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

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	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).	NA
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).	p.14, p.15
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)	_____
Name of the reviewer	☐ **CD** ☐ **SL** ☐ **Other: _____**
Date form completed	|__|__| |__|__| |__|__|__|__|
First author	
Article title	
Year of publication	
Journal	
Volume	
Issue	
Page number	
Language of publication	☐ **French** ☐ **English** ☐ **Other: _____**
Type of report	☐ **Full**

	☐ **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		

PARTICIPANTS

	Description 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 syndrome or positive provocative discography	☐ **Yes:** ☐ **No** ☐ **Unclear**	

Consistent IVD lesion on imaging (X-Ray, MRI or CT-scan)	**IVDDD** ☐ **Yes:** ☐ **No** ☐ **Unclear** **Modic 1** ☐ **Yes** ☐ **No** ☐ **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)	|__|__|__|	
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** ☐ **≥ 3**	

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

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

OUTCOMES

LOW BACK PAIN

Tick box if outcome was reported	**Multiple intervention** ☐ **Multifactorial intervention** ☐			**CONTROL**			**SUMMARY ESTIMATE**	
	Mean	**SD**	**Total**	**Mean**	**SD**	**Total**	**Mean difference between groups**	**95% confidence interval**
LBP ☐ **T*ype of validated scale used for measurement (i.e. NRS, VAS.)*** **SHORT TERM < 3 months**								
LBP ☐ **T*ype of validated scale used for measurement (i.e. NRS, VAS.)*** **MEDIUM TERM≥ 3 months and <6 months**								
LBP ☐ **T*ype of validated scale used for measurement (i.e. NRS, VAS.)*** **LONG TERM ≥ 6 months**								

ACTIVITY LIMITATIONS

Tick box if outcome was reported	**Multiple intervention** ☐ **Multifactorial 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 ☐ Multifactorial intervention ☐	INTERVENTION		CONTROL		SUMMARY ESTIMATE	
Tick box if outcome was reported	**Total number of patients on sick leave**	**Number of person months**	**Total number of patients on sick leave**	**Number of person months**	**Odds ratio**	**95% confidence interval**
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 ☐ Multifactorial intervention ☐	INTERVENTION		CONTROL		SUMMARY ESTIMATE	
Tick box if outcome was reported	**Total number of major adverse event**	**Number of person months**	**Total number of major adverse event**	**Number of person months**	**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 ☐ **Multifactorial intervention** ☐	**INTERVENTION**		**CONTROL**		**SUMMARY ESTIMATE**	
Tick box if outcome was reported	**Total number of minor adverse event**	**Number of person months**	**Total number of minor adverse event**	**Number of person months**	**Odds ratio**	**95% confidence interval**
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.

	Reported as randomized	Randomization is appropriate	Double blinding is reported	Double blinding is appropriate	Withdrawals are reported by number and reason per arm
Cao, 2011	+	?	+	?	+
Cohen	+	?	+	+	-
Sainoh, 2015	+	?	-	-	+
Sainoh, 2016	+	?	-	?	+
Peng, 2010	+	?	+	+	+
Nguyen, 2017	+	+	+	+	+
Tavares, 2018	+	+	+	-	+
Tuakli, 2015	+	+	+	+	+
Yu, 2012	+	+	+	?	-
Khot, 2002	+	?	-	?	+
Elawarmy, 2018	+	?	-	-	+
Kotilainen, 1997	+	?	?	?	-
Niu, 2018	+	?	?	?	-
Feldman, 1986	+	+	+	?	-
NTC 01182337	+	?	+	?	+
NTC 01124006	+	?	+	?	+
Noriega, 2016	+	+	+	?	-
Kallewaard, 2019	+	+	+	+	+

? unclear

reported

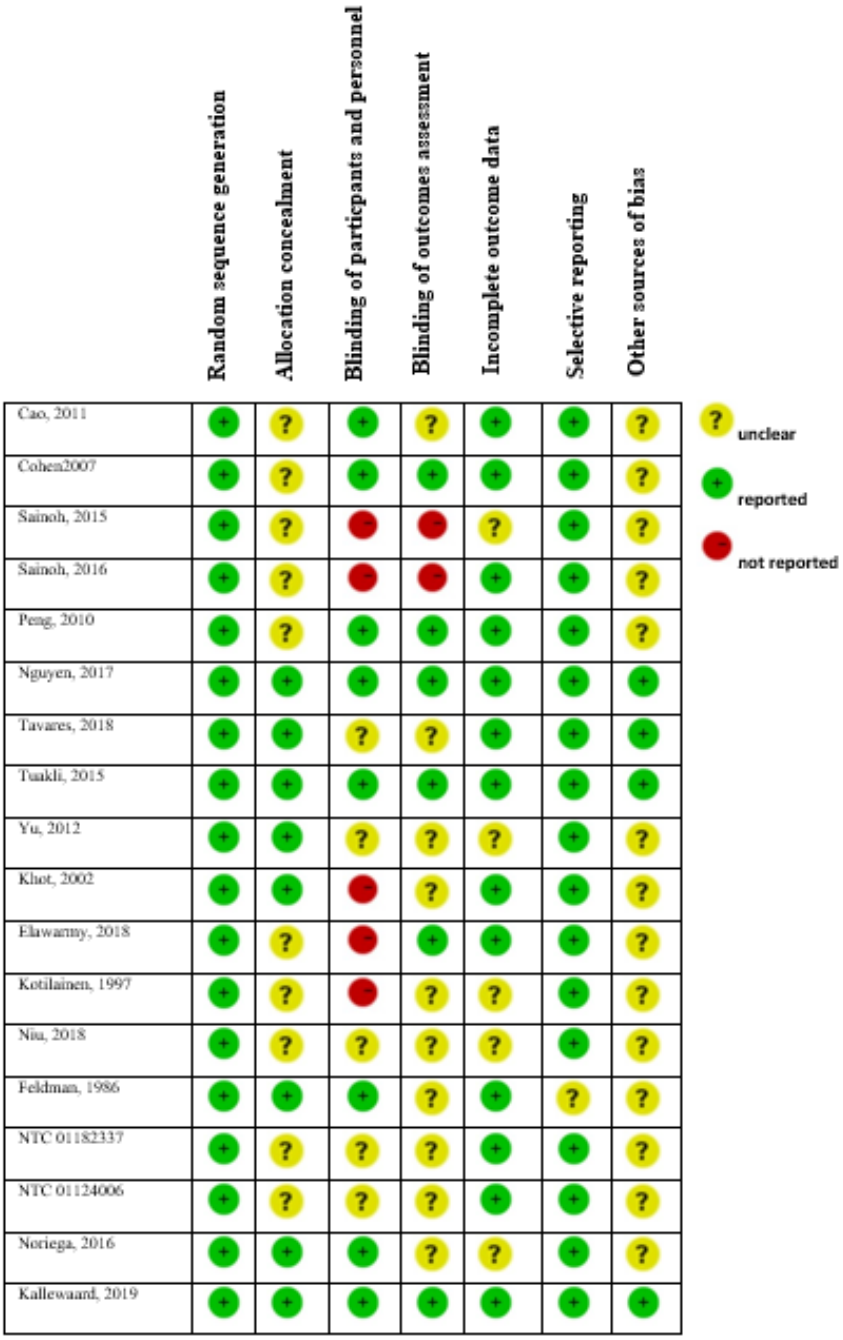
not reported

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

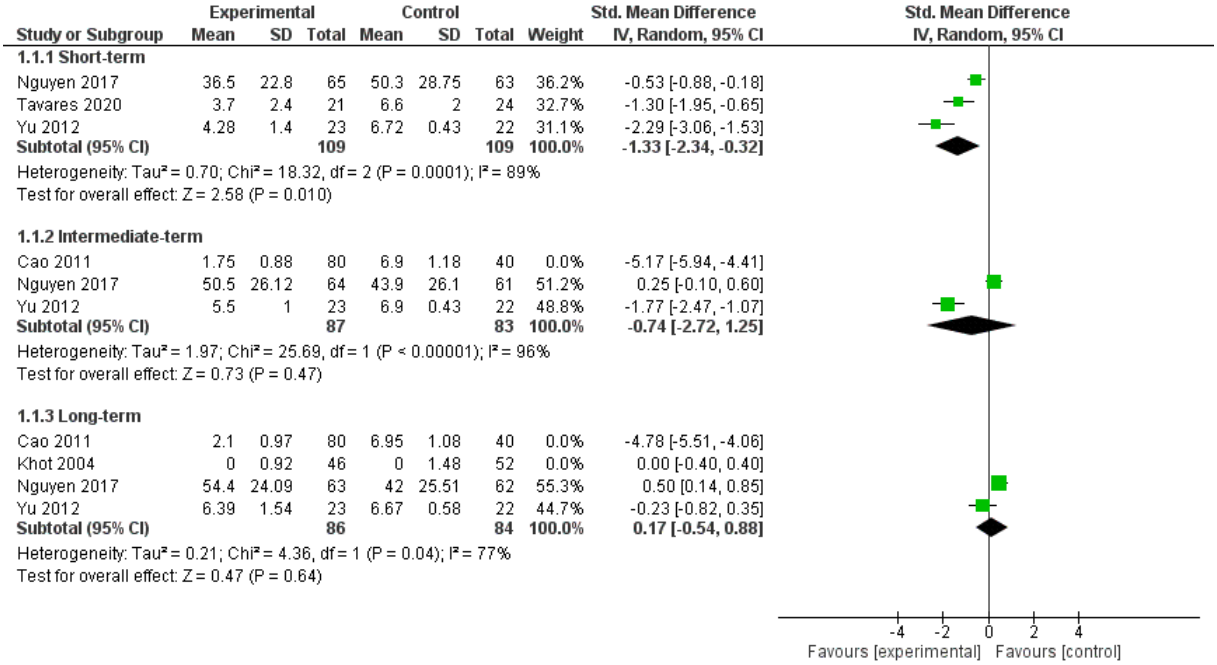
Title	Author	Year	Reason for exclusion
Prospective and randomized study in patients with low back pain or sciatic pain with ozone therapy treatment	Ansede Alonso J.C.	2007	Uncontrolled
Advances in cellular therapies: Clinical trial on lumbar degenerative disease	Ardura Aragón F.	2017	Not Randomized
Single-blind 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 disease--effect 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

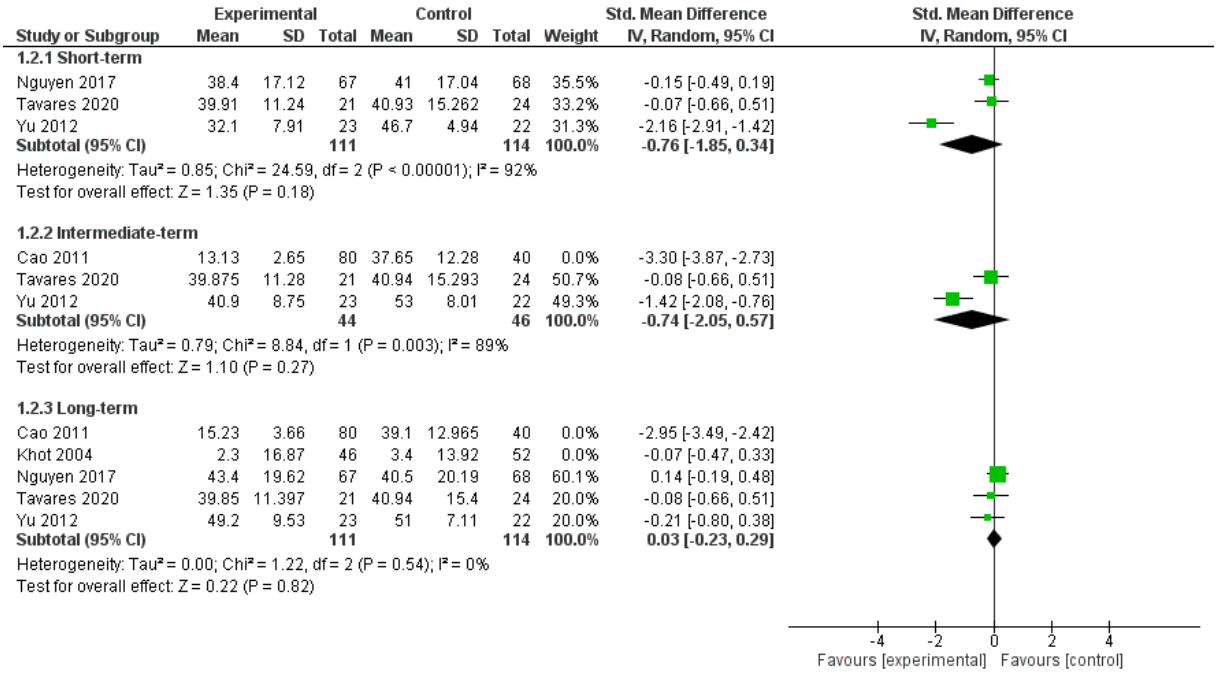
Appendix 18. Risk of bias within studies, using the revised Cochrane Risk of Bias tool.



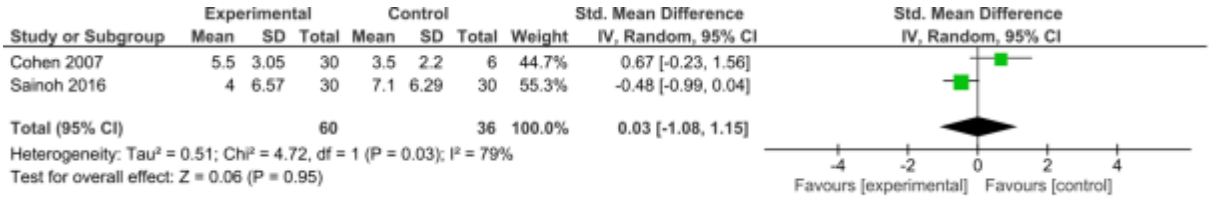
Appendix 8a. Forest plot for pain, comparing intervertebral disc therapy (IDT) of corticosteroid versus placebo: sensitivity analysis.



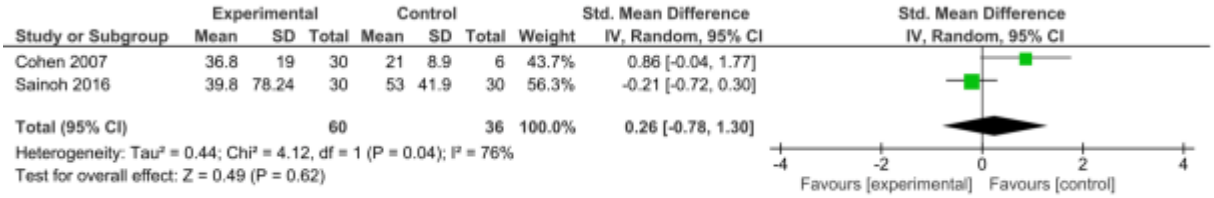
Appendix 8b. Forest plot for activity limitations, comparing IDT of corticosteroid versus placebo: sensitivity analysis.



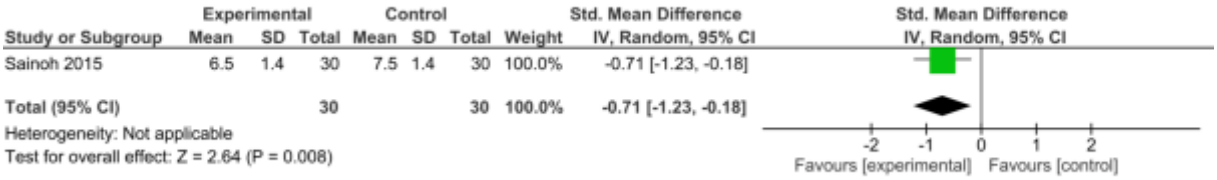
Appendix 9a. Forest plot for pain at short term, comparing IDT of etanercept *versus* placebo.



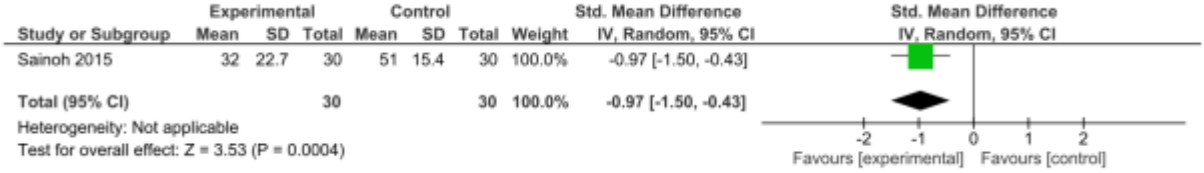
Appendix 9b. Forest plot for activity limitations at short term, comparing IDT of etanercept versus placebo.



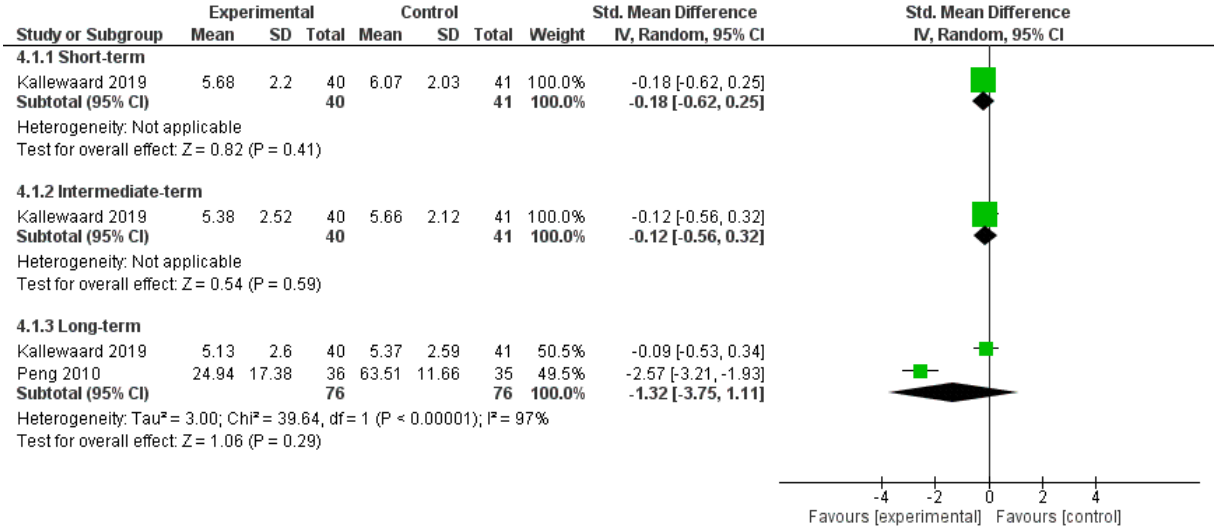
Appendix 10a. Forest plot for pain at short term, comparing IDT of tocilizumab versus placebo.



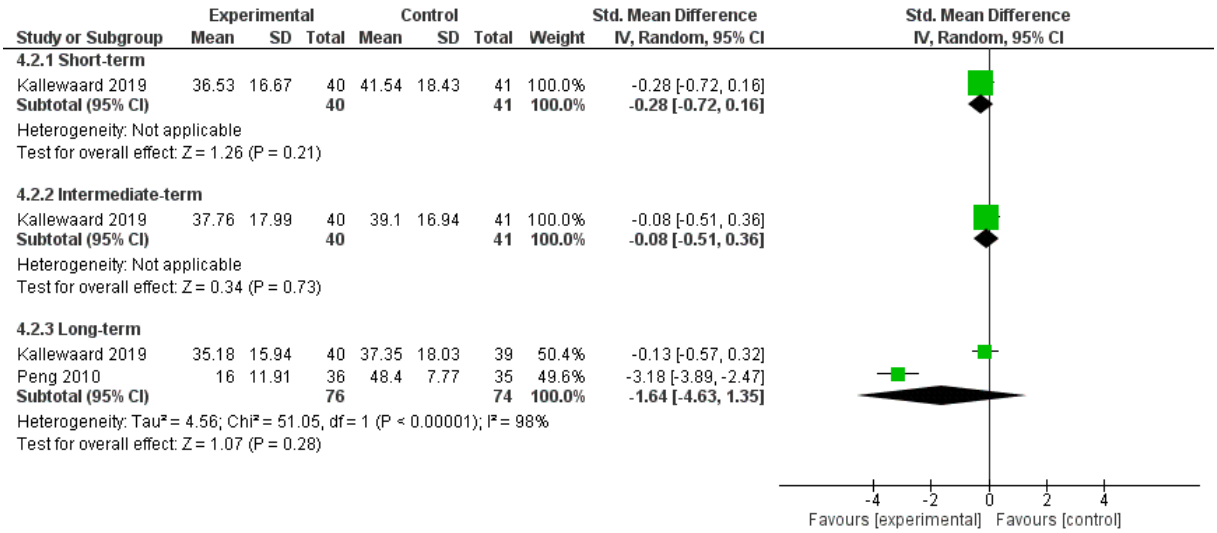
Appendix 10b. Forest plot for activity limitations at short term, comparing IDT of tocilizumab versus placebo.



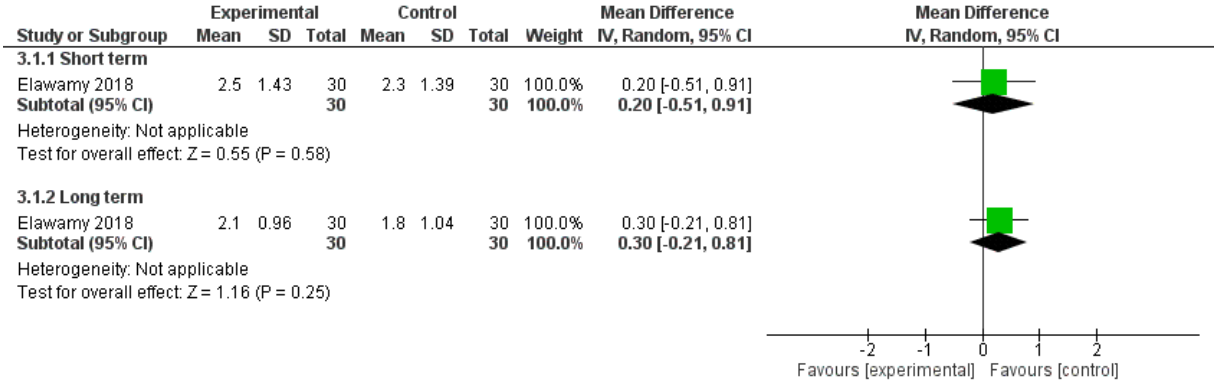
Appendix 11a. Forest plot for pain at short, intermediate and long terms, comparing IDT of methylene blue versus placebo.



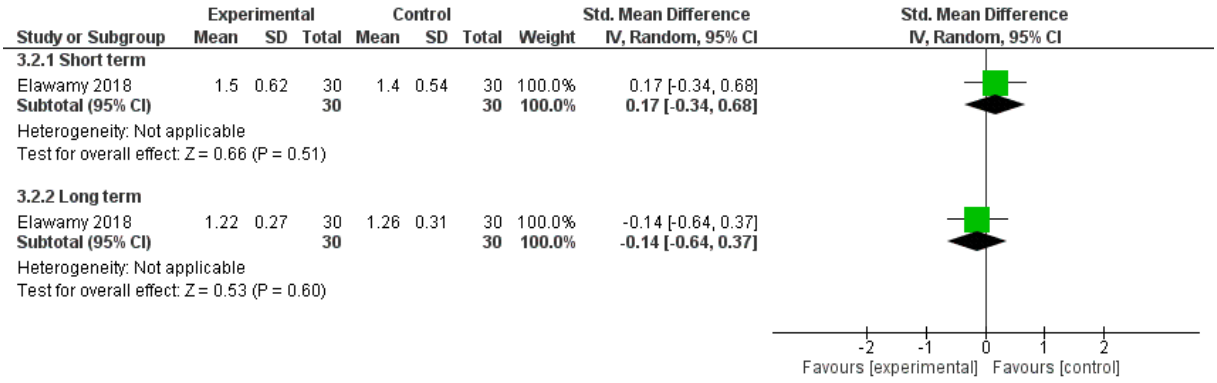
Appendix 11b. Forest plot for activity limitations at short, intermediate and long terms, comparing IDT of methylene blue versus placebo.



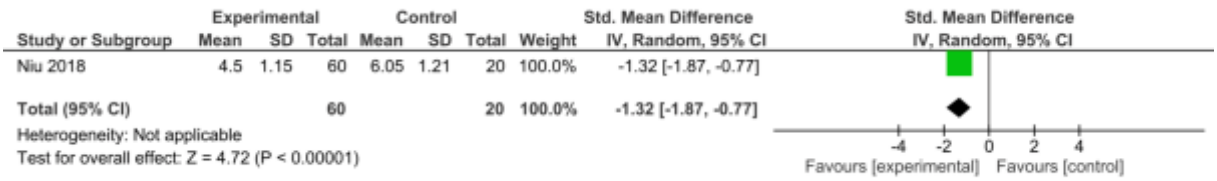
Appendix 12a. Forest plot for pain, comparing IDT of ozone 40 µg/ml versus ozone 30 µg/ml.



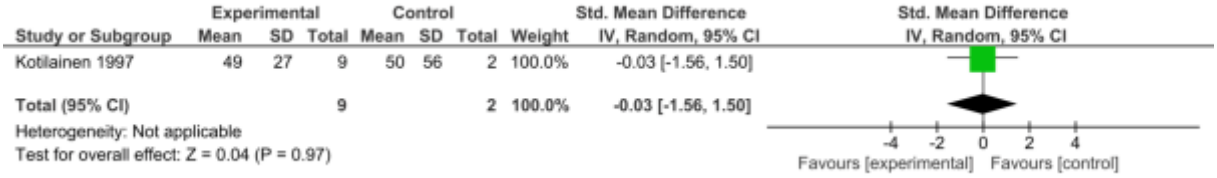
Appendix 12b. Forest plot for activity limitations, comparing IDT of ozone 40 µg/ml versus ozone 30 µg/ml.



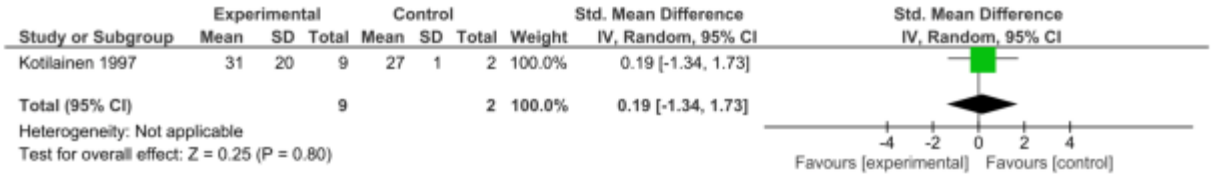
Appendix 13. Forest plot for pain at long term, comparing IDT of ozone versus usual care.



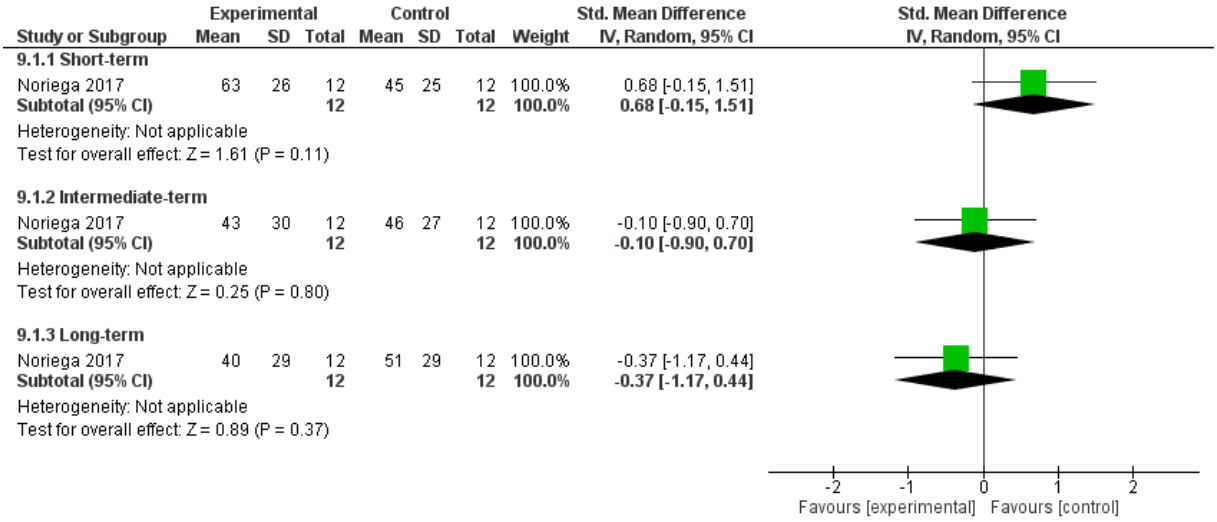
Appendix 14a. Forest plot for pain at short term, comparing IDT of glycerol versus placebo.



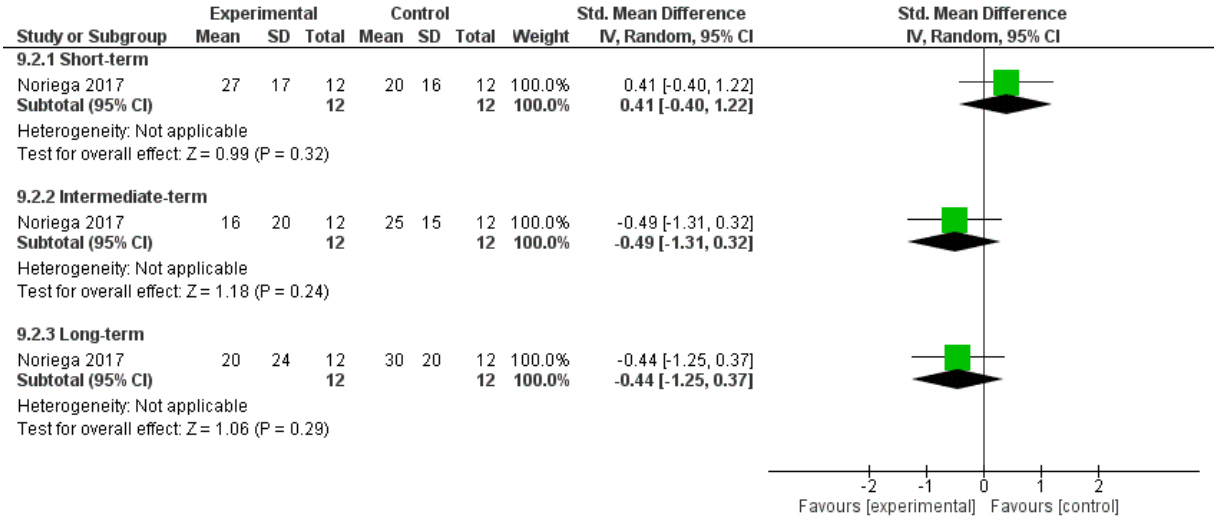
Appendix 14b. Forest plot for activity limitations at short term, comparing IDT of glycerol versus placebo.



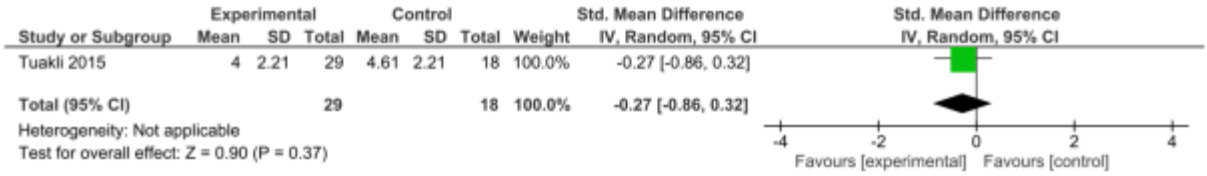
Appendix 15a. Forest plot for pain, comparing IDT of stem cells versus placebo.



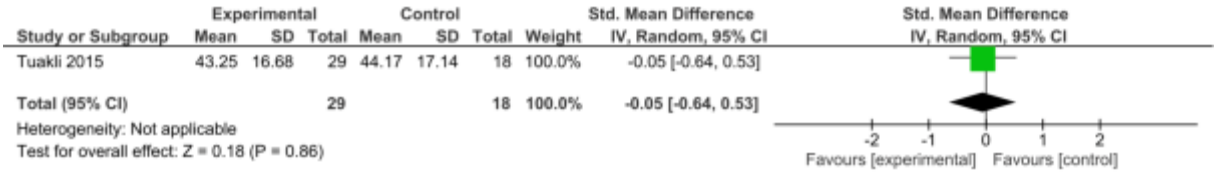
Appendix 15b. Forest plot for activity limitations, comparing IDT of stem cells versus placebo.



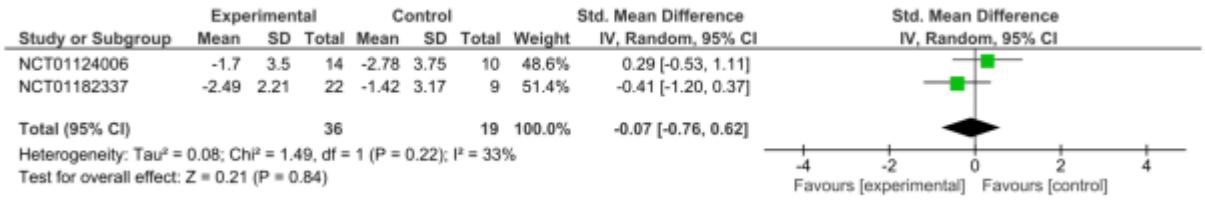
Appendix 16a. Forest plot for pain at short term, comparing IDT of platelet-rich plasma versus placebo.



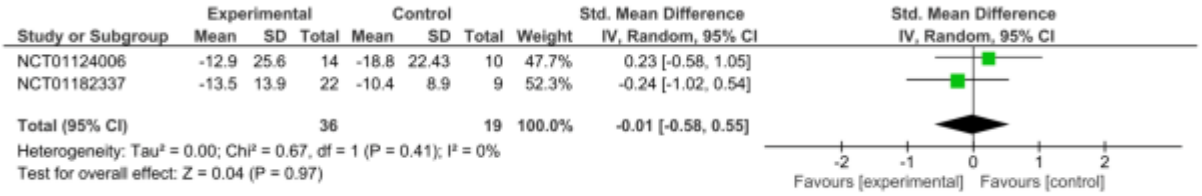
Appendix 16b. Forest plot for activity limitations at short term, comparing IDT of platelet-rich plasma versus placebo.



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



Appendix 17b. Forest plot for activity limitations at long term, comparing IDT of rhGDF-5 versus placebo.



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