National Institute for Health and Care Excellence

Draft for consultation

Fertility problems: assessment and treatment

[L] Intracytoplasmic sperm injection for non-male factor fertility problems

NICE guideline number NGXXX

Evidence reviews underpinning recommendation 1.11.2 in the NICE guideline

September 2025

Draft for consultation

Disclaimer

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Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Intracytoplasmic sperm injection for non-male factor fertility problems

Review question

What is the clinical and cost effectiveness of intracytoplasmic sperm injection (ICSI) compared to standard in vitro fertilisation (IVF) in non-male factor fertility problems?

Introduction

Intracytoplasmic sperm injection (ICSI) is a procedure where a live sperm is injected into the cytoplasm of an egg in a laboratory to fertilise the egg. It is commonly used in IVF for male factor fertility problems to overcome low sperm count. However, it has also been suggested as a technique for non-male factor fertility problems.

The aim of the review is to determine the clinical and cost effectiveness of ICSI compared to standard IVF in non-male factor fertility problems.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Inclusion: • People with non-male factor infertility If some, but not all, of a study's participants are eligible for the review, then a study will be included if at least 80% of its participants are eligible for this review.
Intervention	• Intra-cytoplasmic sperm injection (ICSI)
Comparison	• Standard in vitro fertilisation (IVF)
Outcome	**Critical** • Live birth (as defined by study, risk of bias assessments will reflect where this is not defined as a live birth to include a gestational age of ≥ 20 weeks) • Clinical pregnancy (as defined by study, risk of bias assessments will reflect where this is not defined as an ultrasound scan that has shown at least one foetal heart rate) The primary unit of analysis will be cumulative rates (of each outcome) per participant randomised **Important** • Miscarriage (loss of a baby before 24 weeks gestational age) • Any adverse events

For further details see the review protocol in appendix A.

Methods and process

During the development of this guideline, a recently updated published Cochrane review was identified which matched the committee's intended PICO (Cutting 2023). The Cochrane protocol differed from the committee's intended study type in that the Cochrane protocol excluded studies which compared standard IVF with ICSI using sibling oocytes (randomising

sibling oocytes rather than randomising couples). Studies were identified that were excluded from the review on these grounds, with reasoning given that although the use of sibling oocytes is more common in studies comparing the interventions, live birth was rarely reported in these studies. Most studies excluded on this basis did not report live birth, clinical pregnancy, miscarriage, or adverse events outcomes. The 1 excluded study identified which did report clinical pregnancy as an outcome found no important difference between groups and noted that careful interpretation of pregnancy results was required for studies randomising by sibling oocytes. There was usually some benefit of ICSI over standard IVF in terms of fertilization rates outcomes, but most studies overall concluded that ICSI is not superior to standard IVF in the relevant population. The committee agreed that it is unlikely the inclusion of these studies would have affected the conclusions drawn in the Cochrane review.

Cochrane's methods are closely aligned to standard NICE methods, minor deviations (the use of the original Cochrane risk of bias tool, summary of findings tables instead of full GRADE tables, defining primary and secondary outcomes as opposed to critical and important, clinical pregnancy as a secondary outcome instead of a primary outcome, and adverse events as a primary outcome instead of a secondary outcome) relevant to the topic area were highlighted to the committee and taken into account in discussions of the evidence.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

One Cochrane review comparing the effectiveness of ICSI versus conventional in vitro fertilisation (c-IVF; Cutting 2023) including 3 randomised controlled trials (RCTs: Bhattacharya 2001, Dang 2021, Foong 2006) was considered in this report. This review was used for recommendation making by the committee as it was considered sufficiently relevant, high quality and up to date.

The Cochrane review is summarised in Table 2 and the results of the review summarised in evidence statements in this report, however full details of the Cochrane review including methods are available here: Intracytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in couples with non-male subfertility | Cochrane

See the Cochrane review for the literature search strategy and study selection flow chart.

Excluded studies

See the Cochrane review (Cutting 2023) for the list of excluded studies with reasons for their exclusions: Intracytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in couples with non-male subfertility | Cochrane.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Comparisons	Outcomes
Cutting 2023	Number of studies = 3	ICSI vs c-IVF 3 trials, N=1539 couples undergoing fertility treatment	Primary outcomes

Study	Population	Comparisons	Outcomes
Systematic review	Number of couples undergoing fertility treatment (with normal total sperm count and motility) = 1539	(Bhattacharya 2001, Dang 2021, Foong 2006)	• Live birth rate (per couple), defined as delivery of a live fetus after 20 completed weeks' gestation • Adverse events (per couple): ○ Multiple pregnancy rate, defined as presence of more than one sac at early pregnancy ultrasound six to eight weeks gestation. ○ Ectopic pregnancy, defined as a pregnancy outside the uterine cavity, diagnosed by ultrasound, surgical visualisation or histopathology ○ Stillbirth, defined as the death of a fetus prior to the complete expulsion or extraction from its mother after 20 completed weeks of gestational age. The death is determined by the fact that, after such separation, the fetus does not breathe or show any other evidence of life, such as heartbeat, umbilical cord pulsation or definite movement of voluntary muscles. ○ Pre-Eclampsia ○ Prematurity <u>Secondary outcomes</u> • Clinical pregnancy rate (per couple), defined as evidence of a gestational sac, confirmed by ultrasound. • Viable intrauterine pregnancy rate (per couple), defined as a pregnancy diagnosed by ultrasonographic examination of at least one fetus with a discernible heartbeat. • Miscarriage rate (per pregnancy), defined as the spontaneous loss of an intrauterine pregnancy prior to 20 completed weeks of gestational age. • Fertilisation rate per oocyte inseminated, fertilisation rate per oocyte retrieved, fertilisation failure, implantation rate (defined by number of gestational sacs per number of embryos transferred with embryos as the denominator), embryo quality and blastocyst formation

c-IVF: conventional in-vitro fertilisation; ICSI: intracytoplasmic sperm injection; N: number

See the Cochrane review (Cutting 2023) for characteristics of studies tables and forest plots: Intracytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in couples with non-male subfertility | Cochrane.

Summary of the evidence

The Cochrane review investigated 1 comparison (ICSI versus c-IVF) and found no clinically important difference between ICSI and c-IVF for any of the primary outcomes (live birth, multiple pregnancy, ectopic pregnancy, pre-eclampsia, or prematurity) or the secondary

outcomes (clinical pregnancy, viable intrauterine pregnancy, miscarriage, fertilisation per oocyte inseminated, fertilisation per oocyte retrieved, fertilisation failure, or implantation rate). None of the included studies reported on the primary outcome stillbirth.

See the Cochrane review for summary of findings tables and full results: https://doi.org/10.1002/14651858.CD001301.pub2

Economic evidence

A total of 1,355 studies were identified in the health economic literature search for this review question. After duplicates were removed, 1,032 studies were screened on title and abstract. All studies were excluded at this stage apart from one study which was subsequently included in this evidence review.

Included studies

One economic study was identified which was relevant to this question (Vitek 2013).

See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included economic evidence

See Table 3 for the economic evidence profile of the included study.

Table 3: Economic evidence profile of intracytoplasmic sperm injection (ICSI) compared to standard in vitro fertilisation (IVF) in non-male factor fertility problems?

Study	Limitations	Applicability	Other comments	Incremental[1]			Uncertainty
				Costs	Effect	Cost effectiveness	
Vitek 2013	Potentially serious limitations[2,3,4,5]	Partially applicable[6]	Study employed a decision-analytic model to assess cost-effectiveness at either 1 or 2 cycles of IVF	*Single cycle* $1,763 *2-cycle* $1,355	*Single cycle 0.030* *2-cycle 0.032*	*Single cycle* $58,766 per live birth *2-cycle* $42,343 per live births	Not assessed

[1] *Results are presented for ICSI versus IVF. The paper also assessed split IVF-ICSI but that was not included within the review protocol.*
[2] *No probabilistic sensitivity analysis was undertaken, and parameter uncertainty was not assessed with deterministic sensitivity analysis.*
[3] *Estimates of effectiveness were not derived from randomised studies.*
[4] *The model does not consider possible adverse effects of intervention.*
[5] *QALYs not used to quantify health benefits.*
[6] *The setting was the United States and a cost year of 2012 (using 2005 and 2006 prices adjusted for inflation using the consumer price index).*

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Unit costs

Resource	Unit costs	Source
IVF	£3,649	NHS 2022/23 National Tariff Payment System: Non-mandatory guide and benchmark prices [a] (https://www.england.nhs.uk/publication/2023-25-nhs-payment-scheme/#heading-2)
IVF with ICSI	£4,120	2023-25 NHS Payment Scheme (amended) (https://www.england.nhs.uk/publication/2023-25-nhs-payment-scheme/#heading-2)

(a) Price to include 1 fresh and 1 frozen cycle

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The Cochrane review's primary outcomes included live birth, which the committee agreed was a critical outcome because it is the most important outcome for people with fertility problems. The review also included adverse events as a primary outcome. The committee agreed that adverse events was an important outcome to capture because it is key that risks are considered and weighed up against potential benefits when discussing and deciding on treatment options. The committee agreed that live birth and clinical pregnancy rates should be prioritised above other outcomes to reflect the comparative importance of these outcomes for people with fertility problems.

The Cochrane review included clinical pregnancy as a secondary outcome, whereas the committee considered clinical pregnancy to be a critical outcome as this reflects the evidence available: clinical pregnancy rates tend to be reported in preference to live birth rates throughout the literature. However, the committee were aware that pregnancy rates do not allow for differentiation between full-term pregnancy and pregnancy loss, and agreed live birth was the most important outcome as clinical pregnancy usually only acted as a proxy for live birth in the absence of available evidence. Miscarriage was included in the Cochrane review as a secondary outcome, and the committee agreed this outcome was important to capture because miscarriages can be devastating for people trying to have a baby.

All other outcomes listed in the Cochrane protocol (viable intrauterine pregnancy rate, fertilisation rate per oocyte inseminated, fertilisation rate per oocyte retrieved, fertilisation failure, implantation rate, embryo quality and blastocyst formation) were agreed to be important outcomes by the committee.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology and ranged from low to moderate. All outcomes were downgraded for serious imprecision due to small numbers of events and confidence intervals that include appreciable benefit for either ICSI or IVF. Some outcomes were additionally downgraded for serious risk of bias assessed using version 1 of the Cochrane risk of bias tool.

Where outcomes were downgraded due to risk of bias, this was mainly due to detection bias (non-blind outcome assessment), attrition bias (incomplete outcome data), and performance bias (non-blind participants and personnel). There was also an unclear risk of selection bias

in some of the outcomes (unclear random sequence generation and allocation concealment methods), selective reporting bias, and other bias not defined in the review.

Benefits and harms

The committee reviewed the evidence from the Cochrane review, which found no important difference between ICSI and standard IVF (without ICSI) for non-male factor fertility problems for any outcomes. They agreed that, where infertility is not a result of male factor problems, people should not usually receive ICSI in addition to standard IVF. This would reduce the cost and resource implications of offering a more expensive intervention to people for whom it is unlikely to provide any benefit over standard IVF. The committee agreed that although in most cases ICSI would not be recommended over standard IVF for those with non-male factor fertility problems, there may be some circumstances where ICSI might be indicated such as when a previous IVF treatment cycle has resulted in failed or very poor fertilisation as there could be an undiagnosed sperm factor dysfunction; or when pre-implantation genetic testing is indicated for a monogenic disorder in order to prevent contamination from paternal genes.

Cost effectiveness and resource use

The committee were aware of one study (Vitek 2013) that reported that ICSI had an incremental cost-effectiveness ratio (ICER) of $58,766 per live birth and $42,343 per live birth relative to IVF for 1-cycle and 2-cycles of IVF respectively.

In the absence of any decision rules about the appropriate cost-effectiveness threshold, the committee agreed with the study authors that ICSI is not cost-effective given the stated ICERs. Furthermore, the committee noted that the study was only partially applicable to an NHS setting and had potentially serious limitations which would have made it difficult to support a recommendation for ICSI even if the results had been more favourable.

The committee considered that their recommendations are consistent with current NHS practice and that there would be no significant resource impact as a result.

Recommendations supported by this evidence review

This evidence review supports recommendation 1.11.2.

References – included studies

Effectiveness

Cutting 2023

Cutting E, Horta F, Dang V, van Rumste MME, Mol BWJ. Intracytoplasmic sperm injection versus conventional in vitro fertilisation in couples with males presenting with normal total sperm count and motility. Cochrane Database of Systematic Reviews 2023, Issue 8. Art. No.: CD001301. DOI: 10.1002/14651858.CD001301.pub2. Accessed 07 November 2023.

Economic

Vitek 2013

Vitek WS, Galárraga O, Klatsky PC, Robins JC, Carson SA, Blazar AS. (2013) Management of the first in vitro fertilization cycle for unexplained infertility: a cost-effectiveness analysis of split in vitro fertilization-intracytoplasmic sperm injection. Fertility and Sterility 100(5):1381-8.

Appendices

Appendix A Review protocols

Review protocol for review question: What is the clinical and cost effectiveness of intracytoplasmic sperm injection (ICSI) compared to standard in vitro fertilisation (IVF) in non-male factor fertility problems?

Table 4: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42023460917
1.	Review title	Clinical and cost effectiveness of intracytoplasmic sperm injection (ICSI) in non-male factor fertility problems
2.	Review question	What is the clinical and cost effectiveness of intracytoplasmic sperm injection (ICSI) compared to standard in vitro fertilisation (IVF) in non-male factor fertility problems?
3.	Objective	To determine the clinical and cost effectiveness of ICSI compared to standard IVF in non-male factor fertility problems
4.	Searches	The following databases will be searched (from August 2010 [date of search for Cochrane review; van Rumste 2011] to date search conducted): Clinical searches • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE ALL • Epistemonikos Searches will be restricted by: • English language

ID	Field	Content
		• Human Studies The guideline committee will decide whether and when to re-run the searches to retrieve further studies for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Intracytoplasmic sperm injection (ICSI) for non-male factor fertility problems
6.	Population	Inclusion: • People with non-male factor infertility If some, but not all, of a study's participants are eligible for the review, then a study will be included if at least 80% of its participants are eligible for this review.
7.	Intervention	• Intra-cytoplasmic sperm injection (ICSI)
8.	Comparator	• Standard in vitro fertilisation (IVF)
9.	Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • Parallel RCTs (individual or cluster) * *Cross-over RCTs will be included but only where data can be extracted for the end of the first phase Quasi-RCTs, such as trials in which allocation is determined by alternation or date of birth, will be excluded
10.	Other exclusion criteria	Other exclusion criteria: • Language limitations: non-English-language papers will be excluded (unless data can be obtained, and risk of bias assessed, from an existing systematic review) • Conference abstracts, dissertations and unpublished data will not be included unless the data can be extracted (and risk of bias assessed) from elsewhere (for instance, from an existing systematic review)
11.	Context	This guidance will update and replace the following NICE guideline: Fertility problems: assessment and treatment (last updated 2017; CG156)
12.	Primary outcomes (critical outcomes)	• Live birth (as defined by study, risk of bias assessments will reflect where this is not defined as a live birth to include a gestational age of ≥ 20 weeks) • Clinical pregnancy (as defined by study, risk of bias assessments will reflect where this is not defined as an ultrasound scan that has shown at least one foetal heart rate)

ID	Field	Content
		The primary unit of analysis will be cumulative rates (of each outcome) per participant randomised
13.	Secondary outcomes (important outcomes)	• Miscarriage (loss of a baby before 24 weeks gestational age) • Any adverse events
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies included after full-text review. The following data will be extracted: study details (reference, country where study was carried out, and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions, follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where there is available data, meta-analyses will be conducted using Cochrane Review Manager software, and data will be presented as risk ratios or odds ratios (all included outcomes are dichotomous outcomes). It is considered likely that a random-effects model will be used for meta-analyses (based on assumptions about methodological diversity of studies). Funnel plot asymmetry (relationship between the magnitude of the effect estimate and study size) will be considered (for meta-analyses that include at least 10 studies), and where asymmetry is indicated a fixed-effects model will be conducted (and both random-effects and fixed-effects analyses will be presented) or sensitivity analyses excluding small studies will be considered. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and

ID	Field	Content	
		80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: GRADE home. Importance and imprecision of findings will be assessed against minimally important differences (MIDs). The following MIDs will be used: • Live birth: statistical significance • Dichotomous outcomes (other than live birth): 0.8 and 1.25 for all other relative dichotomous outcomes	
17.	Analysis of sub-groups	Evidence will be sub-grouped by the following only if there is significant heterogeneity in outcomes: • Female age (based on the mean age in the study) ○ <35 years ○ 35-39 years ○ ≥39 years • Fertility problems explained or unexplained ○ Explained infertility ○ Unexplained infertility Where evidence is sub-grouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
18.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery

ID	Field	Content		
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	August 2023		
22.	Anticipated completion date	November 2024		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact Guideline development team A 5b. Named contact e-mail FertilityProblems@nice.org.uk 5c. Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
25.	Review team members	Senior Technical Analyst Technical Analyst		
26.	Funding sources/sponsor	This systematic review is being completed by NICE		

ID	Field	Content	
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10263	
29.	Other registration details	None	
30.	URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=460917	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	infertility, subfertility, intracytoplasmic sperm injection, in vitro fertilisation	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated

ID	Field	Content	
		☐	Discontinued
35..	Additional information	None	
36.	Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What is the clinical and cost effectiveness of intracytoplasmic sperm injection (ICSI) compared to standard in vitro fertilisation (IVF) in non-male factor fertility problems?

See Appendices 1 to 5 of the Cochrane review (Cutting 2023): Intracytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in couples with non-male subfertility | Cochrane

Health Economic Literature Search Strategies

Database: MEDLINE ALL 1946 to November 22, 2023

Date of last search: 27/11/2023

#	Searches
1	Fertilization in Vitro/
2	(vitro fertilization or vitro fertilisation).tw.
3	(conventional adj4 assisted reproduct*).tw.
4	conventional technique*.tw.
5	IVF.tw.
6	or/1-5
7	Sperm Injections, Intracytoplasmic/
8	intracytoplasmic sperm*.tw.
9	intra-cytoplasmic sperm*.tw.
10	ICSI.tw.
11	or/7-10
12	6 and 11
13	limit 12 to english language
14	letter/
15	editorial/
16	news/
17	exp historical article/
18	Anecdotes as topic/
19	comment/
20	case reports/
21	(letter or comment*).ti.
22	or/14-21
23	randomized controlled trial/ or random*.ti,ab.
24	22 not 23
25	animals/ not humans/
26	exp Animals, Laboratory/
27	exp Animal Experimentation/
28	exp Models, Animal/
29	exp Rodentia/
30	(rat or rats or rodent* or mouse or mice).ti.
31	or/24-30
32	13 not 31
33	Economics/
34	Value of life/
35	exp "Costs and Cost Analysis"/
36	exp Economics, Hospital/
37	exp Economics, Medical/

#	Searches
38	exp Resource Allocation/
39	Economics, Nursing/
40	Economics, Pharmaceutical/
41	exp "Fees and Charges"/
42	exp Budgets/
43	budget*.ti,ab.
44	cost*.ti,ab.
45	(economic* or pharmaco?economic*).ti,ab.
46	(price* or pricing*).ti,ab.
47	(financ* or fee or fees or expenditure* or saving*).ti,ab.
48	(value adj2 (money or monetary)).ti,ab.
49	resourc* allocat*.ti,ab.
50	(fund or funds or funding* or funded).ti,ab.
51	(ration or rations or rationing* or rationed).ti,ab.
52	ec.fs.
53	or/33-52
54	quality-adjusted life years/
55	sickness impact profile/
56	(quality adj2 (wellbeing or well being)).ti,ab.
57	sickness impact profile.ti,ab.
58	disability adjusted life.ti,ab.
59	(qal* or qtime* or qwb* or daly*).ti,ab.
60	(euroqol* or eq5d* or eq 5*).ti,ab.
61	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
62	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
63	(hui or hui1 or hui2 or hui3).ti,ab.
64	(health* year* equivalent* or hye or hyes).ti,ab.
65	discrete choice*.ti,ab.
66	rosser.ti,ab.
67	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
68	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
69	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
70	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
71	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
72	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
73	or/54-72
74	32 and (53 or 73)

1 ***Database: Embase 1974 to 2023 November 22***

2 **Date of last search: 27/11/2023**

#	Searches
1	in vitro fertilization/
2	(vitro fertilization or vitro fertilisation).ti.
3	(conventional adj4 assisted reproduct*).ti.
4	conventional technique*.ti.
5	IVF.ti.
6	or/1-5
7	intracytoplasmic sperm injection/
8	intracytoplasmic sperm*.ti.
9	intra-cytoplasmic sperm*.ti.
10	ICSI.ti.

#	Searches
11	or/7-10
12	6 and 11
13	letter.pt. or letter/
14	note.pt.
15	editorial.pt.
16	case report/ or case study/
17	(letter or comment*).ti.
18	or/13-17
19	randomized controlled trial/ or random*.ti,ab.
20	18 not 19
21	animal/ not human/
22	nonhuman/
23	exp Animal Experiment/
24	exp Experimental Animal/
25	animal model/
26	exp Rodent/
27	(rat or rats or rodent* or mouse or mice).ti.
28	or/20-27
29	12 not 28
30	limit 29 to english language
31	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
32	30 not 31
33	health economics/
34	exp economic evaluation/
35	exp health care cost/
36	exp fee/
37	budget/
38	funding/
39	resource allocation/
40	budget*.ti,ab.
41	cost*.ti,ab.
42	(economic* or pharmaco?economic*).ti,ab.
43	(price* or pricing*).ti,ab.
44	(financ* or fee or fees or expenditure* or saving*).ti,ab.
45	(value adj2 (money or monetary)).ti,ab.
46	resourc* allocat*.ti,ab.
47	(fund or funds or funding* or funded).ti,ab.
48	(ration or rations or rationing* or rationed).ti,ab.
49	or/33-48
50	quality adjusted life year/
51	"quality of life index"/
52	short form 12/ or short form 20/ or short form 36/ or short form 8/
53	sickness impact profile/
54	(quality adj2 (wellbeing or well being)).ti,ab.
55	sickness impact profile.ti,ab.
56	disability adjusted life.ti,ab.
57	(qal* or qtime* or qwb* or daly*).ti,ab.
58	(euroqol* or eq5d* or eq 5*).ti,ab.
59	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
60	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
61	(hui or hui1 or hui2 or hui3).ti,ab.
62	(health* year* equivalent* or hye or hyes).ti,ab.

#	Searches
63	discrete choice*.ti,ab.
64	rosser.ti,ab.
65	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
66	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
67	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
68	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
69	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
70	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
71	or/50-70
72	32 and (49 or 71)

Database: INAHTA

Date of last search: 27/11/2023

#	Searches
1	"Fertilization in Vitro"[mh]
2	(vitro fertilization or vitro fertilisation)
3	(conventional AND assisted reproduct*)
4	conventional technique*
5	IVF
6	#5 OR #4 OR #3 OR #2 OR #1
7	"Sperm Injections, Intracytoplasmic"[mh]
8	intracytoplasmic sperm*
9	intra-cytoplasmic sperm*
10	ICSI
11	#10 OR #9 OR #8 OR #7
12	#11 AND #6

Database: HTA via CRD

Date of last search: 27/11/2023

#	Searches
1	MESH DESCRIPTOR Fertilization in Vitro
2	(vitro fertilization or vitro fertilisation)
3	(conventional NEAR4 assisted reproduct*)
4	(conventional technique*)
5	IVF
6	#1 OR #2 OR #3 OR #4 OR #5
7	MESH DESCRIPTOR Sperm Injections, Intracytoplasmic
8	intracytoplasmic sperm*
9	intra-cytoplasmic sperm*
10	ICSI
11	#7 OR #8 OR #9 OR #10
12	#6 AND #11
13	(#6 AND #11) IN HTA

Appendix C Effectiveness evidence study selection

Study selection for: What is the clinical and cost effectiveness of intracytoplasmic sperm injection (ICSI) compared to standard in vitro fertilisation (IVF) in non-male factor fertility problems?

See Results of the search – figure 1 from the Cochrane review (Cutting 2023): Intracytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in couples with non-male subfertility | Cochrane

Appendix D Characteristics of studies tables

Characteristics of studies tables for review question: What is the clinical and cost effectiveness of intracytoplasmic sperm injection (ICSI) compared to standard in vitro fertilisation (IVF) in non-male factor fertility problems?

See the Characteristics of included studies tables from the Cochrane review (Cutting 2023): Intracytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in couples with non-male subfertility | Cochrane

Appendix E Data and analyses tables

Data and analyses for review question: What is the clinical and cost effectiveness of intracytoplasmic sperm injection (ICSI) compared to standard in vitro fertilisation (IVF) in non-male factor fertility problems?

See the Data and analyses tables from the Cochrane review (Cutting 2023): Intracytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in couples with non-male subfertility | Cochrane

Appendix F Summary of findings tables

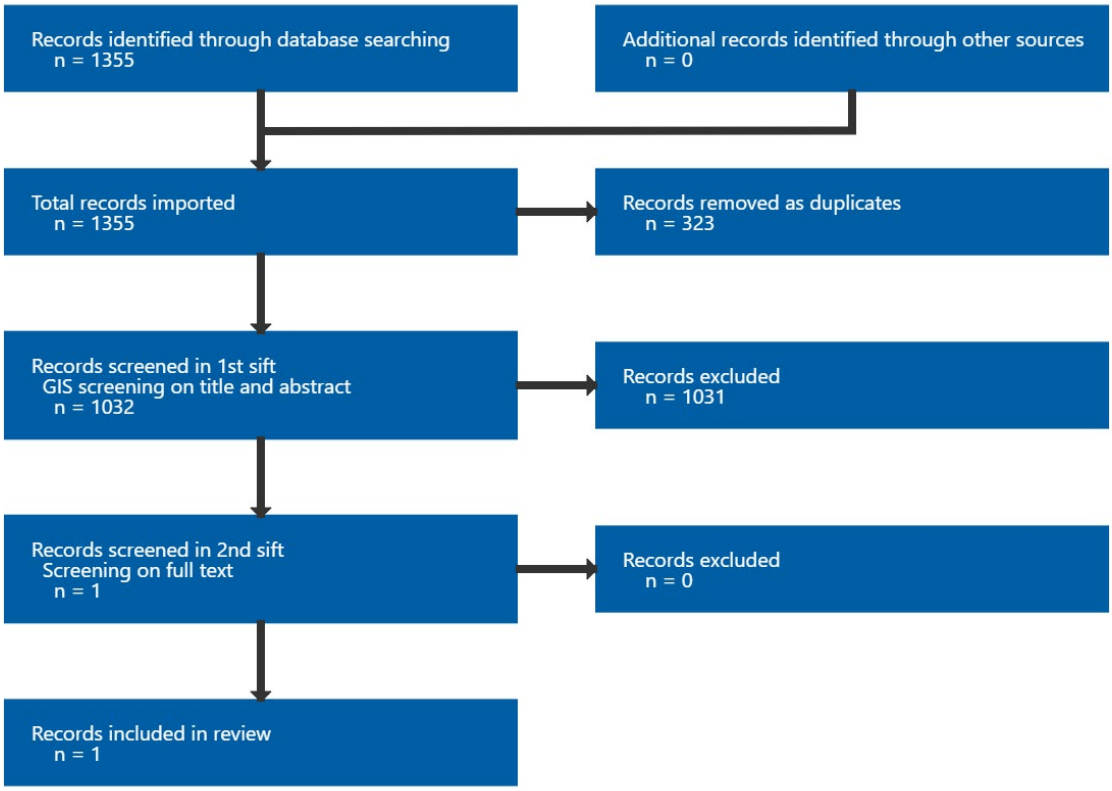
Summary of findings tables for review question: What is the clinical and cost effectiveness of intracytoplasmic sperm injection (ICSI) compared to standard in vitro fertilisation (IVF) in non-male factor fertility problems?

See the Summary of findings tables from the Cochrane review (Cutting 2023): Intracytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in couples with non-male subfertility | Cochrane

Appendix G Economic evidence study selection

Study selection for review question: What is the clinical and cost effectiveness of intracytoplasmic sperm injection (ICSI) compared to standard in vitro fertilisation (IVF) in non-male factor fertility problems?

Figure 1: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the clinical and cost effectiveness of intracytoplasmic sperm injection (ICSI) compared to standard in vitro fertilisation (IVF) in non-male factor fertility problems?

Table 5: Economic evidence tables for intracytoplasmic sperm injection (ICSI) compared to standard in vitro fertilisation (IVF) in non-male factor fertility problems

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Author and year: Vitek 2013 **Country:** United States **Type of economic analysis:** CEA **Source of funding:** Not stated	**Intervention:** <u>i) ICSI</u> First cycle of ICSI with subsequent treatment of donor IUI if failed fertilisation. <u>ii) Split IVF-ICSI</u> First cycle of split IVF-ICSI with subsequent treatment of donor IUI if failed fertilisation. **Comparator:** <u>iii) IVF</u> First cycle of IVF with subsequent treatment with ICSI if failed fertilisation	**Population characteristics:** Women <35 years old with unexplained infertility undergoing IVF. **Modelling approach:** Decision analytic model **Source of baseline data:** Center for Reproduction and infertility SART 2009 national data **Source of effectiveness data:** Center for Reproduction and infertility	**Costs:** Payer perspective (implicit) **Mean cost per participant:** *Single cycle* Intervention: <u>i) ICSI</u> $15,605 <u>ii) Split IVF-ICSI</u> $15,605 Control: <u>iii) IVF</u> $13,842 Difference: $1,763	ICERs: *Single cycle* $58,766 per live birth Sensitivity analysis: *2-cycle* $29,666 per live birth ICSI dominated by split IVF-ICSI	**Currency:** USD **Cost year:** 2012 **Time horizon:** 1 or 2 cycles of IVF Discounting: N/A **Applicability:** Partially applicable **Limitations:** Potentially serious limitations **Other comments:**

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		SART 2009 national data **Source of cost data:** Analysis only costed the treatments **Source of unit cost data:** Published surveys	*2-cycle* Intervention: i) ICSI $22,552 ii) Split IVF-ICSI $22,176 Control: iii) IVF $21,197 Difference: Split IVF-ICSI V IVF $979 ICSI v Split IVF-ICSI $376 **Primary measure of outcome:** Live birth rates **Mean outcome per participant:**		ICERs not correctly reported in paper so calculated values are presented in this table. Uncertainty not addressed in sensitivity analysis. Effectiveness estimates were not derived from randomised clinical studies. Split IVF-ICSI intervention not part of the review question. The model does not consider or address possible adverse events of intervention.

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			1-cycle IVF Intervention: i) ICSI 0.418 ii) Split IVF-ICSI 0.418 Control: iii) IVF 0.388 Difference: 0.030 *2-cycle IVF* Intervention: i) ICSI 0.648 ii) Split IVF-ICSI 0.649 Control: iii) IVF 0.616 Difference:		

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			Split IVF-ICSI V IVF 0.033 ICSI v Split IVF-ICSI -0.001		

CEA = Cost-effectiveness analysis; ICER = Incremental cost-effectiveness ratio; ICSI = Intracytoplasmic sperm injection; IVF = In vitro fertilisation ; N/A = Not applicable; SART = Society for Assisted Reproductive Technology; USD = United States dollar

Appendix I Economic model

Economic model for review question: What is the clinical and cost effectiveness of intracytoplasmic sperm injection (ICSI) compared to standard in vitro fertilisation (IVF) in non-male factor fertility problems?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What is the clinical and cost effectiveness of intracytoplasmic sperm injection (ICSI) compared to standard in vitro fertilisation (IVF) in non-male factor fertility problems?

Excluded effectiveness studies

See the Characteristics of excluded studies table from the Cochrane review (Cutting 2023): Intracytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in couples with non-male subfertility | Cochrane

Excluded economic studies

No economic evidence was excluded for this review.

Appendix K Research recommendations – full details

Research recommendations for review question: What is the clinical and cost effectiveness of intracytoplasmic sperm injection (ICSI) compared to standard in vitro fertilisation (IVF) in non-male factor fertility problems?

No research recommendations were made for this review question.