National Institute for Health and Care Excellence

Final

Fertility problems: assessment and treatment

[P] Endometrial scratch as a treatment add-on

NICE guideline number NG257

Evidence report underpinning recommendation 1.40.1 in the NICE guideline

March 2026

Final

Developed by NICE

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Review question

What is the clinical and cost effectiveness of endometrial scratch 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.

Endometrial scratch involves injuring, or scratching, the lining of the womb in a controlled procedure with the intention of triggering the body's repair response, in theory resulting in a womb lining that's more receptive to an embryo implanting and thereby reducing the chance for embryo implantation failure. However, it is unclear whether endometrial scratch is beneficial for fertility patients, including for those who have a history of embryos not implanting during assisted reproductive therapy.

The aim of this review is to determine the effectiveness of endometrial scratch 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 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.
Intervention	• Endometrial scratching, also known as endometrial injury, performed prior to embryo transfer or intrauterine insemination (IUI)
Comparison	• Standard embryo transfer without endometrial scratching • Standard IUI without endometrial scratching • Sham procedure Comparisons between different instruments used for endometrial scratching (for example, pipelle, Tao brush), or between different numbers of procedures, will be included
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 fetal heart rate) **Important** • Miscarriage (loss of a baby before 24 weeks gestational age) • Multiple gestation • Adverse effects, including pain during endometrial scratching, abnormal bleeding during or after endometrial scratching, or infection as a result of endometrial scratching

IUI: intrauterine insemination

Methods and process

During the development of the guideline, the fertility treatment add-ons rating system developed by the Human Fertilisation and Embryology Authority (HFEA) was identified as relevant to the effectiveness of endometrial scratching. 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 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, a published Cochrane review was identified which matched the committee's intended PICO and which was referred to by the HFEA, comparing the effectiveness of endometrial injury versus no procedure or a sham procedure (Lensen 2021). The Cochrane review also compared higher versus lower degree of endometrial injury, however in order to be consistent with the HFEA's approach and the intended approach as specified by the committee for this guideline, only the comparison of endometrial injury versus no procedure or a sham procedure was considered by the committee.

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 review was conducted in 2021, 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 new evidence that would impact the conclusions.

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 endometrial scratching are available from the relevant page 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" (pp8-9, 19-20 and PDF pp34-37 for endometrial scratching evidence). The SCAAC decision making on the ratings is described in the document "SCAAC Minutes July 2023 - Treatment Add-Ons" (pp3-4).

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

Table 2: Summary of included guidelines

Treatment add-on	HFEA ratings
Endometrial scratch	Rated orange for improving the chances of having a baby for most fertility patients undergoing IVF or ICSI: • On balance, it is not clear whether this add-on is effective at improving the treatment outcome. This is because there is conflicting moderate/high quality evidence – in some studies the add-on has been found to be effective, but in other studies it has not. Rated grey for improving the chances of having a baby for patients with recurrent implantation failure (RIF): • Effectiveness cannot be rated due to insufficient moderate/high quality evidence of effectiveness

ICSI: intracytoplasmic sperm injection; IVF: in-vitro fertilisation

HFEA treatment ratings

Endometrial scratching was overall given an orange rating for unclear evidence of effect, indicating that on balance, it is not clear whether this add-on is effective at improving the treatment outcome, because of conflicting evidence considered to be of moderate or high quality.

Contributing to this overall rating, endometrial scratching was rated orange for increasing the chances of having a baby for most fertility patients, primarily based on findings from 5 more recently conducted randomised controlled trials (RCTs: Gibreel 2015; Glanville 2022; Hilton 2019; Mackens 2020; Wong 2022). It is important to note that this rating only applies to participants undergoing IVF/ICSI, as the HFEA felt that the studies they considered to be of moderate or high quality were mostly assessed only in participants undergoing IVF/ICSI, whereas "results for natural/IUI cycles were consistently positive but tended to be from early, small studies at questionable risk of bias." In terms of the 5 more recent studies that were considered moderate or high quality, the HFEA interpreted the evidence as conflicting for the outcome live birth, whereby 3 studies were considered to favour endometrial scratching and 2 were considered to favour control (no or sham procedure). However, within the studies showing a benefit of endometrial scratching, the 95% confidence intervals were all very wide and crossed the line of no effect for the outcome live birth, showing significant uncertainty in the effect estimate. Other included studies which did find that endometrial scratching improved live birth rates were considered to be poor quality, and the HFEA also noted these tended to be older studies. The HFEA also noted some concerns related to endometrial scratching, including that it is an intrusive and potentially painful procedure, plus some safety concerns relating to the potential for patients to experience blood loss or for the procedure to cause existing infection in the cervix to spread to the uterus. However, there are no additional known risks of endometrial scratching for the child born as a result of fertility treatment, thereby not justifying a red treatment rating.

Endometrial scratching was given a grey rating both for improving the chances of having a baby for patients with recurrent implantation failure due to the fact that most of the studies investigating the effectiveness of endometrial scratching in this population were non-randomised trials, and none of the RCTs were considered to be moderate or high quality.

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

Further information about the HFEA's rating system can be found on the relevant page of the HFEA website.

Cochrane review

One Cochrane review investigating the effectiveness of endometrial injury (Lensen 2021), including 37 RCTs comparing the effectiveness of endometrial injury versus no procedure or a sham procedure, was considered in this report. This Cochrane review had a different protocol to the HFEA's review, with stricter inclusion criteria (for example restricting included studies to RCTs only) and implementation of data synthesis. Additionally, a post-hoc decision was made by Cochrane to restrict primary analyses to studies at low risk of selection or other bias, due to the high risk of bias associated with many of the included studies. Sensitivity analyses were conducted by Cochrane to assess whether review conclusions would have been different if eligibility had been restricted to studies without high risk of bias in any domain, or if all studies were included regardless of risk of bias. Eight studies were included in the primary analyses (Berntsen 2020; Hilton 2019; Lensen 2019; Metwally 2020; Olesen 2019; Polanski 2015; van Hoogenhuijze 2020; Yeung 2014).

There was overlap between Cochrane and the HFEA, as most studies included in the Cochrane review were also included in the HFEA's. The Cochrane review was considered sufficiently relevant, high quality and up to date, and therefore was 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. See the benefits and harms section for the committee's discussion of the Cochrane evidence.

Full details of the Cochrane review (Lensen 2011) including methods are available, as linked.

Economic evidence

A total of 615 studies were identified in the health economic literature search for this review question. After duplicates were removed, 398 studies were screened on title and abstract. Three of these studies were included and screened on full text. One of these studies was excluded, and two were included for this review question.

Included studies

Two economic studies were identified that were relevant to this question (Metwally 2022 and van Hoogenhuijze 2022).

An overview of the included health economic evidence is presented in Table 3. For a more detailed summary of the included studies see appendix E.

Also see the literature search strategy in appendix J 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 H.

Summary of included economic evidence

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

Table 3: Economic evidence profile of a systematic review of economic evaluations for endometrial scratching prior to IVF

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectiveness	
Metwally 2022 Endometrial scratching prior to IVF (with or without ICSI) compared to IVF (with or without ICSI) without endometrial scratching	Potentially serious limitations[1]	Directly applicable[2]	Within trial cost-effectiveness analysis with a 1-year time horizon UK HTA analysis Cost year 2018/19	£316.25	0.015 live births	£11.90 per additional live birth	70% chance that endometrial scratching is cost-effective with a willingness to pay threshold of £1,000
Hoogenhuijze 2022 Endometrial scratching prior to the second IVF/ICSI cycle (due to first cycle failure) compared to no endometrial scratching prior to the second IVF/ICSI cycle (due to first cycle failure)	Potentially serious limitations[3,4]	Partially applicable[5]	Within trial cost-effectiveness analysis with a 1-year time horizon	£148	0.048	£3,062 per additional live birth	80% chance that endometrial scratching is cost-effective with a willingness to pay threshold ~£12 000 per additional live birth

[1] Calculation of ICER appears to be incorrect. Recalculated ICER as £21.08 per additional live birth (£316.25/15). Of note, this recalculation is still uncertain as insufficient explanation was provided in the study as to how the authors calculated their ICERs.
[2] Economic analysis conducted as part of a Health Technology Assessment: UK costs, baseline and effectiveness data from a UK population being treated in the NHS. This RCT was included in the clinical review
[3] Base case economic analysis used costs from the Netherlands and was conducted from a societal perspective.

[4] UK unit healthcare and treatment costs were obtained from only one NHS hospital in the UK (university hospitals Coventry and Warwickshire). It is stated that medication costs were obtained from a NICE guideline and complications costs were estimated based on NHS prices. References for these costs are not provided. However, a breakdown of cost components were.

[5] Primary analysis conducted from a societal perspective and based on clinical data from an RCT conducted in the Netherlands. Results displayed in Table 6 are from a sensitivity analysis conducted where costs were obtained from the UK and a healthcare perspective was employed. Primary analysis results with details on the societal perspective costs in the study can be found in Table 8 (Appendix E)

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 reported in included studies. Both live birth and clinical pregnancy were reported in the Cochrane review.

The committee originally considered miscarriage, multiple gestation, and adverse events (including pain, abnormal bleeding, and infection) as important outcomes. The HFEA review reported on miscarriage, but did not report on multiple gestation or adverse events. The Cochrane review reported on miscarriage, multiple gestation, pain, and abnormal bleeding, but did not report on infection as an adverse event.

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 prior to 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 endometrial scratching and its underpinning evidence and agreed the uncertainty in the evidence base meant it is unclear whether the add-on has the potential to harm, provide benefit, or have no effect on outcomes. During the consultation of the draft guideline, the committee were made aware that several of the studies included in the HFEA's underpinning evidence review had either been retracted or had trustworthiness issues related to the authorship group having retraction watch notices for other articles (Gibreel 2015, Maged 2018, Helmy 2017, El Khayat 2015, and Karimzadeh 2009). The HFEA's treatment rating was primarily based on five RCTs determined by the HFEA to be high quality (Gibreel 2015, Hilton 2019, Wong 2022, Mackens 2020, Glanville 2022). The critical review of studies included assessment of risk of bias from allocation method, blinding, selective reporting, unexplained attrition, unplanned interim analysis and other miscellaneous errors in the design, conduct or reporting of results, however trustworthiness checks were not a part of the HFEA's methods. The committee agreed the exclusion of Gibreel 2015 did not affect their interpretation of the results compiled by the HFEA as being uncertain. The other 4 studies with trustworthiness issues did not have substantial influence on decision-making or the HFEA's evidence statement due to their low quality. The committee also noted the Cochrane review referred to by the HFEA, which compared the effectiveness of endometrial injury versus no intervention or sham procedure (Lensen 2021). Under the comparison of endometrial scratching versus no intervention or sham procedure, 37 studies were included. However, Cochrane limited their primary

analyses to include only studies at low risk of selection or other bias because of the high risk of bias associated with many of the included studies. As a result, 8 studies were included in the primary analyses. The evidence contributing to the primary analyses was of moderate quality but the outcomes were all downgraded for serious imprecision because of wide confidence intervals compatible with appreciable benefit, no effect, and harm. Sensitivity analyses were conducted to assess whether review conclusions would have been different if eligibility had been restricted to studies without high risk of bias in any domain, or if all studies were included regardless of risk of bias, and these were all consistent with the primary findings. Cochrane concluded that endometrial injury does not appear to affect the chance of miscarriage, but the effect of endometrial injury on live birth and clinical pregnancy among women undergoing IVF is unclear because the results of the meta-analyses are consistent with an increased chance, no effect and a small reduction in these outcomes.

Endometrial scratching is an invasive procedure which is associated with a time and monetary cost, as it is not possible to conduct it as part of another procedure. As a result of the uncertainty in the evidence base, the committee's concerns about the high level of inconsistency between studies, and the potential for endometrial scratching to have a negative impact on IVF outcomes or no impact at all, the committee agreed it could not be recommended.

The existing evidence base was significantly contradictory despite the volume and quality of it, including moderate to high quality evidence as assessed by both the HFEA and Cochrane. The committee therefore additionally agreed that further research on endometrial scratch in the general infertility population is unlikely to resolve the issues in the existing body of evidence. Therefore, the committee did not make a research recommendation on this topic although they acknowledged the lack of RCTs among those with recurrent implantation failure and further studies could help determine the effectiveness of endometrial scratch in this sub-population.

Cost effectiveness and resource use

Two health economic studies were included for this review question (Metwally 2022 and Hoogenhuijze 2022). The most applicable health economic study (Metwally 2022) was a Health Technology Assessment (HTA) which consisted of an RCT and systematic literature review. The economic component of the HTA was conducted alongside the RCT from an NHS and PSS perspective. However, within this study it was unclear exactly how the ICER had been calculated. The ICER was subsequently recalculated, however, the committee acknowledged there was still a level uncertainty of this calculation due to insufficient methodological descriptions reported in the HTA for the cost-effectiveness analysis.

The other health economic study included for this review question (Hoogenhuijze 2022) was a within-trial cost-effectiveness analysis of the SCRaTCH trial. Both RCTs (Metwally 2022 and Hoogenhuijze 2021) were included in the Cochrane review that informed the HFEAs recommendations on endometrial scratching. The HTA assessed the clinical and cost effectiveness of endometrial scratching for people undergoing an initial cycle of IVF whereas the economic analysis conducted alongside the SCRaTCH trial assessed the clinical and cost effectiveness of endometrial scratching for people undergoing their second round of IVF.

Even though the results of both health economic studies indicated that endometrial scratching could be cost-effective, as the cost per additional live birth was low, the committee concluded they were unable to make a recommendation due to the high degree of uncertainty associated with the clinical evidence used to inform both cost-effectiveness analyses. The committee reflected that this uncertainty was reflected in the large discrepancy between the two reported ICERs for the costs per additional live birth reported in both studies (£11.90 and £3,062 for Metwally 2022 and Hoogenhuijze 2022 respectively).

The committee acknowledged that the two included health economic studies were based on RCTs that were included in the Cochrane clinical review. However, noted that these two RCTs only represent a small proportion of the total evidence base, as a total of 37 studies were included in the Cochrane review. In addition, the authors of both studies concluded that endometrial scratching should not be recommended. The conclusion from Metwally 2022 was that endometrial scratching should not be undertaken as they found no evidence that endometrial scratching improved the live birth rate. In addition, Hoogenhuijze 2022 noted that there was a high degree of uncertainty surrounding the effects – especially the clinical effects – and therefore a conclusion on recommending endometrial scratching could not be ascertained. The committee therefore concluded that endometrial scratching should not be recommended due to the high degree of uncertainty of clinical effectiveness.

As the committee made a recommendation reflective of current clinical practice – stating that endometrial scratching should not be offered as a pre-treatment means of improving the outcomes of IVF. No significant resource impact will be associated with this recommendation.

Other factors the committee took into account

The committee were also aware of the recommendation made on endometrial scratching by the European Society of Human Reproduction and Embryology (ESHRE; Good practice recommendations on add-ons in reproductive medicine). This recommendation was based on existing RCTs and systematic reviews (including the Cochrane review referred to by the HFEA: Lensen 2021), as well as consideration of the cost of endometrial scratching and any safety concerns (ESHRE Add-ons working group 2023). The committee agreed the NICE recommendation aligns with ESHRE's findings that endometrial scratching 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 recommendation 1.40.1.

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Effectiveness

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Appendices

Appendix A Review protocols

Review protocol for review question: What is the clinical and cost effectiveness of endometrial scratching as a treatment add-on for people undergoing fertility treatment?

Table 4: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42023451326
1.	Review title	Clinical and cost effectiveness of endometrial scratching as a treatment add-on for people undergoing fertility treatment
2.	Review question	What is the clinical and cost effectiveness of endometrial scratching as a treatment add-on for people undergoing fertility treatment?
3.	Objective	To determine the clinical and cost effectiveness of endometrial scratching 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. 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 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	• Endometrial scratching, also known as endometrial injury, performed prior to embryo transfer or intrauterine insemination (IUI)
8.	Comparators	• Standard embryo transfer without endometrial scratching • Standard IUI without endometrial scratching • Sham procedure Comparisons between different instruments used for endometrial scratching (for example, pipelle, Tao brush), or between different numbers of procedures, will be included
9.	Types of study to be included	• Systematic reviews of RCTs • RCTs (individual or cluster) • If no RCT evidence: ○ 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) • Multiple gestation • Adverse effects, including pain during endometrial scratching, abnormal bleeding during or after endometrial scratching, or infection as a result of endometrial scratch
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.
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:
		• Fertility treatment:
		  ○ In vitro fertilisation (IVF)
		  ○ IUI
		
		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:
		• Previous implantation failure
		  ○ First embryo transfer
		  ○ After previous failed embryo transfer
		• Timing of endometrial scratching

		○ follicular phase prior cycle ○ luteal phase prior cycle ○ early follicular phase IVF cycle ○ late follicular phase IVF cycle 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			
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 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?ID=CRD42023451326		
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, endometrial scratching, endometrial injury	
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 endometrial scratching as a treatment add-on for people undergoing fertility treatment?

Table 5: 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%**

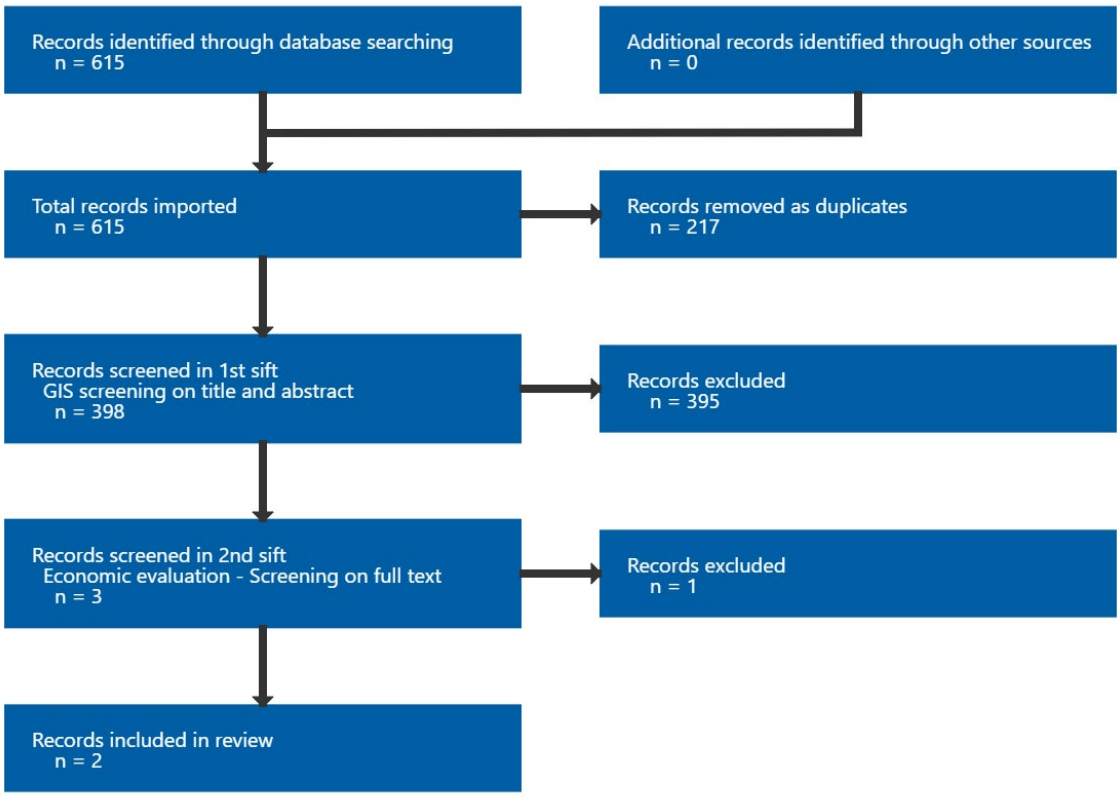
Appendix C Economic evidence study selection

Study selection for review question: What is the clinical and cost effectiveness of endometrial scratching as a treatment add-on for people undergoing fertility treatment?

Two health economic studies were included in this review and one study was excluded after screening on full text. Reasons for exclusion are listed in appendix H.

A summary of the included health economic evidence can be found in appendix E.

Figure 1: Study selection flow chart



Appendix E Economic evidence tables

Economic evidence tables for review question: What is the clinical and cost effectiveness of endometrial scratching as a treatment add-on for people undergoing fertility treatment?

Table 6: Economic evidence tables for the clinical and cost effectiveness of endometrial scratching as a treatment add-on for people undergoing fertility treatment

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Author and year: Metwally 2022 **Country:** UK **Type of economic analysis:** CEA **Source of funding:** National Institute for Health Research (NIHR) Health Technology	**Intervention:** Endometrial scratching (ES) undertaken in the mid-luteal phase of menstrual cycle prior to IVF for women undergoing their first IVF cycle – with or without ICSI **Comparator:** IVF only (TAU) – women undergoing	**Population characteristics:** Women aged 18 – 37 undergoing their first IVF cycle (with or without ICSI) Women were expected to be receive treatment using fresh embryos and expected to be good responders to treatment – having an ovulatory menstrual cycle and normal uterine cavity. Exclusion criteria: women with severe endometriosis, BMI ≥35kg/m^2, previous endometrium trauma. **Modelling approach:** Within-trial analysis *A pragmatic, multicentre, superiority, open-label, parallel-group,*	**Costs:** Health care perspective **Mean cost per participant** **Intervention:** £6,819.38 **Comparator:** £6,503.00 **Difference:** £316.25 **Primary measure of outcome:** Cost per successful birth *If there were multiple live births per person this was noted as a single event.* **Mean outcome per participant**	**ICER:** £11.90 per successful live birth ***Recalculated ICER of £21.08 (£316.25/15)*** **Probability of being cost effective:** 70% chance of being cost effective with a WTP for a live birth of £1,000 **Subgroup analysis:** To assess differences in costs: 1. Day of embryo transfer (day, 2,3,4,5 or 6), 2. Fertilisation method (IVF, ICSI, or split ICSI)	**Currency:** UK pounds **Cost year:** 2018/19 **Time horizon:** 12 months **Discounting:** NA **Applicability:** Directly applicable **Limitations:** Potentially serious limitations **Other comments:** Bootstrapping undertaken to assess uncertainty in parameter estimates

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Assesment Programme	their first IVF cycle – with or without ICSI	*individually randomised controlled trial undertaken at 16 UK fertility units* *n=1048, ES=523, TAU=525* **Source of baseline data:** Metwally 2020 **Source of effectiveness data:** Metwally 2020 **Source of cost data:** RCT – health resource use was measured at baseline and 3 and 10.5 months (or at 6 weeks post-partum) post egg collections. Patients cost estimated 3 months post egg collection – both outcomes were collected using a bespoke questionnaire. **Source of unit cost data:** NHS reference costs, PSS unit costs, ONS data	**Intervention:** NR **Control:** NR **Difference:** 0.015 ***Recalculated value of 15*** *This value was the same in all analyses:* • *Worst case* • *Best case* • *Complete case*	3. Type of protocol (long treatment or antagonist) 4. Embryo transfer (single or double) 5. History of miscarriages (0-2 or ≥3) 6. Cycle programming (yes/no) 7. For ES, delaying the start of IVF *A significant difference in costs was only observed for the day of embryo transfer, so a SA analysis was conducted for this.* **Sensitivity analysis:** Societal perspective: £2.67 per successful live birth Adjusting for baseline costs: £5.38 per successful live birth Adjusting for baseline costs and day of embryo transfer: £10.06 per successful live birth	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Author and year: van Hoogenhuijze 2022 **Country:** Netherlands **Type of economic analysis:** CEA **Source of funding:** Dutch organization for funding healthcare research (ZonMW)	**Intervention :** Endometrial scratching prior to the second IVF/ICSI cycle (due to first cycle failure) – n=467 Single endometrial scratch 5– 10 days before the expected menstrual or withdrawal bleeding, after which ovarian hyperstimulation was started. Endometrial scratching was performed with an endometrial biopsy catheter	**Population characteristics:** Women who had undergone one full IVF/ICSI cycle with at least one embryo transfer that did not result in a clinical pregnancy were eligible. Additional inclusion criteria were 18–44 years old, primary or secondary infertility and a normal transvaginal ultrasound. Exclusion criteria were endometriosis grade III/IV, untreated hydrosalpinx, oocyte donation and preimplantation genetic diagnosis. **Modelling approach:** Within-trial analysis **Source of baseline data:** van Hoogenhuijze 2020 (SCRaTCH trial) **Source of effectiveness data:** van Hoogenhuijze 2020 (SCRaTCH trial) **Source of cost data:** van Hoogenhuijze 2020 (SCRaTCH trial) **Source of unit cost data:** Calculated estimate for ES • *Based on the average time and medical equipment needed for a scratch. Costs for placement of an*	**Costs:** Societal perspective (healthcare perspective with UK costs conducted as a sensitivity analysis) *Societal costs were for lost productivity costs associated with treatment, OHSS and complications for both females and males (no further detailed reported in study).* **Mean cost per participant:** **Intervention:** €8,477 **Control:** €8,194 **Difference**: €283 **Primary measure of outcome:** Cost per live birth *Biochemical pregnancy leading to live birth within the full follow-up period (i.e. biochemical pregnancy must be reached within 10 months and 2 weeks—*	**ICERs:** €5,846 **Probability of being cost effective:** 80% chance that endometrial scratching is cost-effective if society is willing to pay €17,500 for each additional live birth **Subgroup analysis:** Cost per live birth with the secondary outcome of biochemical pregnancy leading to live birth after just the fresh cycle directly after randomisation (instead of within the full follow-up period): ICER of €9,776 per additional live birth *Mean cost per participant:* *Intervention: €5,337* *Control: €4,900* *Difference: €437* *Mean outcome per participant:* *Intervention: 0.236* *Control: 0.191* *Difference: 0.045*	**Currency:** Euros (€) **Cost year:** 2018 **Time horizon:** 12 months **Discounting:** NA **Applicability:** Partially applicable **Limitations:** Potentially serious limitations **Other comments:** Bootstrapping undertaken to assess uncertainty in parameter estimates

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
	without additional anaesthetics or sedatives. The residual tissue was not histologically or cytologically evaluated **Comparator:** No endometrial scratching prior to the second IVF/ICSI cycle (due to first cycle failure) – n=466 Women started directly with ovarian hyperstimulation.	*intrauterine device (without the product costs), a regular ultrasound, and costs of an endometrial biopsy catheter* Dutch expert panel Dutch healthcare institute	*323 days—after randomization).* **Mean outcome per participant:** **Intervention:** 0.441 **Control:** 0.393 **Difference:** 0.048	80% chance that endometrial scratching is cost-effective if society is willing to pay ~€20 000 **Sensitivity analysis:** Using a lower and higher price for endometrial scratching (base case price €104): • At a price of €50 the ICER was €4,096 per additional live birth with an80% chance that endometrial scratching is cost-effective if society is willing to pay ~€13 000 per additional live birth. • At a price of €350 the ICER was €9,935 per additional live birth with an 80% chance that endometrial scratching is cost-effective if society is willing to pay ~€26,500 per additional live birth.	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
				Using UK costs and taking a healthcare payer perspective: • Endometrial scratching costs: £7,065 • Comparator costs: £6,917 • Cost difference: £148 • ICER: £3,062 per additional live birth • 80% chance that endometrial scratching is cost-effective if the UK is willing to pay ~£12 000 per additional live birth *Cost year 2019 and unit cost for endometrial scratching £180. Cost per live birth calculated using the primary outcome measure.*	

CEA= cost-effectiveness analysis, ES= endometrial scratching, ICER= incremental cost effectiveness ratio, ICSI= Intracytoplasmic sperm injection, IVF= In vitro fertilization, NA= not applicable, NHS= National health service, NR= not reported, ONS= Office for National Statistics, RCT= randomised control trial, SA= sensitivity analysis, TAU= treatment as usual, UK= United Kingdom,

Appendix G Economic model

Economic model for review question: What is the clinical and cost effectiveness of endometrial scratching as a treatment add-on for people undergoing fertility treatment?

No economic analysis was conducted for this review question.

Appendix H Excluded studies

Excluded studies for review question: What is the clinical and cost effectiveness of endometrial scratching 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

Table 7: Excluded health economic studies

Study	Code [Reason]
van Hoogenhuijze, N E; Mol, F; Laven, J S E; Groenewoud, E R; Traas, M A F; Janssen, C A H; Teklenburg, G et al. (2021) Endometrial scratching in women with one failed IVF/ICSI cycle-outcomes of a randomised controlled trial (SCRaTCH); Human reproduction (Oxford, England); 2021; vol. 36 (no. 1); 87-98	- Not an economic evaluation

Appendix I Research recommendations – full details

Research recommendations for review question: What is the clinical and cost effectiveness of endometrial scratching as a treatment add-on for people undergoing fertility treatment?

No research recommendations were made for this review question.

Appendix J Literature search strategies

Literature search strategies for review question: What is the clinical and cost effectiveness of endometrial scratching as a treatment add-on for people undergoing fertility treatment?

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

Date of last search: 04/06/2024

#	Searches
1	exp Infertility/
2	(steril* or sub-fertil* or subfertil* or infertil* or infecund* or sub-fecund* or subfecund* or hypofertil*).tw.
3	exp Fertilization in Vitro/
4	exp Embryo Transfer/ or Embryo Implantation/
5	Blastocyst/
6	(embryo* or blastocyst* or blastomer*).tw.
7	(vitro adj1 fertili*).tw.
8	(ivf or ICSI).tw.
9	((intracytoplas* or intra-cytoplas*) adj2 (sperm or injection*)).tw.
10	Reproductive Techniques, Assisted/
11	(assisted adj1 (reproduct* or conception)).tw.
12	((artificial* or intrauter* or uter* or oviduct*) adj2 inseminat*).tw.
13	IUI.tw.
14	FET.tw.
15	((implant* or transfer*) adj2 fail*).tw.
16	(poor prognos* or RIF).tw.
17	or/1-16
18	Endometrium/in, su
19	Endometrium/ and ("Wounds and Injuries"/ or Biopsy/)
20	(endometri* adj4 (injur* or trauma* or biop* or harm* or damag* or inflam* or wound* or lesion* or insult* or scratch* or sampl* or disrupt* or prim* or brush* or stimulat* or activat* or curett*)).tw.
21	(Pipelle* or Novak* or Novac* or Tao brush*).tw.
22	((mock or dummy) adj3 (transfer* or cycle*)).tw.
23	or/18-22
24	17 and 23
25	letter/
26	editorial/
27	news/
28	exp historical article/
29	Anecdotes as topic/
30	comment/
31	case reports/
32	(letter or comment*).ti.
33	or/25-32
34	randomized controlled trial/ or random*.ti,ab.
35	33 not 34
36	animals/ not humans/
37	exp Animals, Laboratory/
38	exp Animal Experimentation/
39	exp Models, Animal/
40	exp Rodentia/
41	(rat or rats or rodent* or mouse or mice).ti.
42	or/35-41

#	Searches
43	24 not 42
44	limit 43 to english language
45	Economics/
46	Value of life/
47	exp "Costs and Cost Analysis"/
48	exp Economics, Hospital/
49	exp Economics, Medical/
50	exp Resource Allocation/
51	Economics, Nursing/
52	Economics, Pharmaceutical/
53	exp "Fees and Charges"/
54	exp Budgets/
55	budget*.ti,ab.
56	cost*.ti,ab.
57	(economic* or pharmaco?economic*).ti,ab.
58	(price* or pricing*).ti,ab.
59	(financ* or fee or fees or expenditure* or saving*).ti,ab.
60	(value adj2 (money or monetary)).ti,ab.
61	resourc* allocat*.ti,ab.
62	(fund or funds or funding* or funded).ti,ab.
63	(ration or rations or rationing* or rationed).ti,ab.
64	ec.fs.
65	or/45-64
66	quality-adjusted life years/
67	sickness impact profile/
68	(quality adj2 (wellbeing or well being)).ti,ab.
69	sickness impact profile.ti,ab.
70	disability adjusted life.ti,ab.
71	(qal* or qtime* or qwb* or daly*).ti,ab.
72	(euroqol* or eq5d* or eq 5*).ti,ab.
73	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
74	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
75	(hui or hui1 or hui2 or hui3).ti,ab.
76	(health* year* equivalent* or hye or hyes).ti,ab.
77	discrete choice*.ti,ab.
78	rosser.ti,ab.
79	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
80	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
81	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
82	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
83	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
84	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
85	or/66-84
86	44 and (65 or 85)

Database: Embase <1974 to 2024 June 03>

Date of last search: 04/06/2024

#	Searches
1	exp infertility/
2	(steril* or sub-fertil* or subfertil* or infertil* or infecund* or sub-fecund* or subfecund* or hypofertil*).tw.
3	exp in vitro fertilization/

#	Searches
4	exp embryo transfer/
5	blastocyst/
6	(embryo* or blastocyst* or blastomer*).tw.
7	(vitro adj1 fertili*).tw.
8	(ivf or ICSI).tw.
9	((intracytoplas* or intra-cytoplas*) adj2 (sperm or injection*)).tw.
10	exp infertility therapy/
11	(assisted adj1 (reproduct* or conception)).tw.
12	((artificial* or intrauter* or uter* or oviduct*) adj2 inseminat*).tw.
13	IUI.tw.
14	FET.tw.
15	((implant* or transfer*) adj2 fail*).tw.
16	(poor prognos* or RIF).tw.
17	or/1-16
18	endometrium/su [Surgery]
19	endometrium/ and injury/
20	endometrium biopsy/
21	(endometri* adj4 (injur* or trauma* or biop* or harm* or damag* or inflam* or wound* or lesion* or insult* or scratch* or sampl* or disrupt* or prim* or brush* or stimulat* or activat* or curett*)).tw.
22	(Pipelle* or Novak* or Novac* or Tao brush*).tw.
23	((mock or dummy) adj3 (transfer* or cycle*)).tw.
24	or/18-23
25	17 and 24
26	letter.pt. or letter/
27	note.pt.
28	editorial.pt.
29	case report/ or case study/
30	(letter or comment*).ti.
31	or/26-30
32	randomized controlled trial/ or random*.ti,ab.
33	31 not 32
34	animal/ not human/
35	nonhuman/
36	exp Animal Experiment/
37	exp Experimental Animal/
38	animal model/
39	exp Rodent/
40	(rat or rats or rodent* or mouse or mice).ti.
41	or/33-40
42	25 not 41
43	limit 42 to english language
44	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
45	43 not 44
46	health economics/
47	exp economic evaluation/
48	exp health care cost/
49	exp fee/
50	budget/
51	funding/
52	resource allocation/
53	budget*.ti,ab.
54	cost*.ti,ab.
55	(economic* or pharmaco?economic*).ti,ab.

#	Searches
56	(price* or pricing*).ti,ab.
57	(financ* or fee or fees or expenditure* or saving*).ti,ab.
58	(value adj2 (money or monetary)).ti,ab.
59	resourc* allocat*.ti,ab.
60	(fund or funds or funding* or funded).ti,ab.
61	(ration or rations or rationing* or rationed).ti,ab.
62	or/46-61
63	quality adjusted life year/
64	"quality of life index"/
65	short form 12/ or short form 20/ or short form 36/ or short form 8/
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/63-83
85	45 and (62 or 84)

Database: INAHTA

Date of last search: 04/06/2024

#	Searches
1	"Infertility"[mhe]
2	(steril* or "sub-fertile" or "sub-fertility" or "sub fertile" or "sub fertility" or subfertil* or infertil* or infecund* or "sub-fecund" or "sub-fecundity" or "sub fecund" or "sub fecundity" or subfecund* or hypofertil*)
3	"Fertilization in Vitro"[mhe]
4	"Embryo Transfer"[mhe]
5	"Embryo Implantation"[mh]
6	"Blastocyst"[mh]
7	(embryo* or blastocyst* or blastomer*)
8	(vitro and fertili*)
9	(ivf or ICSI)
10	((intracytoplas* or "intra-cytoplasm" or "intra-cytoplasmic" or "intra cytoplasm" or "intra cytoplasmic") and (sperm or injection*))
11	"Reproductive Techniques, Assisted"[mhe]
12	(assisted and (reproduct* or conception))
13	((artificial* or intrauter* or uter* or oviduct*) and inseminat*)
14	IUI
15	FET
16	((implant* or transfer*) and fail*)

#	Searches
17	((poor and prognosis) or RIF)
18	#17 OR #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
19	"Endometrium"[mh]
20	(endometri* and (injur* or trauma* or biop* or harm* or damag* or inflam* or wound* or lesion* or insult* or scratch* or sampl* or disrupt* or prim* or brush* or stimulat* or activat* or curett*))
21	(Pipelle* or Novak* or Novac* or (Tao and brush*))
22	((mock or dummy) and (transfer* or cycle*))
23	#22 OR #21 OR #20 OR #19
24	#23 AND #18

Database: HTA via CRD

Date of last search: 04/06/2024

#	Searches
1	MESH DESCRIPTOR Infertility EXPLODE ALL TREES
2	(steril* or (sub next fertil*) or subfertil* or infertil* or infecund* or (sub next fecund*) or subfecund* or hypofertil*)
3	MESH DESCRIPTOR Fertilization in Vitro EXPLODE ALL TREES
4	MESH DESCRIPTOR Embryo Transfer EXPLODE ALL TREES
5	MESH DESCRIPTOR Embryo Implantation
6	MESH DESCRIPTOR Blastocyst
7	(embryo* or blastocyst* or blastomer*)
8	(vitro near1 fertili*)
9	(ivf or ICSI)
10	((intracytoplas* or (intra next cytoplas*)) near2 (sperm or injection*))
11	MESH DESCRIPTOR Reproductive Techniques, Assisted
12	(assisted near1 (reproduct* or conception))
13	((artificial* or intrauter* or uter* or oviduct*) near2 inseminat*)
14	IUI
15	FET
16	((implant* or transfer*) near2 fail*)
17	((poor next prognos*) or RIF)
18	#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 or #17
19	MESH DESCRIPTOR Endometrium
20	(endometri* near4 (injur* or trauma* or biop* or harm* or damag* or inflam* or wound* or lesion* or insult* or scratch* or sampl* or disrupt* or prim* or brush* or stimulat* or activat* or curett*))
21	(Pipelle* or Novak* or Novac* or (Tao next brush*))
22	((mock or dummy) near3 (transfer* or cycle*))
23	#19 or #20 or #21 or #22
24	#18 and #23
25	(#18 and #23) IN HTA