

Fertility problems: assessment and treatment

[P] Evidence report for endometrial scratch as a treatment add-on

NICE guideline number NGXXX

Evidence report underpinning recommendation 1.10.3 in the NICE guideline

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Draft for consultation

This evidence review was developed by NICE

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Endometrial scratching as a treatment add-on

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	<p>Inclusion:</p> <ul style="list-style-type: none">• People undergoing treatment for a health-related fertility problem. <p>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:</p> <ul style="list-style-type: none">• after 12 months of regular unprotected sexual intercourse or• after 6 cycles of artificial insemination.
Intervention	<ul style="list-style-type: none">• Endometrial scratching, also known as endometrial injury, performed prior to embryo transfer or intrauterine insemination (IUI)
Comparison	<ul style="list-style-type: none">• Standard embryo transfer without endometrial scratching• Standard IUI without endometrial scratching• Sham procedure <p>Comparisons between different instruments used for endometrial scratching (for example, pipelle, Tao brush), or between different numbers of procedures, will be included</p>
Outcome	<p>Critical</p> <ul style="list-style-type: none">• 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

1 *IUI: intrauterine insemination*

2 **Methods and process**

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

12 The quality of the HFEA evidence statements were assessed independently by 2 reviewers
13 using the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool. This
14 instrument is intended for assessing the quality of systematically developed clinical practice
15 guidelines, including assessments of methodological rigour, transparency, and applicability.
16 The AGREE II instrument is an internationally validated tool that is used to assess the
17 methodological rigour and transparency of clinical practice guidelines. The evidence
18 statements considered by the committee have all been produced with the intention of helping
19 practitioners and service users make informed treatment decisions based on the available
20 evidence for fertility treatment add-ons and in this sense were considered by the committee
21 as being appropriate for inclusion in the evidence base and assessed using AGREE II.
22 However, the fact that the quality of these documents has been assessed by an instrument
23 designed for use on guidelines should be borne in mind. For example, some of the
24 terminology used in AGREE II is based on the assumption that specific recommendations
25 have been made, and therefore domains such as 'Clarity of presentation' and 'Applicability'
26 include questions directly related to the quality of guidance given and its relevance to clinical
27 practice. The HFEA evidence statements were assessed as the AGREE II tool sets out
28 because all domains are important and form part of this validated instrument, but it is
29 important to acknowledge that some of the low ratings are due to the applicability of the tool
30 to the statements and not necessarily a reflection of the quality of the statements
31 themselves.

32 The HFEA ratings are available at [the treatment add-ons page of the HFEA website](#).

33 During the development of this guideline, a published Cochrane review was identified which
34 matched the committee's intended PICO and which was referred to by the HFEA, comparing
35 the effectiveness of endometrial injury versus no procedure or a sham procedure (Lensen
36 2021). The Cochrane review also compared higher versus lower degree of endometrial
37 injury, however in order to be consistent with the HFEA's approach and the intended
38 approach as specified by the committee for this guideline, only the comparison of
39 endometrial injury versus no procedure or a sham procedure was considered by the
40 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 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 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	<p>Rated orange for improving the chances of having a baby for most fertility patients undergoing IVF or ICSI:</p> <ul style="list-style-type: none">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. <p>Rated grey for improving the chances of having a baby for patients with recurrent implantation failure (RIF):</p> <ul style="list-style-type: none">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.

1 Contributing to this overall rating, endometrial scratching was rated orange for increasing the
2 chances of having a baby for most fertility patients, primarily based on findings from 5 more
3 recently conducted randomised controlled trials (RCTs: Gibreel 2015; Glanville 2022; Hilton
4 2019; Mackens 2020; Wong 2022). It is important to note that this rating only applies to
5 participants undergoing IVF/ICSI, as the HFEA felt that the studies they considered to be of
6 moderate or high quality were mostly assessed only in participants undergoing IVF/ICSI,
7 whereas “results for natural/IUI cycles were consistently positive but tended to be from early,
8 small studies at questionable risk of bias.” In terms of the 5 more recent studies that were
9 considered moderate or high quality, the HFEA interpreted the evidence as conflicting for the
10 outcome live birth, whereby 3 studies were considered to favour endometrial scratching and
11 2 were considered to favour control (no or sham procedure). However, the 95% confidence
12 intervals were very wide and all crossed the line of no effect for this outcome, showing
13 significant uncertainty in the effect estimate. Other included studies which did find that
14 endometrial scratching improved live birth rates were considered to be poor quality, and the
15 HFEA also noted these tended to be older studies. The HFEA also noted some concerns
16 related to endometrial scratching, including that it is an intrusive and potentially painful
17 procedure, plus some safety concerns relating to the potential for patients to experience
18 blood loss or for the procedure to cause existing infection in the cervix to spread to the
19 uterus. However, there are no additional known risks of endometrial scratching for the child
20 born as a result of fertility treatment, thereby not justifying a red treatment rating.

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

25 Further information about the HFEA rating for endometrial scratching can be found on [the](#)
26 [relevant page of the HFEA website.](#)

27 Further information about the HFEA’s rating system can be found on [the relevant page of the](#)
28 [HFEA website.](#)

29 **Cochrane review**

30 One Cochrane review investigating the effectiveness of endometrial injury (Lensen 2021),
31 including 37 RCTs comparing the effectiveness of endometrial injury versus no procedure or
32 a sham procedure, was considered in this report. This Cochrane review had a different
33 protocol to the HFEA’s review, with stricter inclusion criteria (for example restricting included
34 studies to RCTs only) and implementation of data synthesis. Additionally, a post-hoc decision
35 was made by Cochrane to restrict primary analyses to studies at low risk of selection or other
36 bias, due to the high risk of bias associated with many of the included studies. Sensitivity
37 analyses were conducted by Cochrane to assess whether review conclusions would have
38 been different if eligibility had been restricted to studies without high risk of bias in any
39 domain, or if all studies were included regardless of risk of bias. Eight studies were included
40 in the primary analyses (Berntsen 2020; Hilton 2019; Lensen 2019; Metwally 2020; Olesen
41 2019; Polanski 2015; van Hoogenhuijze 2020; Yeung 2014).

42 There was overlap between Cochrane and the HFEA, as most studies included in the
43 Cochrane review were also included in the HFEA’s. The Cochrane review was considered
44 sufficiently relevant, high quality and up to date, and therefore was additionally considered by
45 the committee to ensure all evidence had been reviewed, and used to supplement the HFEA
46 evidence statements to guide recommendation making by the committee. See the benefits
47 and harms section for the committee’s discussion of the Cochrane evidence.

48 Full details of [the Cochrane review \(Lensen 2011\)](#) including methods are available, as linked.

1 **Economic evidence**

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

6 **Included studies**

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

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

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

13 **Excluded studies**

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

2 **Summary of included economic evidence**

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

4 **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

5 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
6 explanation was provided in the study as to how the authors calculated their ICERs.

7 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
8 was included in the clinical review

9 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)

1 **Economic model**

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

4 **The committee's discussion and interpretation of the evidence**

5 **The outcomes that matter most**

6 Originally, the committee prioritised live birth and clinical pregnancy as critical outcomes for
7 decision making because they are the most important outcomes for people with fertility
8 problems, and the committee agreed they should be prioritised above other outcomes to
9 reflect their comparative importance. Of these outcomes, the HFEA only stated that live birth
10 would be given specific consideration in the review and when creating the evidence ratings,
11 but the review did also report information on pregnancy rates when reported in included
12 studies. Both live birth and clinical pregnancy were reported in the Cochrane review.

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

18 **The quality of the evidence statements**

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

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

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

37 The score for rigour of development was 40%. A literature search was performed but there is
38 no publicly available information on the search strategy and searches which are therefore not
39 replicable. The committee also noted the review was not systematic and only one database
40 was searched for relevant studies, although they agreed it was unlikely that any critical
41 evidence was missed. The criteria for selecting the evidence are partially described including
42 detailed information about study selection, but an explicit list of inclusion/exclusion criteria,
43 excluded studies lists and protocols are not reported. Detailed descriptions of the evidence
44 are provided narratively but GRADE tables were not reported. There was also no synthesis
45 of the evidence reported. The committee therefore agreed to use the Cochrane reviews to
46 supplement their understanding of the evidence base, and to ensure any synthesised

1 evidence was considered where possible. The risk of bias domains assessed are described
2 but it is unclear whether an appropriate, certified checklist was used for each study type.
3 Details on the methodology used by the HFEA to arrive at each evidence rating are provided,
4 including a decision tree and descriptions of each rating. There is detailed information about
5 specific discussions the committee had about the evidence, benefits, harms, risks, and,
6 where appropriate, costs of each add-on. There are limited descriptions of how the evidence
7 was interpreted to influence the statements, though it is usually unclear what evidence
8 contributes to each statement and there is some inconsistency in how the evidence has been
9 used to inform evidence statements between add-ons. There is no information about an
10 external review of the evidence statements prior to publication, but an explicit statement of
11 intent to update the evidence statements is provided with a review date. Information about
12 the HFEA's methods for evidence surveillance and updating the statements is provided.

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

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

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

30 See Appendix B for the AGREE II reviewer scoring tables.

31 **Benefits and harms**

32 The committee reviewed the HFEA treatment rating for endometrial scratching and its
33 underpinning evidence and agreed the uncertainty in the evidence base meant it is unclear
34 whether the add-on has the potential to harm, provide benefit, or have no effect on
35 outcomes. The committee also noted the Cochrane review referred to by the HFEA, which
36 compared the effectiveness of endometrial injury versus no intervention or sham procedure
37 (Lensen 2021). Under the comparison of endometrial scratching versus no intervention or
38 sham procedure, 37 studies were included. However, Cochrane limited their primary
39 analyses to include only studies at low risk of selection or other bias because of the high risk
40 of bias associated with many of the included studies. As a result, 8 studies were included in
41 the primary analyses. The evidence contributing to the primary analyses was of moderate
42 quality but the outcomes were all downgraded for serious imprecision because of wide
43 confidence intervals compatible with appreciable benefit, no effect, and harm. Sensitivity
44 analyses were conducted to assess whether review conclusions would have been different if
45 eligibility had been restricted to studies without high risk of bias in any domain, or if all
46 studies were included regardless of risk of bias, and these were all consistent with the
47 primary findings. Cochrane concluded that endometrial injury does not appear to affect the
48 chance of miscarriage, but the effect of endometrial injury on live birth and clinical pregnancy
49 among women undergoing IVF is unclear because the results of the meta-analyses are
50 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

1 outcomes of IVF. No significant resource impact will be associated with this
2 recommendation.

3 **Other factors the committee took into account**

4 The committee were also aware of the recommendation made on endometrial scratching by
5 the European Society of Human Reproduction and Embryology (ESHRE; Good practice
6 recommendations on add-ons in reproductive medicine). This recommendation was based
7 on existing RCTs and systematic reviews (including the Cochrane review referred to by the
8 HFEA: Lensen 2021), as well as consideration of the cost of endometrial scratching and any
9 safety concerns (ESHRE Add-ons working group 2023). The committee agreed the NICE
10 recommendation aligns with ESHRE's findings that endometrial scratching could not be
11 recommended for routine clinical use.

12 The full guideline can be found on ESHRE's website: [https://www.eshre.eu/Guidelines-and-](https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Addons)
13 [Legal/Guidelines/Addons](https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Addons)

14 **Recommendations supported by this evidence review**

15 This evidence review supports recommendation 1.10.3.

16 **References**

17 **Effectiveness**

18 **ESHRE Add-ons working group 2023**

19 ESHRE Add-ons working group, K Lundin, J G Bentzen, G Bozdog, T Ebner, J Harper, N Le
20 Clef, A Moffett, S Norcross, N P Polyzos, S Rautakallio-Hokkanen, I Sfontouris, K Sermon, N
21 Vermeulen, A Pinborg, Good practice recommendations on add-ons in reproductive
22 medicine, Human Reproduction, Volume 38, Issue 11, November 2023, Pages 2062–2104,
23 <https://doi.org/10.1093/humrep/dead184>

24 **HFEA**

25 HFEA, Endometrial scratching, October 2023, [https://www.hfea.gov.uk/treatments/treatment-](https://www.hfea.gov.uk/treatments/treatment-add-ons/endometrial-scratching/)
26 [add-ons/endometrial-scratching/](https://www.hfea.gov.uk/treatments/treatment-add-ons/endometrial-scratching/) <accessed 04/04/2024>

27 **HFEA**

28 HFEA, Scientific and Clinical Advances Advisory Committee (SCAAC) – Agenda (Hybrid),
29 July 2023, available at [https://www.hfea.gov.uk/about-us/our-authority-committees-and-](https://www.hfea.gov.uk/about-us/our-authority-committees-and-panels/scientific-and-clinical-advances-advisory-committee-scaac/)
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31 **HFEA**

32 HFEA, Scientific and Clinical Advances Advisory Committee (SCAAC) – minutes –
33 Treatment add-ons, July 2023, available at [https://www.hfea.gov.uk/about-us/our-authority-](https://www.hfea.gov.uk/about-us/our-authority-committees-and-panels/scientific-and-clinical-advances-advisory-committee-scaac/)
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35 <accessed 04/04/2024>

36 **Lensen 2021**

37 Lensen SF, Armstrong S, Gibreel A, Nastri CO, Raine-Fenning N, Martins WP. Endometrial
38 injury in women undergoing in vitro fertilisation (IVF). Cochrane Database of Systematic
39 Reviews 2021, Issue 6. Art. No.: CD009517. DOI: 10.1002/14651858.CD009517.pub4.
40 <accessed 04/04/2024>

1 **Economic**

- 2 Metwally, Mostafa; Chatters, Robin; Pye, Clare et al. Endometrial scratch to increase live
3 birth rates in women undergoing first-time in vitro fertilisation: RCT and systematic
4 review. Health technology assessment (Winchester, England); 2022; vol. 26 (no. 10); 1-212
- 5 van Hoogenhuijze, N E; van Eekelen, R; Mol, F et al. Economic evaluation
6 of endometrial scratching before the second IVF/ICSI treatment: a cost-effectiveness
7 analysis of a randomized controlled trial (SCRaTCH trial). Human reproduction (Oxford,
8 England); 2022; vol. 37 (no. 2); 254-263
- 9

1 Appendices

2 Appendix A Review protocols

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

5 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	<p>The following databases will be searched (with no date limit):</p> <p>Clinical searches</p> <ul style="list-style-type: none"> • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE ALL • Epistemonikos <p>Searches will be restricted by:</p> <ul style="list-style-type: none"> • English language • Human studies

		<p>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.</p> <p>The full search strategies for MEDLINE database will be published in the final review.</p>
5.	Condition or domain being studied	Fertility treatment add-ons
6.	Population	<p>Inclusion:</p> <ul style="list-style-type: none"> • People undergoing treatment for a health-related fertility problem. <p>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:</p> <ul style="list-style-type: none"> • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination.
7.	Interventions	<ul style="list-style-type: none"> • Endometrial scratching, also known as endometrial injury, performed prior to embryo transfer or intrauterine insemination (IUI)
8.	Comparators	<ul style="list-style-type: none"> • Standard embryo transfer without endometrial scratching • Standard IUI without endometrial scratching • Sham procedure <p>Comparisons between different instruments used for endometrial scratching (for example, pipelle, Tao brush), or between different numbers of procedures, will be included</p>
9.	Types of study to be included	<ul style="list-style-type: none"> • Systematic reviews of RCTs • RCTs (individual or cluster) • If no RCT evidence: <ul style="list-style-type: none"> ◦ 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	<p>Other exclusion criteria:</p> <ul style="list-style-type: none"> • Language limitations: non-English-language papers will be excluded (unless data can be obtained, and risk of bias assessed, from an existing systematic review)

		<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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)	<ul style="list-style-type: none"> 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)	<p>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.</p> <p>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.</p> <p>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.</p>
15.	Risk of bias (quality) assessment	<p>Quality assessment of individual studies will be performed using the following checklists:</p> <ul style="list-style-type: none"> ROBIS tool for systematic reviews Cochrane RoB tool v.2 for RCTs (and quasi-RCTs, if no RCT evidence identified) <p>The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.</p>
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

		<p>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.</p> <p>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.</p> <p>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/</p> <p>Importance and imprecision of findings will be assessed against minimally important differences (MIDs). The following MIDs will be used:</p> <ul style="list-style-type: none"> • Live birth: statistical significance • All other outcomes: 0.8 and 1.25 for all relative dichotomous outcomes
17.	Analysis of sub-groups	<p>Evidence will be stratified by:</p> <ul style="list-style-type: none"> • Fertility treatment: <ul style="list-style-type: none"> ◦ In vitro fertilisation (IVF) ◦ IUI <p>Evidence will be sub-grouped by the following:</p> <ul style="list-style-type: none"> • Female age (based on the mean age in the study): <ul style="list-style-type: none"> ◦ <35 years ◦ 35-39 years ◦ ≥39 years <p>Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes:</p> <ul style="list-style-type: none"> • Previous implantation failure <ul style="list-style-type: none"> ◦ First embryo transfer ◦ After previous failed embryo transfer • Timing of endometrial scratching

		<ul style="list-style-type: none"> o follicular phase prior cycle o luteal phase prior cycle o early follicular phase IVF cycle o late follicular phase IVF cycle <p>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.</p>		
18.	Type and method of review	<input checked="" type="checkbox"/>	Intervention	
		<input type="checkbox"/>	Diagnostic	
		<input type="checkbox"/>	Prognostic	
		<input type="checkbox"/>	Qualitative	
		<input type="checkbox"/>	Epidemiologic	
		<input type="checkbox"/>	Service Delivery	
		<input type="checkbox"/>	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	<input type="checkbox"/>	<input type="checkbox"/>
		Piloting of the study selection process	<input type="checkbox"/>	<input type="checkbox"/>
		Formal screening of search results against eligibility criteria	<input type="checkbox"/>	<input type="checkbox"/>

		Data extraction	<input type="checkbox"/>	<input type="checkbox"/>
		Risk of bias (quality) assessment	<input type="checkbox"/>	<input type="checkbox"/>
		Data analysis	<input type="checkbox"/>	<input type="checkbox"/>
24.	Named contact	<p>5a. Named contact Guideline development team A</p> <p>5b. Named contact e-mail FertilityProblems@nice.org.uk</p> <p>5c. Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)</p>		
25.	Review team members	<p>Senior Technical Analyst</p> <p>Technical Analyst</p>		
26.	Funding sources/sponsor	This systematic review is being completed by NICE.		
27.	Conflicts of interest	<p>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.</p>		
28.	Collaborators	<p>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</p>		
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	<input type="checkbox"/>	Ongoing
		<input type="checkbox"/>	Completed but not published
		<input type="checkbox"/>	Completed and published
		<input type="checkbox"/>	Completed, published and being updated
		<input checked="" type="checkbox"/>	Discontinued
35..	Additional information	None	
36.	Details of final publication	www.nice.org.uk	

1 CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE:
 2 Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline
 3 Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation
 4

1 Appendix B Quality assessment (AGREE II)

2 **AGREE II reviewer scoring tables for review question: What is the clinical and cost effectiveness of endometrial scratching**
 3 **as a treatment add-on for people undergoing fertility treatment?**

4 **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%

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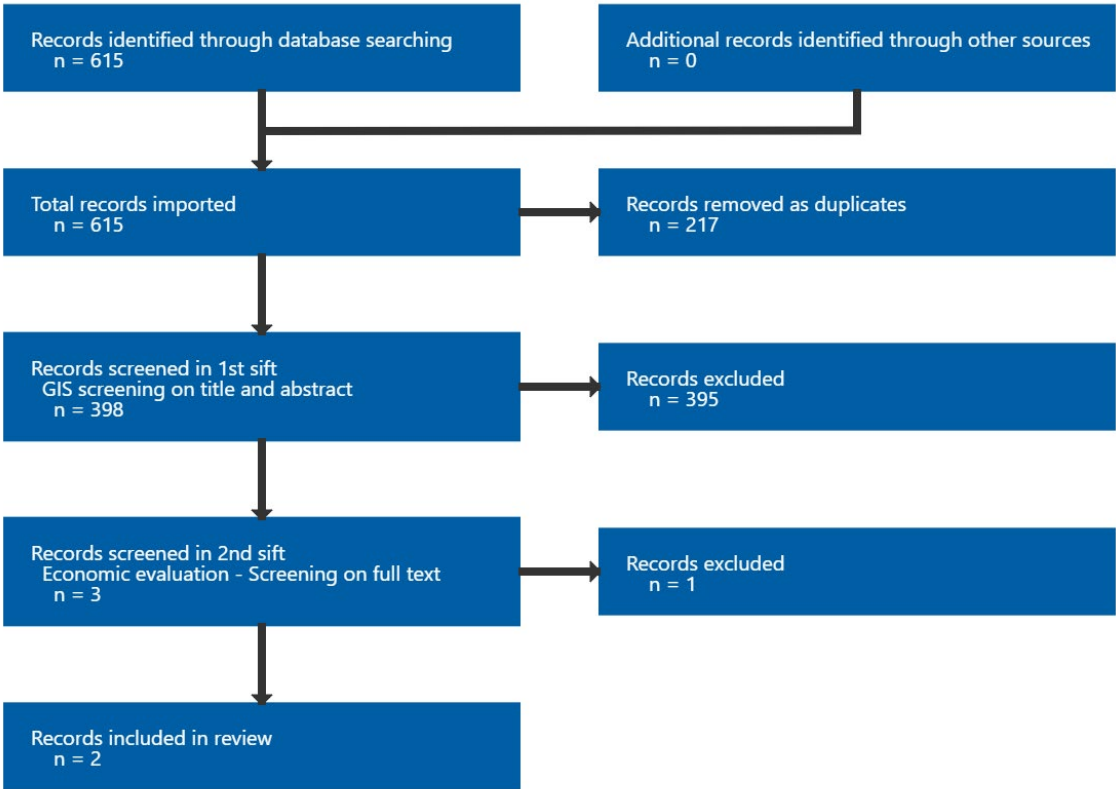
Appendix C Economic evidence study selection

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
<p>Author and year: Metwally 2022</p> <p>Country: UK</p> <p>Type of economic analysis: CEA</p> <p>Source of funding: National Institute for Health Research (NIHR) Health</p>	<p>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</p> <p>Comparator: IVF only (TAU) – women</p>	<p>Population characteristics: Women aged 18 – 37 undergoing their first IVF cycle (with or without ICSI)</p> <p>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.</p> <p>Exclusion criteria: women with severe endometriosis, BMI $\geq 35\text{kg/m}^2$, previous endometrium trauma.</p> <p>Modelling approach: Within-trial analysis</p>	<p>Costs: Health care perspective</p> <p><u>Mean cost per participant</u> Intervention: £6,819.38 Comparator: £6,503.00 Difference: £316.25</p> <p>Primary measure of outcome: Cost per successful birth</p> <p><i>If there were multiple live births per person this was noted as a single event.</i></p>	<p>ICER: £11.90 per successful live birth</p> <p>Recalculated ICER of £21.08 (£316.25/15)</p> <p>Probability of being cost effective: 70% chance of being cost effective with a WTP for a live birth of £1,000</p> <p>Subgroup analysis: <u>To assess differences in costs:</u></p> <ol style="list-style-type: none"> 1. Day of embryo transfer (day, 2,3,4,5 or 6), 2. Fertilisation method (IVF, ICSI, or split ICSI) 	<p>Currency: UK pounds</p> <p>Cost year: 2018/19</p> <p>Time horizon: 12 months</p> <p>Discounting: NA</p> <p>Applicability: Directly applicable</p> <p>Limitations: Potentially serious limitations</p> <p>Other comments: Bootstrapping undertaken to assess</p>

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Technology Assessment Programme	undergoing their first IVF cycle – with or without ICSI	<p><i>A pragmatic, multicentre, superiority, open-label, parallel-group, individually randomised controlled trial undertaken at 16 UK fertility units n=1048, ES=523, TAU=525</i></p> <p>Source of baseline data: Metwally 2020</p> <p>Source of effectiveness data: Metwally 2020</p> <p>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.</p> <p>Source of unit cost data: NHS reference costs, PSS unit costs, ONS data</p>	<p><u>Mean outcome per participant</u></p> <p>Intervention: NR</p> <p>Control: NR</p> <p>Difference: 0.015</p> <p><i>Recalculated value of 15</i></p> <p><i>This value was the same in all analyses:</i></p> <ul style="list-style-type: none"> • <i>Worst case</i> • <i>Best case</i> • <i>Complete case</i> 	<ol style="list-style-type: none"> 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 <p><i>A significant difference in costs was only observed for the day of embryo transfer, so a SA analysis was conducted for this.</i></p> <p>Sensitivity analysis:</p> <p>Societal perspective: £2.67 per successful live birth</p> <p>Adjusting for baseline costs: £5.38 per successful live birth</p> <p>Adjusting for baseline costs and day of embryo transfer:</p>	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
				£10.06 per successful live birth	
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	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)	Costs: Societal perspective (healthcare perspective with UK costs conducted as a sensitivity analysis) <i>Societal costs were for lost productivity costs associated with treatment, OHSS and complications for both females and males (no further detailed reported in study).</i> <u>Mean cost per participant:</u> Intervention: €8,477 Control: €8,194 Difference: €283 Primary measure of outcome: Cost per live birth <i>Biochemical pregnancy leading to live birth within the full follow-up</i>	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 <u><i>Mean cost per participant:</i></u> <i>Intervention: €5,337</i> <i>Control: €4,900</i> <i>Difference: €437</i> <u><i>Mean outcome per participant:</i></u> <i>Intervention: 0.236</i>	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
	<p>endometrial biopsy catheter without additional anaesthetics or sedatives. The residual tissue was not histologically or cytologically evaluated</p> <p>Comparator: No endometrial scratching prior to the second IVF/ICSI cycle (due to first cycle failure) – n=466</p> <p>Women started directly with ovarian</p>	<p>Source of unit cost data: Calculated estimate for ES</p> <ul style="list-style-type: none"> Based on the average time and medical equipment needed for a scratch. Costs for placement of an intrauterine device (without the product costs), a regular ultrasound, and costs of an endometrial biopsy catheter <p>Dutch expert panel Dutch healthcare institute</p>	<p><i>period (i.e. biochemical pregnancy must be reached within 10 months and 2 weeks—323 days—after randomization).</i></p> <p><u>Mean outcome per participant:</u> Intervention: 0.441 Control: 0.393 Difference: 0.048</p>	<p><i>Control: 0.191</i> <i>Difference: 0.045</i></p> <p>80% chance that endometrial scratching is cost-effective if society is willing to pay ~€20 000</p> <p>Sensitivity analysis: Using a lower and higher price for endometrial scratching (base case price €104):</p> <ul style="list-style-type: none"> At a price of €50 the ICER was €4,096 per additional live birth with an 80% 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 	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
	hyperstimulation.			<p>~€26,500 per additional live birth.</p> <p>Using UK costs and taking a healthcare payer perspective:</p> <ul style="list-style-type: none"> • 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 <p><i>Cost year 2019 and unit cost for endometrial scratching £180. Cost per live birth calculated using the primary outcome measure.</i></p>	

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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,

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1 **Appendix G Economic model**

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

5 No economic analysis was conducted for this review question.

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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

1 **Appendix I Research recommendations – full details**

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

5 No research recommendations were made for this review question.
6

1 Appendix J Literature search strategies

2 Literature search strategies for review question: What is the clinical and cost 3 effectiveness of endometrial scratching as a treatment add-on for people 4 undergoing fertility treatment?

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

6 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)

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

2 **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)

1 Database: INAHTA

2 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

1 Database: HTA via CRD

2 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 fertil*)
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

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