National Institute for Health and Care Excellence

Draft for consultation

Fertility problems: assessment and treatment

[M] Advanced sperm selection techniques as a fertility treatment add-on

NICE guideline number NGXXX

Evidence report underpinning recommendations 1.11.3 and 1.11.4 in the NICE guideline

September 2025

Draft for consultation

This evidence review was developed by NICE

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Advanced sperm selection techniques as a fertility treatment add-on

Review question

What is the clinical and cost effectiveness of alternatives to standard sperm selection techniques as a treatment add-on for people undergoing fertility treatment?

Introduction

Fertility treatment add-ons to core treatments such as in-vitro fertilisation (IVF) and intrauterine insemination (IUI) are sometimes offered to patients looking to improve their chances of a live birth or to reduce the risk of adverse events during or after treatment, such as ovarian hyperstimulation syndrome (OHSS). However, the effects of fertility treatment add-ons on these outcomes are often unclear.

Sperm selection is sometimes offered to people with male factor fertility problems and encompasses a range of techniques used to choose sperm according to a set of criteria, with the aim of selecting the best quality sperm for intracytoplasmic sperm injection (ICSI). However, it is unclear whether sperm selection improves fertility patients' chances of live birth.

The aim of this review is to determine the effectiveness of alternatives to standard sperm selection techniques as a fertility-treatment add-on.

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 undergoing treatment using assisted reproductive technology (ART) for a health-related fertility problem
Intervention	Alternatives to standard sperm selection techniques that select based on: • Sperm morphology (intracytoplasmic morphologically selected sperm injection, IMSI) • Hyaluronic acid binding (HA-ICSI; physiological intracytoplasmic sperm injection [PICSI] or Spermslow) • Surface charge (electrophorectic sperm selection or zeta potential selection) • Sperm apoptosis (magnetic-activated cell sorting [MACS]) • Sperm birefringence (polarised light microscopy) • Microfluidic selection, including chemotactic and thermotactic techniques
Comparison	• Head-to-head comparison between alternatives to standard sperm selection techniques (listed above)

	• Standard sperm selection techniques (density gradient centrifugation [DGC] or swim up [SU])
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) **Important** • Miscarriage (loss of a baby before 24 weeks gestational age) • Pregnancy loss (including miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy) • Fetal abnormalities • Fertilisation rate

For further details see the review protocol in appendix A.

Methods and process

During the development of the guideline, the fertility treatment add-ons rating system developed by Human Fertilisation and Embryology Authority (HFEA) was identified as relevant to the effectiveness of sperm selection procedures. Given the potential for efficiencies to the guideline development process and the applicability of the HFEA's work to the UK setting, the committee took the pragmatic decision to draft recommendations relevant to this review question based on the evidence identified by the HFEA, and the HFEA ratings and as such no new systematic review of evidence was conducted for this review question. This approach is consistent with the principles outlined in Appendix N of Developing NICE guidelines: the manual.

The HFEA ratings system considered intracytoplasmic morphologically selected sperm injection (IMSI) and physiological intracytoplasmic sperm injection (PICSI) as alternatives to standard sperm selection techniques. However, the HFEA did not cover the other interventions listed in the protocol. The committee were not aware of any studies that could influence recommendation-making for any of the other interventions, and additionally reviewed the relevant Cochrane reviews to ensure no important evidence was missed – please see the section below for further information on these Cochrane reviews.

The quality of the HFEA evidence statements were assessed independently by 2 reviewers using the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool. This instrument is intended for assessing the quality of systematically developed clinical practice guidelines, including assessments of methodological rigour, transparency, and applicability. The AGREE II instrument is an internationally validated tool that is used to assess the methodological rigour and transparency of clinical practice guidelines. The evidence statements considered by the committee have all been produced with the intention of helping practitioners and service users make informed treatment decisions based on the available evidence for fertility treatment add-ons and in this sense were considered by the committee as being appropriate for inclusion in the evidence base and assessed using AGREE II. However, the fact that the quality of these documents has been assessed by an instrument designed for use on guidelines should be borne in mind. For example, some of the terminology used in AGREE II is based on the assumption that specific recommendations have been made, and therefore domains such as 'Clarity of presentation' and 'Applicability'

include questions directly related to the quality of guidance given and its relevance to clinical practice. The HFEA evidence statements were assessed as the AGREE II tool sets out because all domains are important and form part of this validated instrument, but it is important to acknowledge that some of the low ratings are due to the applicability of the tool to the statements and not necessarily a reflection of the quality of the statements themselves.

The HFEA ratings are available at the treatment add-ons page of the HFEA website.

During the development of this guideline, two published Cochrane reviews were identified which matched the committee's intended PICO and which were referred to by the HFEA, comparing the effectiveness of regular (ICSI) versus ultra-high magnification (IMSI) sperm selection (Teixeira 2020), and comparing the effectiveness of advanced sperm selection techniques such as Hyaluronic acid selected sperm-ICSI (HA-ICSI), including PICSI (Lepine 2019). In the Cochrane review on advanced sperm selection techniques, the comparison of HA-ICSI with regular ICSI includes both PICSI and Spermslow. As these interventions were analysed together, the committee kept this in mind when considering Cochrane's analysis of the evidence alongside the HFEA's when drafting recommendations.

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, differences between outcomes as further discussed in the committee's discussion and interpretation of the evidence below) relevant to the topic area were highlighted to the committee and taken into account in discussions of the evidence.

The HFEA work was conducted in 2023 and the Cochrane reviews were conducted in 2019/2020, so the guideline committee were consulted as to whether further important evidence had been published since the completion of the external reviews that could affect decision-making. However, the guideline committee were not aware of any such evidence.

Full details of the HFEA review methods are available through the HFEA website, and the Scientific and Clinical Advances Advisory Committee (SCAAC) decision tree for rating add-ons is available in the document "SCAAC Meeting Papers July 2023" (p17).

Further description of the methods used in this and other similar reviews are available from the methods document (supplement 1).

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

HFEA ratings

The HFEA ratings for PICSI and the HFEA ratings for IMSI are available from the relevant pages of the HFEA website, as linked. The evidence review commissioned by the HFEA which underpins these ratings is available from the HFEA SCAAC website, under heading 'Meeting minutes and papers' from July 2023, in the document "SCAAC Meeting Papers July 2023" (pp11-12,22 and PDF pp49-51 for PICSI evidence; pp10, 20-21 and PDF pp41-43 for IMSI evidence). The SCAAC decision making on the ratings is described in the document "SCAAC Minutes July 2023 - Treatment Add-Ons" (pp6-7 for PICSI evidence; p6 for IMSI evidence) and in the document "SCAAC Minutes February 2023" (pp5-6 for PICSI evidence).

Summaries of the HFEA ratings and evidence on which the ratings were based are presented in Table 2.

Table 2: Summary of HFEA ratings

Treatment add-on	HFEA ratings
Sperm selection technique based on HA-ICSI: PICSI	Rated black for male factor infertility, and for older women receiving ICSI due to male factor infertility:

Treatment add-on	HFEA ratings
	• On balance, the evidence from moderate/high quality evidence shows that this add-on has no effect on the treatment outcome Rated grey for miscarriage for women over 35 years old receiving ICSI for male factor infertility: • Effectiveness cannot be rated due to insufficient moderate/high quality evidence of effectiveness
Sperm selection technique based on sperm morphology: IMSI	Rated grey for increasing the chances of having a baby for most fertility patients, and for patients undergoing treatment due to male factor infertility: • Effectiveness cannot be rated due to insufficient moderate/high quality evidence of effectiveness

HA-ICSI: hyaluronic acid ICSI; HFEA: Human Fertilisation and Embryology Authority; ICSI: intracytoplasmic sperm injection; IMSI: intracytoplasmic morphologic sperm injection; PICSI: physiological ICSI

HFEA treatment ratings

PICSI was overall given a black rating, to indicate that "On balance, the evidence from moderate/high quality evidence shows that this add-on has no effect on the treatment outcome". In particular, the HFEA stated the findings from moderate or high quality evidence showed PICSI did not increase the chances of live birth for people receiving ICSI for male factor fertility problems. This statement was primarily based on evidence from 1 large RCT which compared PICSI with standard ICSI and was considered to be of high quality, where couples used their own gametes and were scheduled for fresh transfer on days 3 to 5 (Miller 2019).

PICSI was also given a black rating for older women receiving ICSI for male factor fertility problems, based on the findings from studies considered to be of moderate or high quality which showed PICSI did not increase the chances of live birth for this population. This statement was also primarily based on evidence from Miller 2019; specifically, the subgroup analysis by maternal age showing results for older women were similar to those for most fertility patients, as above.

For reducing the chances of miscarriage in women over 35 years old receiving ICSI for male factor fertility problems, PICSI was given a grey rating for insufficient evidence of effectiveness, to indicate that "We cannot rate the effectiveness of this add-on at improving the treatment outcome as there is insufficient moderate/high quality evidence". This was because the only study considered to be of high quality (Miller 2019) was not powered to investigate miscarriage (as it was assessed as a secondary outcome), however results showed miscarriage rates were lower for those who received PICSI.

The HFEA noted no safety concerns from performing PICSI additional to those present when performing ICSI.

Further information about the HFEA rating for PICSI can be found on the relevant page of the HFEA website.

IMSI was overall given a grey rating for insufficient evidence of effectiveness. In particular, the HFEA stated there was insufficient moderate or high quality evidence to assess whether IMSI improved chances of having a baby for most fertility patients. 1 RCT comparing IMSI to standard ICSI provided moderate to high quality evidence showing IMSI resulted in an improved ongoing pregnancy rate (Setti 2013), but this was a small study and the HFEA noted the link between IMSI and older eggs is not fully understood. Studies reporting live birth rates were rare, primarily considered to be of low quality, and found no significant difference in live birth rates between participants receiving IMSI or ICSI.

IMSI was also given a grey rating for people receiving ART for male factor fertility problems, due to a similar evidence base to that for the general population, as described above: 1 RCT considered to be of moderate to high quality showed an improved ongoing pregnancy rate with IMSI (Antinori 2008), but evidence considered to be of low quality showed no significant difference in live birth rates between participants receiving IMSI or ICSI.

The HFEA noted no safety concerns from performing IMSI additional to those present when performing ICSI.

Further information about the HFEA rating for IMSI can be found on the relevant page of the HFEA website.

Further information about the HFEA's rating system can be found on the treatment add-ons page of the HFEA website.

Cochrane reviews

Two Cochrane reviews comparing the effectiveness of regular (ICSI) versus ultra-high magnification (IMSI) sperm selection (Teixeira 2020), and comparing the effectiveness of advanced sperm selection techniques, including PICSI (Lepine 2019) were considered in this report. The Cochrane review on IMSI included 13 randomised controlled trials in the comparison between IMSI and regular ICSI (RCTs: Antinori 2008, Balaban 2011, Check 2013, Figueira 2011, Knez 2011, Knez 2012, Leandri 2013, Mahmoud 2011, Mangoli 2019, Marci 2013, Setti 2011, Setti 2012a, Setti 2012b), and the review on advanced sperm selection techniques included 4 RCTs on the comparison between HA-ICSI (including both PICSI and Spermslow) and regular ICSI (Majumdar 2013, Miller 2019, Troya 2015, Worrilow 2013). The Cochrane reviews had a different protocols to the HFEA's review, with stricter inclusion criteria (for example restricting included studies to RCTs only) and implementation of data synthesis. Additionally, the Cochrane review on sperm selection techniques compared a wider selection of advanced sperm selection techniques including Spermslow (included in the comparison between HA-ICSI and ICSI), magnetic-activated cell sorting (MACS), and surface charge selection (zeta potential selection). No evidence was found on sperm birefringence or microfluidic selection. As a result, different studies were included by Cochrane in their reviews compared to the HFEA's, although there was some overlap. These reviews were additionally considered by the committee to ensure all evidence had been reviewed, and used to supplement the HFEA evidence statements to guide recommendation making by the committee as they were considered sufficiently relevant, high quality and up to date. See the benefits and harms section for the committee's discussion of the Cochrane evidence.

Full details of the Cochrane reviews including methods are available for the Cochrane review on IMSI (Teixeira 2020) and the Cochrane review on advanced sperm selection techniques (Lepine 2019).

Economic evidence

A total of 543 studies were identified in the health economic literature search for this review question. After duplicates were removed, 351 studies were sifted on title and abstract of which all were excluded at this stage.

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Also see the literature search strategy in appendix H and the economic study selection flow chart in appendix C.

Excluded studies

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

Economic model

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

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Originally, the committee prioritised live birth and clinical pregnancy as critical outcomes for decision making because they are the most important outcomes for people with fertility problems, and the committee agreed they should be prioritised above other outcomes to reflect their comparative importance. Of these outcomes, the HFEA only stated that live birth would be given specific consideration in the review and when creating the evidence ratings, but the review did also report information on pregnancy rates when data were provided in included studies. Both live birth and ongoing (clinical) pregnancy were reported in the Cochrane reviews, although in the case of the review on IMSI, ongoing pregnancy was only used as a surrogate outcome in case live birth was not reported.

The committee originally considered miscarriage, pregnancy loss, foetal abnormalities and fertilisation rate as important outcomes. The HFEA review reported on miscarriage, but did not report on pregnancy loss, foetal abnormalities, or fertilisation rate. The Cochrane reviews reported on miscarriage and foetal or congenital abnormalities but not pregnancy loss or fertilisation rate.

The quality of the evidence statements

The quality of the HFEA evidence statements were assessed independently by 2 reviewers using the AGREE II tool and scored between 4% and 61% in all domains. Although the HFEA statements received low scores in some of the domains, the committee was confident this was primarily due to the purpose of the AGREE II tool to assess guidelines, and therefore did not reflect on the quality of the work conducted. Please see the Methods and process section for further information on the use of the AGREE II tool.

The evidence statements scored 50% for scope and purpose. The overall scope of the evidence statements, the health questions covered, and intended population are generally described. However, specific information including the expected benefits/ outcomes of the evidence statements and protocols are not reported.

The evidence statements scored 61% for stakeholder involvement. The SCAAC included a range of individuals from relevant professional groups, and detailed information about the specific professions of the members is linked. A patient representative was a part of the SCAAC, but there is no other information on whether views were sought from the target population/stakeholders or considered during the development of the evidence statements. The target users of the guideline are not well-defined but the intention of the evidence statements (to ensure patients are fully informed about whether add-ons are likely to be effective and to inform clinical decision-making) is made clear.

The score for rigour of development was 40%. A literature search was performed but there is no publicly available information on the search strategy and searches which are therefore not replicable. The committee also noted the review was not systematic and only one database was searched for relevant studies, although they agreed it was unlikely that any critical

evidence was missed. The criteria for selecting the evidence are partially described including detailed information about study selection, but an explicit list of inclusion/exclusion criteria, excluded studies lists and protocols are not reported. Detailed descriptions of the evidence are provided narratively but GRADE tables were not reported. There was also no synthesis of the evidence reported. The committee therefore agreed to use the Cochrane reviews to supplement their understanding of the evidence base, and to ensure any synthesised evidence was considered where possible. The risk of bias domains assessed are described but it is unclear whether an appropriate, certified checklist was used for each study type. Details on the methodology used by the HFEA to arrive at each evidence rating are provided, including a decision tree and descriptions of each rating. There is detailed information about specific discussions the committee had about the evidence, benefits, harms, risks, and, where appropriate, costs of each add-on. There are limited descriptions of how the evidence was interpreted to influence the statements, though it is usually unclear what evidence contributes to each statement and there is some inconsistency in how the evidence has been used to inform evidence statements between add-ons. There is no information about an external review of the evidence statements before publication, but an explicit statement of intent to update the evidence statements is provided with a review date. Information about the HFEA's methods for evidence surveillance and updating the statements is provided.

The evidence statements scored 17% for clarity of presentation. The evidence statements themselves are clearly defined and provided along with a description of each rating. However, the ratings themselves are not recommendations for practice and are therefore usually non-specific and ambiguous. Recommended actions are not provided, and it is rare that advice for how the evidence statements should be interpreted and applied is given.

The score for applicability was 6%. There is no discussion of barriers and facilitators of application and no information is given about feedback from key stakeholders, or whether this type of feedback was sought. There is no advice on how the evidence statements can be put into practice because the intention of the evidence statements is not to provide advice on how practice should be influenced. The cost of each add-on and resource implications are described for add-ons in order to aid decision-making. No monitoring and/or auditing criteria have been reported.

The evidence statements also scored low for editorial independence at 4%. There is very little information reported about funding. An independent reviewer carried out the reviews of the evidence but there is no statement that the funding body did not influence the content of the evidence statements themselves. There is no information about the competing interests of the SCAAC, including no declarations of interest section.

See Appendix B for the AGREE II reviewer scoring tables.

Benefits and harms

The committee reviewed the HFEA treatment rating for IMSI and its underpinning evidence and agreed although there was evidence of an effect of IMSI on pregnancy rates, however noted there was insufficient evidence of an effect of IMSI on live birth. Additionally, meta-analysed data from the Cochrane review found no important difference between IMSI and ICSI for either live birth or clinical pregnancy, and the evidence for both outcomes was very low quality. Based on the HFEA evidence statements, the conclusions from the Cochrane review that the benefits of IMSI over ICSI are very uncertain, and the committee’s expertise and knowledge, they agreed participants should not be offered IMSI to reduce the likelihood of fertility patients seeking a more expensive intervention that has not been proven to provide any benefit over standard ICSI.

The recommendation not to offer PICSI to any fertility patients was based on the HFEA treatment rating and underpinning moderate to high quality evidence that showed no difference between PICSI and standard ICSI for the outcome live birth. The committee were aware of a secondary analysis (West 2022a) of the large RCT examining PICSI (Miller 2019).

The committee discussed the results of the secondary analyses that suggested that PICSI might benefit older fertility patients more. However, the committee noted that, as the study authors acknowledge, the aim of these analyses was to generate mechanistic hypotheses and as such a cohort was sampled from the RCT population making this an observational mechanistic study without the full benefits of random allocation. The committee also emphasised that in the primary RCT analysis, there was no evidence for differential effects of PICSI on outcome based on maternal age. The committee discussed the only significant finding in the Miller 2019 study, namely a lower rate of miscarriage with PICSI relative to ICSI and noted that this was a secondary outcome that the trial was not powered to investigate. In the Cochrane review, in the comparison between HA-ICSI and ICSI, no important difference was found between groups for the outcomes of clinical pregnancy and live birth, but there was a lower chance of miscarriage in the HA-ICSI group. However, this evidence was of low quality with serious imprecision due to low event rate and included both PICSI and other HA-ICSI interventions in the analysis. Overall, the committee agreed the evidence of effectiveness was not sufficient to recommend PICSI over standard ICSI, especially in light of the additional cost without clear benefit.

Cost effectiveness and resource use

No economic evidence was identified for this review question. Therefore, the committee made a qualitive assessment of cost-effectiveness.

The committee noted that intracytoplasmic morphologically selected sperm injection (IMSI) is an adjunct to standard intracytoplasmic sperm injection (ICSI). Therefore, given the nature of the treatment, the committee concluded it would be more expensive than ICSI alone. As the clinical evidence identified in the Cochrane review indicated the effects of IMSI compared to ICSI were uncertain, the committee concluded that ICSI would be the most cost-effective intervention of the two.

When assessing the cost-effectiveness of physiological intracytoplasmic sperm injection (PICSI), the same conclusions were made regarding the costs. That being, PICSI is more expensive than standard ICIS as PICSI is an add-on. Therefore, given the uncertainty of the clinical benefit – in line with higher costs – the committee concluded that offering ICSI alone would be the most cost-effective use of NHS resources.

The recommendations made are reflective of current practice and therefore not expected to result in a significant resource impact.

Other factors the committee took into account

The committee also considered the recommendations made on IMSI and PICSI by the European Society of Human Reproduction and Embryology (ESHRE; Good practice recommendations on add-ons in reproductive medicine) when drafting their recommendations, which were primarily based on the findings of Cochrane reviews on each intervention, as well as consideration of any safety concerns. The committee agreed the NICE recommendation aligns with ESHRE's findings that IMSI and PICSI could not be recommended for routine clinical use.

The full guideline can be found on ESHRE's website: https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Addons

Recommendations supported by this evidence review

This evidence review supports recommendations 1.11.3 and 1.11.4.

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Appendices

Appendix A Review protocols

Review protocol for review question: What is the clinical and cost effectiveness of alternatives to standard sperm selection techniques as a treatment add-on for people undergoing fertility treatment?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42023451152
1.	Review title	Clinical and cost effectiveness of alternatives to standard sperm selection techniques as a treatment add-on for people undergoing fertility treatment
2.	Review question	What is the clinical and cost effectiveness of alternatives to standard sperm selection techniques as a treatment add-on for people undergoing fertility treatment?
3.	Objective	To determine the clinical and cost effectiveness of alternatives to standard sperm selection techniques as a treatment add-on for people undergoing fertility treatment
4.	Searches	The following databases will be searched (with no date limit): 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 • Human studies The guideline committee will decide whether and when to re-run the searches before final submission of the review to retrieve further studies for inclusion.

ID	Field	Content
		The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Fertility treatment add-ons
6.	Population	Inclusion: • People undergoing treatment using assisted reproductive technology (ART) for a health-related fertility problem. In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination.
7.	Interventions	Alternatives to standard sperm selection techniques, that select based on: • Sperm morphology: ○ Intracytoplasmic morphologically selected sperm injection (IMSI), using ultra-high magnification • Hyaluronic acid binding (HA-ICSI): ○ Physiological intracytoplasmic sperm injection (PICSI) ○ Spermslow • Surface charge: ○ Electrophorectic sperm selection ○ Zeta potential selection • Sperm apoptosis: ○ Magnetic-activated cell sorting (MACS) • Sperm birefringence: ○ Polarised light microscopy • Microfluidic selection, including chemotactic and thermotactic techniques
8.	Comparators	• Head-to-head comparison between alternatives to standard sperm selection techniques (listed above) • Standard sperm selection techniques: ○ Density gradient centrifugation (DGC) ○ Swim up (SU)
9.	Types of study to be included	Systematic reviews of RCTs • RCTs (individual or cluster) • If no RCT evidence:

ID	Field	Content
		○ Quasi-randomised controlled trials (experimental studies using a non-randomly assigned control group design with matched comparison or another method of controlling for confounding variables)
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 fully update 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 fetal heart rate)
13.	Secondary outcomes (important outcomes)	• Miscarriage (loss of a baby before 24 weeks gestational age) • Pregnancy loss (including miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy) • Fetal abnormalities • Fertilisation rate
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 two 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, participant characteristics, inclusion and exclusion criteria, details of the interventions, setting and 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 (and quasi-RCTs, if no RCT evidence identified) The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.

ID	Field	Content
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 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: http://www.gradeworkinggroup.org/ Importance and imprecision of findings will be assessed against minimally important differences (MIDs). The following MIDs will be used: • Live birth: statistical significance • All other outcomes: 0.8 and 1.25 for all relative dichotomous outcomes

17.	Analysis of sub-groups	Evidence will be stratified by the following (for comparisons with standard sperm selection techniques):
		• Standard sperm selection techniques:
		  ○ Density gradient centrifugation (DGC)
		  ○ Swim up (SU)
		
		Evidence will be sub-grouped by the following:
		• Female age (based on the mean age in the study):
		  ○ <35 years
		  ○ 35-39 years
		  ○ ≥39 years
		
		Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes:
		• History of miscarriage:
		  ○ Previous miscarriage
		  ○ No previous miscarriage

ID	Field	Content	
		• Previous implantation failure: ○ First embryo transfer ○ After previous failed embryo transfer • Sperm quality: ○ Poor sperm quality ○ Normal (or unselected) sperm quality • Sperm source: ○ Ejaculate ○ Surgical • For ejaculated sperm: ○ Fresh ejaculated sperm ○ Frozen ejaculated sperm Where evidence is stratified or 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
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	July 2023	

ID	Field	Content		
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.		
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		

ID	Field	Content	
		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=451152	
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	Fertility treatment add-on, infertility, sperm selection	
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
		☒	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 Quality assessment (AGREE II)

AGREE II reviewer scoring tables for review question: What is the clinical and cost effectiveness of alternatives to standard sperm selection techniques as a treatment add-on for people undergoing fertility treatment?

Table 4: AGREE II quality assessment of HFEA evidence statements

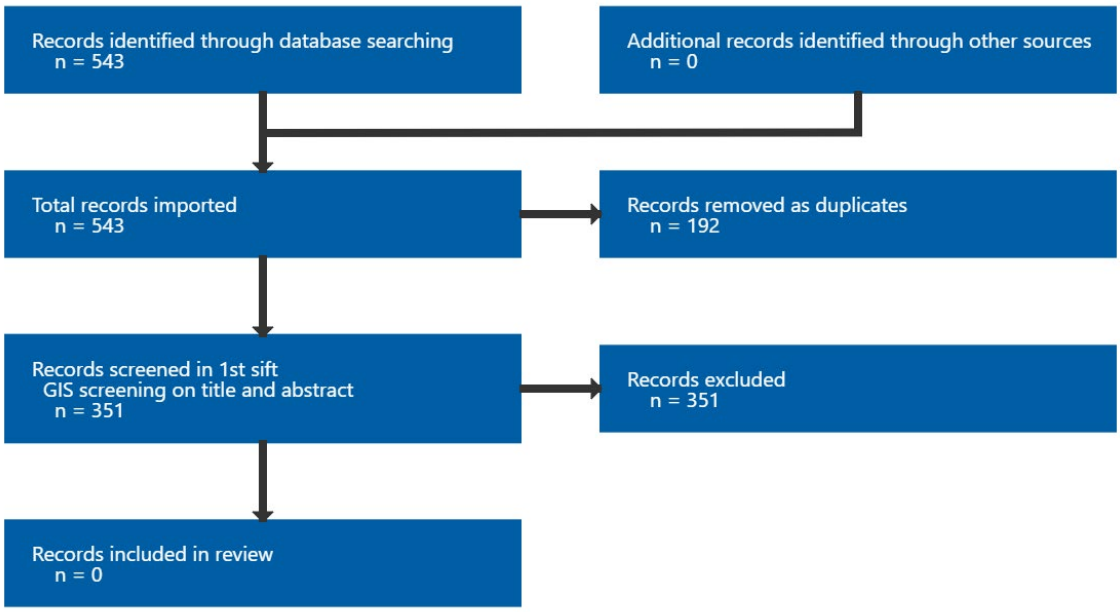
	1. Scope and purpose				2. Stakeholder involvement				3. Rigour of development									4. Clarity of presentation				5. Applicability					6. Editorial independence		
Reviewer	Objectives	Question	Population	Totals and **scores%**	Group membership	Target population	Target users	Totals and **scores%**	Search methods	Evidence selection criteria	Evidence strengths and limitations	Formulation of recs	Consideration of benefits/harms	Link between recommendations and evidence	External review	Updating procedure	Totals and **scores%**	Specific and unambiguous recs	Management options	Identifiable key recs	Totals and **scores%**	Facilitators and barriers to implementation	Implementation advice/tools	Resource implications	Monitoring/auditing criteria	Totals and **scores%**	Funding body	Competing interests	Totals and **scores%**
R1	5	5	6	16	7	4	5	16	3	4	6	7	7	5	1	6	39	2	1	5	8	1	1	4	1	7	2	1	3
R2	2	3	3	8	7	3	2	12	3	2	3	1	2	2	1	1	15	2	1	1	4	1	1	1	1	4	1	1	2
Score%				**50%**				**61%**									**40%**				**17%**					**6%**			**4%**

Appendix C Economic evidence study selection

Study selection for review question: What is the clinical and cost effectiveness of alternatives to standard sperm selection techniques as a treatment add-on for people undergoing fertility treatment?

No economic evidence was identified which was applicable to this review question.

Figure 1: Study selection flow chart



Appendix D Economic evidence tables

Economic evidence tables for review question: What is the clinical and cost effectiveness of alternatives to standard sperm selection techniques as a treatment add-on for people undergoing fertility treatment?

No evidence was identified which was applicable to this review question.

Appendix E Economic model

Economic model for review question: What is the clinical and cost effectiveness of alternatives to standard sperm selection techniques as a treatment add-on for people undergoing fertility treatment?

No economic analysis was conducted for this review question.

Appendix F Excluded studies

Excluded studies for review question: What is the clinical and cost effectiveness of alternatives to standard sperm selection techniques as a treatment add-on for people undergoing fertility treatment?

Excluded effectiveness studies

No effectiveness evidence review was conducted, therefore there are no excluded studies.

Excluded economic studies

No economic evidence was identified for this review.

Appendix G Research recommendations – full details

Research recommendations for review question: What is the clinical and cost effectiveness of alternatives to standard sperm selection techniques as a treatment add-on for people undergoing fertility treatment?

No research recommendations were made for this review question.

Appendix H Health economic literature search strategies

Health economic literature search strategies for review question: What is the clinical and cost effectiveness of alternatives to standard sperm selection techniques as a treatment add-on for people undergoing fertility treatment?

Database: Ovid MEDLINE(R) ALL <1946 to April 03, 2024>

Date of last search: 04/04/2024

#	Searches
1	exp embryo transfer/ or exp fertilization in vitro/
2	embryo transfer*.tw.
3	vitro fertili?ation.tw.
4	ivf.tw.
5	icsi.tw.
6	((intracytoplasmic or intra-cytoplasmic) adj1 sperm injection*).tw.
7	(blastocyst* adj2 transfer*).tw.
8	exp Infertility/
9	(infertil* or subfertil*).tw.
10	exp Ovulation Induction/
11	((ovari* or ovulat*) adj2 (induct* or stimulat* or hyperstimula*)).tw.
12	superovulat*.tw.
13	COH.tw.
14	exp Reproductive Techniques, Assisted/
15	(ART or assisted reproduct*).tw.
16	or/1-15
17	((sperm* or semen*) adj4 (selection* or separat* or prepar*)).tw.
18	surface charge.tw.
19	electrophore*.tw.
20	(zeta adj2 (potential* or method* or select*)).tw.
21	magnetic cell sorting.tw.
22	glass wool.tw.
23	membrane matur*.tw.
24	(magnetic activated cell sort* or MACS).tw.
25	ultramorpholog*.tw.
26	(hyaluron* adj2 (bind* or bound)).tw.
27	(sperm* adj5 birefringence).tw.
28	(ultrahigh magnification* or high-magnification*).tw.
29	motile sperm* organelle.tw.
30	MSOME.tw.
31	IMSI.tw.
32	Raman spectroscop*.tw.
33	confocal light absorption.tw.
34	((scattering or polari*) adj3 microscop*).tw.
35	polscop*.tw.
36	((nonapoptotic* or apopto* or morpholog*) adj3 (sperm* or semen*)).tw.
37	((microfluid* or chemota* or thermota*) and (semen* or sperm*)).tw.
38	(physiological intracytoplas* adj5 sperm*).tw.
39	PICSI.tw.
40	Spermslow*.tw.
41	or/17-40

#	Searches
42	16 and 41
43	limit 42 to english language
44	Economics/
45	Value of life/
46	exp "Costs and Cost Analysis"/
47	exp Economics, Hospital/
48	exp Economics, Medical/
49	exp Resource Allocation/
50	Economics, Nursing/
51	Economics, Pharmaceutical/
52	exp "Fees and Charges"/
53	exp Budgets/
54	budget*.ti,ab.
55	cost*.ti,ab.
56	(economic* or pharmaco?economic*).ti,ab.
57	(price* or pricing*).ti,ab.
58	(financ* or fee or fees or expenditure* or saving*).ti,ab.
59	(value adj2 (money or monetary)).ti,ab.
60	resourc* allocat*.ti,ab.
61	(fund or funds or funding* or funded).ti,ab.
62	(ration or rations or rationing* or rationed).ti,ab.
63	ec.fs.
64	or/44-63
65	quality-adjusted life years/
66	sickness impact profile/
67	(quality adj2 (wellbeing or well being)).ti,ab.
68	sickness impact profile.ti,ab.
69	disability adjusted life.ti,ab.
70	(qal* or qtime* or qwb* or daly*).ti,ab.
71	(euroqol* or eq5d* or eq 5*).ti,ab.
72	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
73	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
74	(hui or hui1 or hui2 or hui3).ti,ab.
75	(health* year* equivalent* or hye or hyes).ti,ab.
76	discrete choice*.ti,ab.
77	rosser.ti,ab.
78	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
79	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
80	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
81	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
82	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
83	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
84	or/65-83
85	64 or 84
86	43 and 85
87	letter/
88	editorial/
89	news/
90	exp historical article/
91	Anecdotes as topic/
92	comment/
93	case reports/

#	Searches
94	(letter or comment*).ti.
95	or/87-94
96	randomized controlled trial/ or random*.ti,ab.
97	95 not 96
98	animals/ not humans/
99	exp Animals, Laboratory/
100	exp Animal Experimentation/
101	exp Models, Animal/
102	exp Rodentia/
103	(rat or rats or rodent* or mouse or mice).ti.
104	or/97-103
105	86 not 104

1 **Database: Embase <1974 to 2024 April 03>**

2 **Date of last search: 04/04/2024**

#	Searches
1	exp in vitro fertilization/
2	embryo transfer*.tw.
3	vitro fertili?ation.tw.
4	ivf.tw.
5	icsi.tw.
6	((intracytoplasmic or intra-cytoplasmic) adj1 sperm injection*).tw.
7	(blastocyst* adj2 transfer*).tw.
8	exp infertility/
9	(infertil* or subfertil*).tw.
10	((ovari* or ovulat*) adj2 (induct* or stimulat* or hyperstimula*)).tw.
11	superovulat*.tw.
12	COH.tw.
13	infertility therapy/ or exp artificial insemination/ or fertility preservation/ or gamete intrafallopian transfer/ or oocyte donation/ or exp oocyte preparation/ or exp sperm retrieval/ or zygote intrafallopian transfer/
14	(ART or assisted reproduct*).tw.
15	or/1-14
16	sperm preparation/ or sperm selection/
17	((sperm* or semen*) adj4 (selection* or separat* or prepar*)).tw.
18	surface charge.tw.
19	electrophore*.tw.
20	(zeta adj2 (potential* or method* or select*)).tw.
21	magnetic cell sorting.tw.
22	glass wool.tw.
23	membrane matur*.tw.
24	(magnetic activated cell sort* or MACS).tw.
25	ultramorpholog*.tw.
26	(hyaluron* adj2 (bind* or bound)).tw.
27	(sperm* adj5 birefringence).tw.
28	(ultrahigh magnification* or high-magnification*).tw.
29	motile sperm* organelle.tw.
30	MSOME.tw.
31	IMSI.tw.
32	Raman spectroscop*.tw.
33	confocal light absorption.tw.
34	((scattering or polari*) adj3 microscop*).tw.

#	Searches
35	polscop*.tw.
36	((nonapoptotic* or apopto* or morpholog*) adj3 (sperm* or semen*)).tw.
37	((microfluid* or chemota* or thermota*) and (semen* or sperm*)).tw.
38	(physiological intracytoplas* adj5 sperm*).tw.
39	PICSI.tw.
40	Spermslow*.tw.
41	or/16-40
42	15 and 41
43	limit 42 to english language
44	health economics/
45	exp economic evaluation/
46	exp health care cost/
47	exp fee/
48	budget/
49	funding/
50	resource allocation/
51	budget*.ti,ab.
52	cost*.ti,ab.
53	(economic* or pharmaco?economic*).ti,ab.
54	(price* or pricing*).ti,ab.
55	(financ* or fee or fees or expenditure* or saving*).ti,ab.
56	(value adj2 (money or monetary)).ti,ab.
57	resourc* allocat*.ti,ab.
58	(fund or funds or funding* or funded).ti,ab.
59	(ration or rations or rationing* or rationed).ti,ab.
60	or/44-59
61	quality adjusted life year/
62	"quality of life index"/
63	short form 12/ or short form 20/ or short form 36/ or short form 8/
64	sickness impact profile/
65	(quality adj2 (wellbeing or well being)).ti,ab.
66	sickness impact profile.ti,ab.
67	disability adjusted life.ti,ab.
68	(qal* or qtime* or qwb* or daly*).ti,ab.
69	(euroqol* or eq5d* or eq 5*).ti,ab.
70	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
71	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
72	(hui or hui1 or hui2 or hui3).ti,ab.
73	(health* year* equivalent* or hye or hyes).ti,ab.
74	discrete choice*.ti,ab.
75	rosser.ti,ab.
76	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
77	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
78	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
79	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
80	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
81	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
82	or/61-81
83	43 and (60 or 82)
84	letter.pt. or letter/
85	note.pt.
86	editorial.pt.

#	Searches
87	case report/ or case study/
88	(letter or comment*).ti.
89	or/84-88
90	randomized controlled trial/ or random*.ti,ab.
91	89 not 90
92	animal/ not human/
93	nonhuman/
94	exp Animal Experiment/
95	exp Experimental Animal/
96	animal model/
97	exp Rodent/
98	(rat or rats or rodent* or mouse or mice).ti.
99	or/91-98
100	83 not 99
101	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
102	100 not 101

1 **Database: INAHTA**

2 **Date of last search: 04/04/2024**

#	Searches
1	"Embryo Transfer"[mhe]
2	"Fertilization in Vitro"[mhe]
3	embryo transfer*
4	("vitro fertilisation" or "vitro fertilization")
5	ivf
6	icsi
7	((intracytoplasmic or "intra-cytoplasmic" or "intra cytoplasmic") AND sperm injection*)
8	(blastocyst* AND transfer*)
9	"Infertility"[mhe]
10	(infertil* or subfertil*)
11	"Ovulation Induction"[mhe]
12	((ovari* or ovulat*) AND (induct* or stimulat* or hyperstimula*))
13	superovulat*
14	COH
15	"Reproductive Techniques, Assisted"[mhe]
16	(ART or assisted reproduct*)
17	#16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
18	((sperm* or semen*) AND (selection* or separat* or prepar*))
19	"surface charge"
20	electrophore*
21	(zeta AND (potential* or method* or select*))
22	"magnetic cell sorting"
23	"glass wool"
24	membrane matur*
25	(magnetic activated cell sort* or MACS)
26	ultramorpholog*
27	(hyaluron* AND (bind* or bound))
28	(sperm* AND birefringence)
29	(ultrahigh magnification* or "high-magnification" or "high magnification" or "high magnifications" or "high-magnifications")

#	Searches
30	motile sperm* organelle
31	MSOME
32	IMSI
33	Raman spectroscop*
34	"confocal light absorption"
35	((scattering or polari*) AND microscop*)
36	polscop*
37	((nonapoptotic* or apopto* or morpholog*) AND (sperm* or semen*))
38	((microfluid* or chemota* or thermota*) AND (semen* or sperm*))
39	(physiological intracytoplas* AND sperm*)
40	PICSI
41	Spermslow*
42	#41 OR #40 OR #39 OR #38 OR #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18
43	#42 AND #17

1 **Database: HTA via CRD**

2 **Date of last search: 04/04/2024**

#	Searches
1	MESH DESCRIPTOR Embryo Transfer EXPLODE ALL TREES
2	MESH DESCRIPTOR Fertilization in Vitro EXPLODE ALL TREES
3	(embryo NEXT transfer*)
4	("vitro fertilisation" or "vitro fertilization")
5	ivf
6	icsi
7	((intracytoplasmic or (intra NEXT cytoplasmic*)) NEAR1 sperm injection*)
8	(blastocyst* NEAR2 transfer*)
9	MESH DESCRIPTOR Infertility EXPLODE ALL TREES
10	(infertil* or subfertil*)
11	MESH DESCRIPTOR Ovulation Induction EXPLODE ALL TREES
12	((ovari* or ovulat*) NEAR2 (induct* or stimulat* or hyperstimula*))
13	superovulat*
14	COH
15	MESH DESCRIPTOR Reproductive Techniques, Assisted EXPLODE ALL TREES
16	(ART or (assisted NEXT reproduct*))
17	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
18	((sperm* or semen*) NEAR4 (selection* or separat* or prepar*))
19	"surface charge"
20	electrophore*
21	(zeta NEAR2 (potential* or method* or select*))
22	"magnetic cell sorting"
23	"glass wool"
24	(membrane NEXT matur*)
25	(("magnetic activated cell" NEXT sort*) or MACS)
26	ultramorpholog*
27	(hyaluron* NEAR2 (bind* or bound))
28	(sperm* NEAR5 birefringence)
29	((ultrahigh NEXT magnification*) or (high NEXT magnification*))
30	(motile NEXT sperm* NEXT organelle)
31	MSOME

#	Searches
32	IMSI
33	(Raman NEXT spectroscop*)
34	"confocal light absorption"
35	((scattering or polari*) NEAR3 microscop*)
36	polscop*
37	((nonapoptotic* or apopto* or morpholog*) NEAR3 (sperm* or semen*))
38	((microfluid* or chemota* or thermota*) AND (semen* or sperm*))
39	(physiological NEXT intracytoplas* NEAR5 sperm*)
40	PICSI
41	Spermslow*
42	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41
43	#17 AND #42
44	(#43) IN HTA

1

2