concerns

Appendix C2: GRADE



Appendix C3: Pairwise comparison and transitivity

KOOS mid term:

Comparaisons	MF Vs ACI1	MF Vs ACI3	MF Vs AMIC	Spheroids Vs MF
Trials included/total available trials	3/3	1/4	1/3	1/1
Patient included in meta-analysis	88	195	24	97
MD [95% CI]	6.6 [-0.42 ;14.0]	-89.0 [-330.0 ;150.0]	15.0 [-21.0 ;51.0]	-2.0 [-11.0 ;7.0
I^2	-	100.0%	-	-

KOOS long term :

Comparaisons	MF Vs ACI1	MF Vs ACI3	MF Vs Spheroids
Trials included/total available trials	1/3	3/4	1/1
Patient included in meta-analysis	77	178	97
MD [95% CI]	7.1 [-0.39 ;15.0]	-98.0 [-330.0 ;140.0]	-5.2 [-410.0 ;410.0]
I^2	-	100.0%	-

Lysholm mid term :

Comparaisons	ACI3 Vs ACI1	MF Vs ACI1	OCT Vs ACI1	MF Vs ACI3	OCT Vs MF
Trials included/total available trials	1/2	1/3	1/3	2/4	1/3
Patient included in meta-analysis	21	80	40	84	40

MD [95% CI]	22.0 [-18.0 ;60.0]	-1.3 [-12.0 ;9.5]	-2.4 [-8.2 ;3.4]	17.0 [-7.9 ;42.0]	-7.1 [-40.0 ;26.0]
I^2	-	-	-	24.5%	-

Lysholm long term :

Comparaisons	ACI3 Vs ACI1	MF Vs ACI1	OCT Vs ACI1	MF Vs ACI3	OCT Vs MF
Trials included/total available trials	1/2	2/3	1/3	1/4	2/3
Patient included in meta-analysis	16	80	50	35	92
MD [95% CI]	20.0 [-13.0 ;52.0]	-5.1 [-22.0 ;9.9]	0.68 [-6.3 ;7.7]	3.0 [-18.0 ;24.0]	2.9 [-3.3;9.1]
I^2	-	27.4%	-	-	63.2%

Tegner long term :

Comparaisons	ACI3 Vs ACI1	MF Vs ACI1	OCT Vs ACI1	MF Vs ACI3	OCT Vs MF
Trials included/total available trials	1/2	1/3	1/3	1/4	1/3
Patient included in meta-analysis	16	43	40	35	47
MD [95% CI]	1.1 [-2.0 ;4.2]	0.0005 [-1.6 ;1.6]	-0.3 [-1.9 ;1.4]	1.8 [-0.03 ;3.6]	-0.30 [-1.6;1.0]
I^2	-	-	-	-	-

IKDC mid term :

Comparaisons	ACI3 Vs ACI1	MF Vs ACI3	OCT Vs ACI3	MF Vs AMIC	OCT Vs MF	MF Vs Spheroids
Trials included/total available trials	1/2	3/3	1/3	1/4	1/3	1/1
Patient included in	21	195	47	24	57	97

meta-analysis						
MD [95% CI]	6.1 [-21.0 ;33.0]	7.6 [-3.7 ;21.0]	-11.0 [-23.0 ;1.5]	-10.0 [-25.0 ;4.5]	-10.0 [-14.0;-7.3]	-1.6 [-14.0 ;11.0]
I^2	-	0.0%	-	-	-	-

IKDC long term :

Comparaisons	ACI3 Vs ACI1	MF Vs ACI3	OCT Vs MF	MF Vs Spheroids
Trials included/total available trials	1/2	3/3	1/3	1/1
Patient included in meta-analysis	16	178	57	97
MD [95% CI]	10.0 [-13.0 ;34.0]	3.8 [-8.1 ;16.0]	-14.0 [-16.0;-12.0]	-4.0 [-16.0 ;7.8]
I^2	-	0.0%	-	-

Infections rate :

Comparaisons	ACI3 Vs ACI1	ACI3 Vs MF	ACI3 Vs OCT	AMIC Vs MF	ACI2 Vs ACI1	OCT Vs MF	ACI1 Vs OCT	ACI1 Vs MF
Trials included/total available trials	1/2	2/4	1/3	1/3	1/1	2/3	1/3	1/3
Patient included in meta-analysis	21	108	55	30	68	100	40	80
RR [95% CI]	2.5^{e}-9 [3.9^{e}-22;1.7^{e}+04]	0.45 [0.009;9.5]	1.3^{e}-9 [2.2^{e}-22;7.3^{e}+03]	1.3^{e}-9 [2.8^{e}-22;6.2^{e}+03]	7.3^{e}-10 [1.5^{e}-22;3.6^{e}+03]	2.3 [0.27 ;27.0]	1.0 [0.03 ;33.0]	2.6^{e}-9[3.5^{e}-22 ;1.9^{e}+04]
I^2	-	41.1%	-	-	-	0.0%	-	-

Symptomatic cartilage loosening rate :

Comparaisons	ACI3 Vs MF	ACI3 Vs ACI1	AMIC Vs MF	ACI1 Vs OCT	ACI1 Vs MF
Trials included/total available trials	1/4	1/2	1/3	1/3	2/3
Patient included in meta-analysis	48	21	30	40	80
RR [95% CI]	2.8 [0.16;51.0]	0.37 [0.021;6.5]	1.1 [0.033;34.0]	4.7^{e}-10 [7.0^{e}-24 ;3.1^{e}+04]	0.061[0.0015 ;0.75]
I^2	-	-	-	-	23.5%

Total failure rate :

Comparaisons	ACI3 Vs MF	ACI2 Vs ACI1	ACI1 Vs MF	ACI1 Vs OCT	OCT Vs MF	Spheroids Vs MF
Trials included/total available trials	3/4	1/1	2/3	2/3	1/3	1/1
Patient included in meta-analysis	252	68	192	84	60	102
RR [95% CI]	1.9 [0.38;11.0]	1.0^{e}-12 [1.1^{e}-29;9.2^{e}+04]	0.86 [0.23 ;3.3]	1.3^{e-}10 [1.1^{e}-36 ;0.10]	0.31 [0.11 ;0.93]	6.7e-13 [5.7^{e}-30;7.8^{e}+04]
I^2	0.0%	-	0.0%	0.0%	-	-

Total reoperation rate :

Comparaisons	ACI3 Vs ACI1	ACI3 Vs MF	AMIC Vs MF	ACI2 Vs ACI1	OCT Vs MF	ACI1 Vs OCT	ACI1 Vs MF	Spheroids Vs MF
Trials included/total available trials	2/2	3/3	2/3	1/1	2/3	2/3	3/3	1/1
Patient included in meta-analysis	41	252	77	68	102	80	240	102
RR [95% CI]	0.81[0.19 ;3.2]	1.0 [0.26 ;3.7]	1.1 [0.14 ;8.4]	0.31[0.18 ;0.54]	0.59 [0.18 ;1.7]	0.94[0.26 ;2.6]	0.75[0.37 ;1.6]	7.1e-13 [1.1^{e}-29;4.7^{e}+04]
I^2	0.0%	0.0%	0.0%	-	0.0%	0.0%	0.0%	-

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