# Appendix 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p.1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	p.3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	p.5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p.6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	p.4, p.6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	p.6, p.7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p.6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendices 2 and 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	p.6, p.7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	p.7, p.8

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Appendix 4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	p.8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	p.8, p.9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	p.8, p.9

#### Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	p.7. p.8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	p.8, p.9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	p.9, figure 1
Study characteristics	cteristics 18 For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.		p.9, p.10, Table 1
Risk of bias within studies 19 Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).		Appendix 5	
Results of individual studies       20       For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.		p.10, p.11, p.12,13, Figures 2 and 3, Appendices 7 to 17	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures 2 and 3, Appendices

			7, 8, 10, 16 and 17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Appendix 7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	p.14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	p.15
FUNDING	•	·	
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	p.4, p.9

#### Appendix 2. Search strategy for EMBASE database.

- 1/ Low back pain
- 2/ Intervertebral disk disease
- 3/ Intradiscal
- 4/ Methylene
- 5/ Tumor necrosis factor antibody
- 6/ Interleukin 6
- 7/ Ethanol
- 8/ Ozone
- 9/ Polyacrylonitrile
- 10/ Chymopapain
- 11/ Collagenase
- 12/ Platelet-rich plasma cell
- 13/ Stem cell
- 14/ glucorticoid
- 15/ OR 3-14
- 16/ 1 AND 2 AND 15

#### Appendix 3. Search strategy for MEDLINE database.

- 1/ "low back pain" [MH]
- 2/ "low back pain" [TW]
- 3/"lumbago"[TW]
- 4/"mechanical low back pain"[TW]
- 5/ "low back ache"[TW]
- 6/"lower back pains"[TW]
- 7/"pain, low back"[TW]
- 8/"low backache"[TW]
- 9/"low back pains"[TW]
- 10/"back pain, low"[TW]
- 11/"backache, low"[TW]
- 12/ "lower back pain"[TW]
- 13/ "back pain, lower"[TW]
- 14/"postural low back pain"[TW]
- 15/ "recurrent low back pain"[TW]
- 16/ "Low back pain (finding)"[TW]
- 17/"Low back syndrome"[TW]
- 18/"Lumbalgia"[TW]
- 19/ "Low back pain (disorder)"[TW]

20/"Lumbar pain"[TW]

#### 21/ 1-20/OR

22/"Intervertebral Disk"[All Fields]

23/ "Intervertebral Disc"[All Fields])

24/"Intervertebral Disc Degeneration"[Mesh]

#### 25/ 22-24/OR

26/"Interleukin-6"[Mesh] OR

27/"anti il6"[All Fields]) OR

28/glucocorticoid[All Fields] OR

29/glucocorticoid\*[All Fields] OR

30/"Glucocorticoids"[Mesh] OR

31/ Stem cell\*[All Fields] OR

32/ "Stem Cells" [Mesh] OR

33/"platelet-rich plasma"[Mesh] OR

34/"platelet-rich"[All Fields]

35/ "platelet-rich plasma"[All Fields] OR

36/ Collagenase[All Fields] OR

37/ collagenase\*[All Fields])OR

38/ "Collagenases"[Mesh])) OR

39/"chymopapain"[MeSH Terms] OR

40/"chymopapain"[All Fields] OR

- 41/"polyacrylonitrile"[Supplementary Concept] OR
- 42/ "polyacrylonitrile"[All Fields] OR
- 43/"ozone"[MeSH Terms] OR
- 44/"ozone"[All Fields] OR
- 45/"ethanol"[All Fields]) OR
- 46/ "Ethanol" [Mesh])) OR
- 47/ il6[All Fields]) OR
- 48/ "anti tnf" [All Fields] OR
- 49/ "Tumor Necrosis Factor-alpha" [Mesh] OR
- 50/ methylene[All Fields] OR
- 51/ "Intervertebral Disc Chemolysis" [Mesh]) OR
- 52/ intradiscal[All Fields] OR
- 53/ intradiskal[All Fields]) OR
- 54/ "disk injection"[All Fields] OR
- 55/ "disc injection" [All Fields] OR
- 56/"disc therapy"[All Fields] OR
- 57/26-56/OR
- 58/21 AND 25 AND 57

### Appendix 4. Extraction form.

#### PART ONE: REVIEW, REVIEWER AND STUDY INFORMATION

Study ID	
(Surname Year:	
as it appears in	
RevMan)	
N. 64	
Name of the	
reviewer	
	Other:
Date form	
completed	
First author	
First author	
Article title	
Year of	
publication	
Fusication	
Journal	
Volume	
Issue	
Page number	
Language of	French
publication	
	English
	Other:
Type of report	<b>Full</b>

	Abstract
	Unpublished
Contact details	 
(email)	

#### PART TWO: STUDY ELIGIBILITY

#### METHODS

	Descriptions as stated in report/paper	Location in text
Aim of study (as stated in the trial report)		
Study Design	Parallel group	
	Cross-over	
	Cluster	
	Factorial	
	Split body	
	Other:	
Number of study arms	2	
	3	
	Other:	
Study centres	Single	
	Multi	
	Unclear	
Study duration	_  months	

Funding source		Yes:	
		No	
		Unclear	
Conflicts of interest		Yes:	
		No	
		Unclear	
Notes	1		I

#### PARTICIPANTS

	Descrip	tion as stated in report/paper	Location in
			text or
			source
Setting		Primary care	
		Secondary care	
		Tertiary care	
		Mixed	
		Unclear	
Country			
Inclusion criteria			
Exclusion criteria			
At least 1 clinical sign consistent with discogenic		Yes:	
syndrome or positive provocative discography		No	
		Unclear	

Consistent IVD lesion on imaging (X-Ray, MRI or CT-scan)     Image: Consistent IVD lesion on imaging (X-Ray, MRI or CT-scan)     Image: CT-scan) <th></th>	
CT-scan)   No   Unclear   Modic 1   Yes	
No   Unclear   Modic 1   Yes	
Modic 1	
Yes	
Yes	
Unclear	
Total number of patients with history of lumbar	
surgery	
Psychosocial Risk factors Low	
Moderate	
High	
Unclear	
Total number of randomised participants       _	
Total number of participants analysed	
Total number of participants lost to follow up       _        (including death)	
(including death)	
Baseline imbalances	
Total number of participants who completed higher       _	
education	
Total number of participants who are on sick leave       _	
Age: mean (SD)         Comparator:  _ _ . _  ( _ . _ )	
Experimental 1:   . _  (  . _ )	
Experimental 2:   . _  (  . _ )	

Sex : n/N (%) females	Comparator:  _ _ / _	
	( _ _ . _)%)	
	Experimental 1:   _/	
	(   %)	
	Experimental 2:   _/	
	(   %)	
Notes		

#### EXPERIMENTAL GROUP

	Description as stated in report/paper	Location in text
Experimental intervention		
Components of the intervention	Contrast	
	Saline	
	Anaesthetics	
	Drug:	
	Device:	
	Other:	
Total volume injected (ml)	ml	
	Unclear	
Number of participants		
randomised		
Number of participants		
analysed		
Number lost to follow-up (and		
reasons)		
Number of IDT	1	
	2	
	<b>□</b> ≥3	

Who delivered the		Radiologists	
intervention?			
		Other	
Was intervention compliance		Yes:	
assessed?			
And if so, how? (includes (a)		No	
compliance of therapists to		Unclear	
intervention protocol (b)			
adherence of participants to			
programme)			
Authorized co-interventions		Analgesics	
(if any)		NSAIDS	
		Other spinal injections	
		Brace	
		Physical therapy	
		Other :	
		Unclear	
Notes	1		1

#### **COMPARATOR GROUP**

	Description as stated in report/paper	Location in text
Comparator intervention	Intradiscal injection	
	Details:	
	Sham procedure	
	Details:	
	Other spinal injection therapy	
	Details:	
	Usual care	
	Details:	

Number of participants		
randomised		
Name have for a state of a second		
Number of participants		
analysed		
Number lost to follow-up (and		
reasons)		
Who delivered the	Radiologists	
intervention?		
	Physician	
	Physiotherapist	
	Nurses	
	Other	
Was intervention compliance	Yes:	
assessed?		
And if so, how? (includes (a)	No	
compliance of therapists to	Unclear	
intervention protocol (b)		
adherence of participants to		
program)		
Authorized co-interventions	Analgesics	
(if any)		
	<b>NSAIDS</b>	
	Other spinal injections	
	Brace	
	Physical therapy	
	Other:	
	Unclear	
Notes		

#### OUTCOMES

#### LOW BACK PAIN

	Multip	le interv	vention					
Tick box if outcome was				CONT	ρητ		SUMMARY ES	TIMATE
reported				CONT	NUL		SUMMART E	
reporteu	Multifa	actorial	_					
	interve	ntion						
	Maria	SD	Total	M	CD	Total	Mean	95%
	Mean	50	Total	Mean	SD	Total		95% confidence
							difference between	interval
								merva
							groups	
LBP								
Type of validated scale								
used for measurement								
( i.e. NRS, VAS.)								
SHORT TERM < 3								
months								
Type of validated scale								
used for measurement								
(i.e. NRS, VAS.)								
MEDIUM TERM≥3								
months and <6 months								
Type of validated scale								
used for measurement								
( i.e. NRS, VAS.)								
LONG TERM $\geq 6$								
months								

#### **ACTIVITY LIMITATIONS**

	Multip	le inter	vention					
Tick box if outcome was reported	Multifa	nctorial	intervention	CONTROL			SUMMARY ESTIMATE	
	Mean	SD	Total	Mean	SD	Total	Mean difference between groups	95% confidence interval
Disability								
Type of validated scale used for measurement (i.e.ODI, RMQDI)								
SHORT TERM < 3 months								
Disability								
Type of validated scale used for measurement (i.e. ODI, RMQDI) MEDIUM TERM ≥ 3 months and < 6 months								
Disability								
Type of validated scale used for measurement (i.e. ODI, RMQDI) LONG TERM ≥6 months								

#### **EMPLOYMENT STATUS**

Multiple intervention	INTERVENTION		CONTRO	)L	SUMMARY ESTIMATE	
Tick box if outcome was reported	Total	Number of	Total	Number of	Odds	95%
	number	person	number	person	ratio	confidence
	of	months	of	months		interval
	patients		patients			
	on sick		on sick			
	leave		leave			
Rate of patients on sick leave     SHORT TERM < 3 months						
Rate of patients on sick leave						
MEDIUM TERM, ≥ 3 months and <6 months						
Rate of patients on sick leave						
LONG TERM ≥ 6 months						

#### MAJOR ADVERSE EVENT

Multiple intervention	INTERVENTION		CONTROI	_	SUMMARY ESTIMATE		
Tick box if outcome was reported	TotalNumber ofnumberpersonof majormonthsadverseevent		TotalNumbernumberof personnof majormonthsadverseevent		Odds ratio	95% confidence interval	
Rate of all major adverse     event							
Rate of major bleeding							

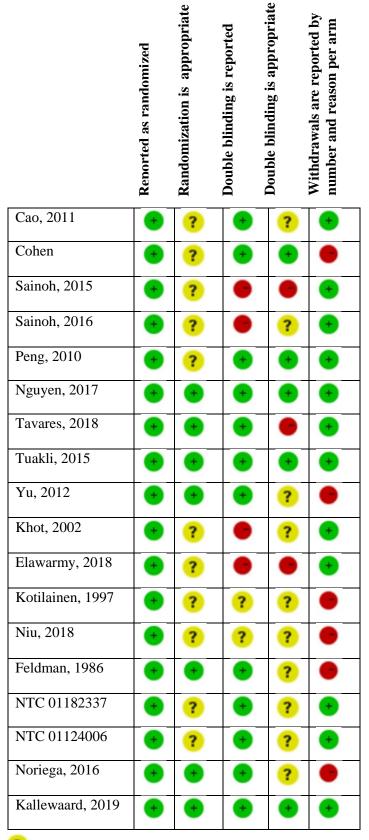
Rate of neurological			
complication			
Rate of serious infections			
Rate of death			
NB: briefly outline how			
participants' major adverse			
event were recorded i.e.			
recorded daily or monthly-			
prospective, retrospective			

#### MINOR ADVERSE EVENT

Multiple intervention	INTERVEN'	TION	CONTROL		SUMMA ESTIMA	
Tick box if outcome was	Total	Number of	Total number	Number of	Odds	95%
reported	number of	person	of minor	person	ratio	confidenc
	minor	months	adverse event	months		e interval
	adverse					
	event					
Rate of over all adverse						
events						
Rate of minor bleeding						
Rate of acute pain per-						
procedure						
Rate of vasovagal						
reaction						
Rate of skin infections						

Rate of IVD narrowing			
Rate of IVD			
calcifications			
NB: Briefly outline how			
participants' minor			
adverse event were			
recorded i.e. recorded			
daily or monthly-			
prospective,			
retrospective			

#### Appendix 5. Risk of bias within studies, using the JADAD scale.





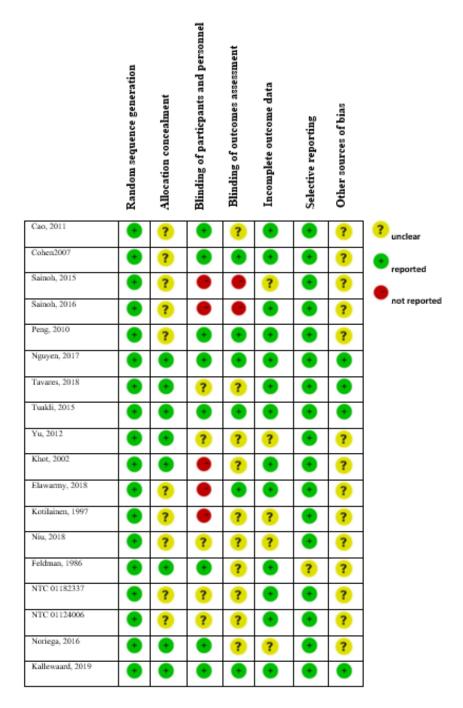


# Appendix 6. Reason for exclusion of full-text reviewed studies.

Title	Author	Year	Reason for exclusion
Prospective and randomized study in patients with low back pain or sciatic pain with ozone therapy treatment	Ansede Alonso J.C.	2007	Uncontrolled
Advances in cellular therapies: Clinical trial on lumbar degenerative disease	Ardura Aragón F.	2017	Not Randomized
Single-blind randomised controlled trial of chemonucleolysis and manipulation in the treatment of symptomatic lumbar disc herniation.	Burton	2007	ID under general anesthesia and assessment of effectiveness for leg pain
Sciatica: treatment with intradiscal and intraforaminal injections of steroid and oxygen- ozone versus steroid only.	Galluci	2007	ID and foraminal injection, assessment for leg pain only
Dexamethasone is not superior to placebo for treating lumbosacral radicular pain.	Haimovic	1986	Intervention reported other than ID therapy
[Experiences with intradisk injection treatment with chymopapain and collagenase]	Hedtmann	1986	Review
Radiopaque Gelified Ethanol Application in Lumbar Intervertebral Soft Disc Herniations: Croatian Multicentric Study.	Houra	2017	Uncontrolled
Intradiskal methylene blue treatment for diskogenic low back pain.	Levi	2014	Uncontrolled
CT-guided ozone/steroid therapy for the treatment of degenerative spinal diseaseeffect of age, gender, disc pathology and multi-segmental changes	Oder	2008	Not randomized
Anti-inflammatory Chitosan/Poly-gamma-glutamic acid nanoparticles control inflammation while remodeling extracellular matrix in degenerated intervertebral disc.	Teixeira	2016	Condition reported other than LBP
[Evaluation of 5 years of nucleolysis treatment in 150 cases of radiculalgia and 10 cases of lumbago of disk origin].	Troisier	1982	Condition reported other than LBP
Treatment of the lumbar disc herniation with intradiscal and intraforaminal injection of oxygen- ozone	Zhang	2013	Off the topic
A randomized, double-blind study to compare low- dose with standard-dose chymopapain in the treatment of herniated lumbar intervertebral discs	Benoist	1993	Assessment of effectiveness for leg pain only
Kinesiatrics and oxygen-ozone therapy for lumbosacral disc-root compression	Romeo A	2001	Intervention reported other than ID therapy
Adipose-derived stem cells improve the viability of nucleus pulposus cells in degenerated intervertebral discs.	Song	2015	Intervention reported other than ID therapy
Five-year results from chemonucleolysis with chymopapain or collagenase: a prospective randomized study.	Wittenberg	2001	Assessment of effectiveness for leg pain only
Implication of Two Doses of O2-O3 Upon the Pain Alleviation in Patients With Low Back Pain	Zarief		Duplicate
Variable Approaches of Intradiscal O3-O2 Injection	Zarief		Refused to communicate data
Efficacy of Intradiscal Injection of Viable Placental Tissue Extract in Subjects With One or Two Level,	Parker		Refused to communicate data because of limited ownership rights

Symptomatic Lumbar Intervertebral Disc Degeneration			
Treatment of Discogenic Back Pain	Caire		Study stopped early
Safety, Tolerability and Efficacy of YH14618 in Patients With Degenerative Disc Disease	Young-Joon Kwon		Awaiting assessment
Implication of Two Doses of O2-O3 Upon the Pain Alleviation in Patients With Low Back Pain			Duplicate
Safety and Preliminary Efficacy Study of Mesenchymal Precursor Cells (MPCs) in Subjects With Lumbar Back Pain	Brown		Refused to communicate data because of limited ownership rights
Treatment of Degenerative Disc Disease With Allogenic Mesenchymal Stem Cells (MSV)			Duplicate
Clinical Trial of YH14618 in Patients With Degenerative Disc Disease	Su Youn Nam		Awaiting assessment
A Study of SI-6603 in Patients With Lumbar Disc Herniation	Seikagaku Corporation		Awaiting assessment
Backache and sciatica. A report of 90 patients treated by intradiscal injection of chymopapain (discase).	Grahams	1974	ID under general anesthesia
Chemonucleolysis. A preliminary report on a double blind study comparing chemonucleolysis and intradiscal administration of hydrocortisone in the treatment of backache and sciatica.	Grahams	1975	ID under general anesthesia, duplicate
Intradiscal steroid: a prospective double blind clinical trial	Simmons	1992	No response

#### Appendix 18. Risk of bias within studies, using the revised Cochrane Risk of Bias tool.



# Appendix 8a. Forest plot for pain, comparing intervertebral disc therapy (IDT) of corticosteroid versus placebo: sensitivity analysis.

	Exp	eriment	tal	0	Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.1.1 Short-term									
Nguyen 2017	36.5	22.8	65	50.3	28.75	63	36.2%	-0.53 [-0.88, -0.18]	-
Tavares 2020	3.7	2.4	21	6.6	2	24	32.7%	-1.30 [-1.95, -0.65]	
Yu 2012	4.28	1.4	23	6.72	0.43	22	31.1%	-2.29 [-3.06, -1.53]	
Subtotal (95% CI)			109			109	100.0%	-1.33 [-2.34, -0.32]	◆
Heterogeneity: Tau <sup>2</sup> :	= 0.70; C	hi² = 18	.32, df:	= 2 (P =	0.0001)	); l <sup>2</sup> = 89	3%		
Test for overall effect	: Z = 2.58	8 (P = 0.	010)						
1.1.2 Intermediate-te	erm								
Cao 2011	1.75	0.88	80	6.9	1.18	40	0.0%	-5.17 [-5.94, -4.41]	
Nguyen 2017	50.5	26.12	64	43.9	26.1	61	51.2%	0.25 [-0.10, 0.60]	<b>+</b>
Yu 2012	5.5	1	23	6.9	0.43	22	48.8%	-1.77 [-2.47, -1.07]	
Subtotal (95% CI)			87			83	100.0%	-0.74 [-2.72, 1.25]	
Heterogeneity: Tau <sup>2</sup> :	= 1.97; C	hi <b>²</b> = 25	.69, df:	= 1 (P <	0.0000	1); I <sup>z</sup> = 9	36%		
Test for overall effect	: Z = 0.73	8 (P = 0.	47)						
1.1.3 Long-term									
Cao 2011	2.1	0.97	80	6.95	1.08	40	0.0%	-4.78 [-5.51, -4.06]	
Khot 2004	0	0.92	46	0	1.48	52	0.0%	0.00 [-0.40, 0.40]	
Nguyen 2017	54.4	24.09	63	42	25.51	62	55.3%	0.50 [0.14, 0.85]	
Yu 2012	6.39	1.54	23	6.67	0.58	22	44.7%	-0.23 [-0.82, 0.35]	
Subtotal (95% CI)			86			84	100.0%	0.17 [-0.54, 0.88]	◆
Heterogeneity: Tau <sup>2</sup> :	= 0.21; C	hi <b>r</b> = 4.3	36, df =	1 (P = 0)	l.04); I²÷	= 77%			
Test for overall effect	: Z = 0.47	7 (P = 0.	64)	-					
								-	-4 -2 0 2 4
									-4 -2 U 2 4 Favours [experimental] Favours [control]
									ravours (experimental) ravours (control)

#### Appendix 8b. Forest plot for activity limitations, comparing IDT of corticosteroid versus

#### placebo: sensitivity analysis.

	Exp	erimenta	al 👘		Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
1.2.1 Short-term									
Nguyen 2017	38.4	17.12	67	41	17.04	68	35.5%	-0.15 [-0.49, 0.19]	-
Tavares 2020	39.91	11.24	21	40.93	15.262	24	33.2%	-0.07 [-0.66, 0.51]	-+-
Yu 2012	32.1	7.91	23	46.7	4.94	22	31.3%	-2.16 [-2.91, -1.42]	
Subtotal (95% Cl)			111			114	<b>100.0</b> %	-0.76 [-1.85, 0.34]	
Heterogeneity: Tau <sup>2</sup> =	= 0.85; Ch	i² = 24.59	9, df = 2	?(P ≤ 0.	00001); P	<sup>2</sup> = 92%			
Test for overall effect	: Z = 1.35	(P = 0.18	)						
1.2.2 Intermediate-te	erm								
Cao 2011	13.13	2.65	80	37.65	12.28	40	0.0%	-3.30 [-3.87, -2.73]	
Tavares 2020	39.875	11.28	21	40.94	15.293	24	50.7%	-0.08 [-0.66, 0.51]	
Yu 2012	40.9	8.75	23	53	8.01	22	49.3%	-1.42 [-2.08, -0.76]	
Subtotal (95% CI)			44			46	100.0%	-0.74 [-2.05, 0.57]	
Heterogeneity: Tau <sup>2</sup> =	= 0.79; Ch	i <sup>z</sup> = 8.84,	df = 1	(P = 0.0	03); <b>I<sup>2</sup> =</b> 8	9%			
Test for overall effect	: Z = 1.10	(P = 0.27	)						
1.2.3 Long-term									
Cao 2011	15.23	3.66	80	39.1	12.965	40	0.0%	-2.95 [-3.49, -2.42]	
Khot 2004	2.3	16.87	46	3.4	13.92	52	0.0%	-0.07 [-0.47, 0.33]	
Nguyen 2017	43.4	19.62	67	40.5	20.19	68	60.1%	0.14 [-0.19, 0.48]	<b>+</b>
Tavares 2020	39.85	11.397	21	40.94	15.4	24	20.0%	-0.08 [-0.66, 0.51]	
Yu 2012	49.2	9.53	23	51	7.11	22	20.0%	-0.21 [-0.80, 0.38]	
Subtotal (95% CI)			111			114	100.0%	0.03 [-0.23, 0.29]	<b>♦</b>
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Ch	i <sup>z</sup> = 1.22,	df = 2	(P = 0.5	4); I <sup>z</sup> = 09	6			
Test for overall effect	: Z = 0.22	(P = 0.82	)						
Heterogeneity: Tau <sup>z</sup> = Test for overall effect				(P = 0.5	4); I² = 09	6			

-4 -2 Ó 2 4 Favours [experimental] Favours [control]

#### Appendix 9a. Forest plot for pain at short term, comparing IDT of etanercept versus

#### placebo.

	Expe	rimen	tal	C	ontrol		:	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Cohen 2007	5.5	3.05	30	3.5	2.2	6	44.7%	0.67 [-0.23, 1.56]	+
Sainoh 2016	4	6.57	30	7.1	6.29	30	55.3%	-0.48 [-0.99, 0.04]	-=-
Total (95% CI)			60			36	100.0%	0.03 [-1.08, 1.15]	+
Heterogeneity: Tau <sup>2</sup> =	0.51; Ch	j <sup>2</sup> = 4.7	72, df =	1 (P =	0.03);	l <sup>2</sup> = 799	%		-4 -2 0 2 4
Test for overall effect:	Z = 0.06	(P = 0	.95)						Favours [experimental] Favours [control]

#### Appendix 9b. Forest plot for activity limitations at short term, comparing IDT of

#### etanercept versus placebo.

	Exp	eriment	tal	С	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Cohen 2007	36.8	19	30	21	8.9	6	43.7%	0.86 [-0.04, 1.77]	
Sainoh 2016	39.8	78.24	30	53	41.9	30	56.3%	-0.21 [-0.72, 0.30]	
Total (95% CI)			60			36	100.0%	0.26 [-0.78, 1.30]	-
Heterogeneity: Tau <sup>2</sup> =				1 (P = 0	.04); I	² = 76%			-4 -2 0 2 4
Test for overall effect:	Z = 0.49	(P = 0.	62)						Favours [experimental] Favours [control]

#### Appendix 10a. Forest plot for pain at short term, comparing IDT of tocilizumab versus

#### placebo.

	Expe	rimen	tal	Co	ontro	d l		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Sainoh 2015	6.5	1.4	30	7.5	1.4	30	100.0%	-0.71 [-1.23, -0.18]	
Total (95% CI) Heterogeneity: Not ap Test for overall effect:		(P = 0	30 .008)			30	100.0%	-0.71 [-1.23, -0.18]	-2 -1 0 1 2 Favours [experimental] Favours [control]

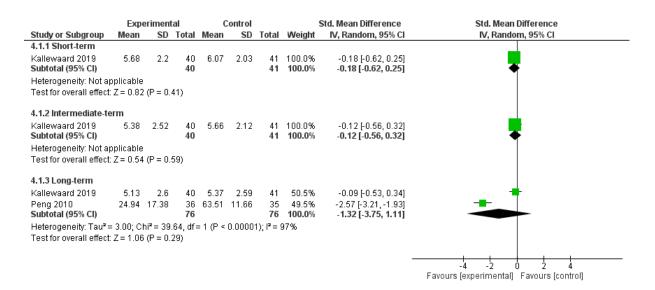
### Appendix 10b. Forest plot for activity limitations at short term, comparing IDT of

#### tocilizumab versus placebo.

	Expe	rimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Sainoh 2015	32	22.7	30	51	15.4	30	100.0%	-0.97 [-1.50, -0.43]	
Total (95% CI)			30			30	100.0%	-0.97 [-1.50, -0.43]	◆
Heterogeneity: Not ap Test for overall effect:		(P = 0	.0004)						-2 -1 0 1 2 Favours [experimental] Favours [control]

#### Appendix 11a. Forest plot for pain at short, intermediate and long terms, comparing IDT

#### of methylene blue versus placebo.



#### Appendix 11b. Forest plot for activity limitations at short, intermediate and long terms,

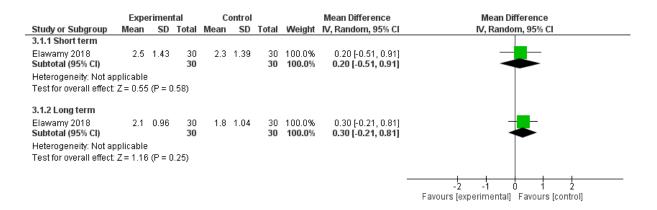
#### comparing IDT of methylene blue versus placebo.

	Exp	eriment	al	0	ontrol		5	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
4.2.1 Short-term									
Kallewaard 2019 Subtotal (95% CI)	36.53	16.67	40 <b>40</b>	41.54	18.43	41 41	100.0% <b>100.0</b> %	-0.28 [-0.72, 0.16] - <b>0.28 [-0.72, 0.16]</b>	-
Heterogeneity: Not ap	oplicable								-
Test for overall effect:	•		21)						
4.2.2 Intermediate-te	erm								
Kallewaard 2019 Subtotal (95% CI)	37.76	17.99	40 40	39.1	16.94	41 41	100.0% <b>100.0</b> %	-0.08 [-0.51, 0.36] - <b>0.08 [-0.51, 0.36]</b>	
Heterogeneity: Not as	oplicable								1
Test for overall effect:	Z = 0.34	(P = 0.3	73)						
4.2.3 Long-term									
Kallewaard 2019	35.18	15.94	40	37.35	18.03	39	50.4%	-0.13 [-0.57, 0.32]	+
Peng 2010	16	11.91	36	48.4	7.77	35	49.6%	-3.18 [-3.89, -2.47]	
Subtotal (95% CI)			76			74	100.0%	-1.64 [-4.63, 1.35]	
Heterogeneity: Tau <sup>2</sup> =	= 4.56; Cl	hi² = 51.	.05, df=	= 1 (P <	0.0000	1); I <b>z</b> = 9	98%		
Test for overall effect:	Z=1.07	(P = 0.)	28)						
								_	

Favours [experimental] Favours [control]

# Appendix 12a. Forest plot for pain, comparing IDT of ozone 40 $\mu g/ml$ versus ozone 30

#### μg/ml.



#### Appendix 12b. Forest plot for activity limitations, comparing IDT of ozone 40 µg/ml

#### versus ozone 30 µg/ml.

	Expe	rimen	tal	C	ontrol		:	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
3.2.1 Short term									
Elawamy 2018 Subtotal (95% Cl)	1.5	0.62	30 <b>30</b>	1.4	0.54	30 <b>30</b>	100.0% <b>100.0</b> %	0.17 [-0.34, 0.68] <b>0.17 [-0.34, 0.68]</b>	
Heterogeneity: Not a	pplicable								
Test for overall effect	:Z=0.66	(P = 0	1.51)						
3.2.2 Long term									
Elawamy 2018 Subtotal (95% Cl)	1.22	0.27	30 <b>30</b>	1.26	0.31	30 <b>30</b>	100.0% <b>100.0</b> %	-0.14 [-0.64, 0.37] - <b>0.14 [-0.64, 0.37]</b>	
Heterogeneity: Not a	pplicable								
Test for overall effect	:Z=0.53	(P = 0	1.60)						
									-2 -1 0 1 2
									Favours [experimental] Favours [control]

# Appendix 13. Forest plot for pain at long term, comparing IDT of ozone versus usual care.

	Expe	rimen	tal	C	ontro	1		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Niu 2018	4.5	1.15	60	6.05	1.21	20	100.0%	-1.32 [-1.87, -0.77]	
Total (95% CI)			60			20	100.0%	-1.32 [-1.87, -0.77]	•
Heterogeneity: Not ap Test for overall effect:		(P < 0	.00001	)					-4 -2 0 2 4 Favours [experimental] Favours [control]

# Appendix 14a. Forest plot for pain at short term, comparing IDT of glycerol versus placebo.

	Exper	imen	tal	Co	ontro	d.		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Kotilainen 1997	49	27	9	50	56	2	100.0%	-0.03 [-1.56, 1.50]	
Total (95% CI)			9			2	100.0%	-0.03 [-1.56, 1.50]	+
Heterogeneity: Not ap Test for overall effect:		(P = 0	.97)						-4 -2 0 2 4 Favours [experimental] Favours [control]

#### Appendix 14b. Forest plot for activity limitations at short term, comparing IDT of glycerol

#### versus placebo.

	Exper	rimen	tal	Co	ontro	d l	:	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Kotilainen 1997	31	20	9	27	1	2	100.0%	0.19 [-1.34, 1.73]	
Total (95% CI)			9			2	100.0%	0.19 [-1.34, 1.73]	• • • • • •
Heterogeneity: Not ap									-4 -2 0 2 4
Test for overall effect:	Z = 0.25	(P = 0	.80)						Favours [experimental] Favours [control]

#### Appendix 15a. Forest plot for pain, comparing IDT of stem cells versus placebo.

Study or Subgroup Mea 9.1.1 Short-term Noriega 2017 8 Subtotal (95% CI)	n SD 3 26		Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Noriega 2017 8	3 26							
	3 26							
000000		12 12	45	25	12 <b>12</b>	100.0% <b>100.0</b> %	0.68 [-0.15, 1.51] <b>0.68 [-0.15, 1.51]</b>	
Heterogeneity: Not applicat	le							
Test for overall effect: $Z = 1$	61 (P =	0.11)						
9.1.2 Intermediate-term								
Noriega 2017 4 Subtotal (95% CI)	3 30	12 <b>12</b>	46	27	12 <b>12</b>	100.0% <b>100.0</b> %	-0.10 [-0.90, 0.70] - <b>0.10 [-0.90, 0.70]</b>	
Heterogeneity: Not applical	le							
Test for overall effect: $Z = 0$	25 (P =	0.80)						
9.1.3 Long-term								
Noriega 2017 4 Subtotal (95% Cl)	0 29	12 <b>12</b>	51	29	12 <b>12</b>	100.0% <b>100.0</b> %	-0.37 [-1.17, 0.44] - <b>0.37 [-1.17, 0.44]</b>	
Heterogeneity: Not applical Test for overall effect: $Z = 0$ .								_

# Appendix 15b. Forest plot for activity limitations, comparing IDT of stem cells versus placebo.

	Expe	rimen	tal	Co	ontro			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
9.2.1 Short-term									
Noriega 2017	27	17	12	20	16	12		0.41 [-0.40, 1.22]	
Subtotal (95% CI)			12			12	<b>100.0</b> %	0.41 [-0.40, 1.22]	-
Heterogeneity: Not ap	pplicable								
Test for overall effect	: Z = 0.99	(P = 0	).32)						
9.2.2 Intermediate-te	erm								
Noriega 2017	16	20	12	25	15	12	100.0%	-0.49 [-1.31, 0.32]	
Subtotal (95% CI)			12			12	100.0%	-0.49 [-1.31, 0.32]	-
Heterogeneity: Not ap	pplicable								
Test for overall effect	: Z = 1.18	(P = 0	).24)						
9.2.3 Long-term									
Noriega 2017	20	24	12	30	20	12	100.0%	-0.44 [-1.25, 0.37]	
Subtotal (95% CI)			12			12	<b>100.0</b> %	-0.44 [-1.25, 0.37]	
Heterogeneity: Not ap	pplicable								
Test for overall effect	:Z=1.06	(P=0	).29)						
								-	
									Favours [experimental] Favours [control]

#### Appendix 16a. Forest plot for pain at short term, comparing IDT of platelet-rich plasma

#### versus placebo.

	Expe	rimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Tuakli 2015	4	2.21	29	4.61	2.21	18	100.0%	-0.27 [-0.86, 0.32]	
Total (95% CI)			29			18	100.0%	-0.27 [-0.86, 0.32]	-
Heterogeneity: Not ap Test for overall effect:		(P = 0	).37)						-4 -2 0 2 4 Favours [experimental] Favours [control]

# Appendix 16b. Forest plot for activity limitations at short term, comparing IDT of platelet-rich plasma versus placebo.

	Exp	eriment	tal	c	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Tuakli 2015	43.25	16.68	29	44.17	17.14	18	100.0%	-0.05 [-0.64, 0.53]	
Total (95% CI)			29			18	100.0%	-0.05 [-0.64, 0.53]	+
Heterogeneity: Not ap Test for overall effect:		(P = 0.	86)						-2 -1 0 1 2 Favours [experimental] Favours [control]

# Appendix 17a. Forest plot for pain at long term, comparing IDT of rhGDF-5 versus placebo.

	Expe	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
NCT01124006	-1.7	3.5	14	-2.78	3.75	10	48.6%	0.29 [-0.53, 1.11]	
NCT01182337	-2.49	2.21	22	-1.42	3.17	9	51.4%	-0.41 [-1.20, 0.37]	
Total (95% CI)			36			19	100.0%	-0.07 [-0.76, 0.62]	+
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:				1 (P =	0.22);	l² = 339	%		-4 -2 0 2 4 Favours [experimental] Favours [control]

#### Appendix 17b. Forest plot for activity limitations at long term, comparing IDT of rhGDF-

#### 5 versus placebo.

	Expe	rimen	tal	0	Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
NCT01124006	-12.9	25.6	14	-18.8	22.43	10	47.7%	0.23 [-0.58, 1.05]	
NCT01182337	-13.5	13.9	22	-10.4	8.9	9	52.3%	-0.24 [-1.02, 0.54]	
Total (95% CI)			36			19	100.0%	-0.01 [-0.58, 0.55]	+
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:				1 (P =	0.41); P	<sup>t</sup> = 0%			-2 -1 0 1 2 Favours [experimental] Favours [control]

# Appendix 18. Forest plot for adverse events of corticosteroid IDT.

	Experim	ental	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.3.1 Major							
Cao 2011	0	0	0	0		Not estimable	
Khot 2004	0	0	0	0		Not estimable	
Nguyen 2017	1	67	0	68	20.4%	3.09 [0.12, 77.21]	
Tavares 2020	3	21	4	24	79.6%	0.83 [0.16, 4.24]	
Yu 2012	0	0	0	0		Not estimable	
Subtotal (95% CI)		88		92	<b>100.0</b> %	1.09 [0.25, 4.65]	
Total events	4		4				
Heterogeneity: Tau <sup>2</sup> :	= 0.00; Chi <sup>a</sup>	<sup>e</sup> = 0.51,	df = 1 (P	= 0.48)	; l² = 0%		
Test for overall effect	t: Z = 0.11 (I	P = 0.91	)				
1.3.2 Minor							
Cao 2011	0	0	0	0		Not estimable	
Khot 2004	0	0	0	0		Not estimable	
Nguyen 2017	34	67	35	68	100.0%	0.97 [0.49, 1.91]	
Tavares 2020	0	21	0	24		Not estimable	
Yu 2012	0	0	0	0		Not estimable	
Subtotal (95% CI)		88		92	100.0%	0.97 [0.49, 1.91]	•
Total events	34		35				
Heterogeneity: Not a	pplicable						
Test for overall effect	t: Z = 0.08 (I	P = 0.93	)				
							0.005 0.1 1 10 200