National Institute for Health and Care Excellence

Draft for consultation

Fertility problems: assessment and treatment

[O] Embryo selection guided by continuous time-lapse sequence as a treatment add-on

NICE guideline number NGXXX

Evidence report

September 2025

Draft for consultation

This evidence review was developed by NICE

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Review question

What is the clinical and cost effectiveness of embryo selection guided by continuous time-lapse monitoring (with or without artificial intelligence algorithms) 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) can be 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 can often be unclear.

Time-lapse monitoring allows for images of the embryo to be taken digitally without the need for the embryo to be removed from incubation or otherwise disturbed, with images taken every few minutes throughout the embryo's development. As a result of this imaging, continuous monitoring of the embryo as it develops is possible, and algorithms have been developed to rank or score embryos according to their viability for transfer. However, it is unclear if embryo selection based on time-lapse imaging improves fertility patients' chances at a live birth.

The aim of this review is to determine the effectiveness of embryo selection guided by continuous time-lapse monitoring (with or without artificial intelligence algorithms) 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 IVF 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	• Embryo selection guided by the use of continuous time-lapse monitoring, with or without artificial intelligence algorithms Exclusion: Comparisons of closed embryo culture incubation versus standard incubation only, with standard embryo selection (guided by morphological criteria alone) across arms, were not included
Comparison	• Standard embryo selection (guided by morphological criteria alone), with standard incubation or closed embryo culture incubation
Outcome	Primary 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) Secondary outcomes • Miscarriage (loss of a baby before 24 weeks gestational age) • Cycles without embryo transfer • Embryo utilisation rate (number of embryos that are used or frozen)

IVF: in-vitro fertilisation

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 time-lapse monitoring. 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.

In their review, the HFEA included studies evaluating the effects of the environment for embryo development only. However, the intended approach as specified by the committee for this guideline was to compare embryo selection guided by the use of continuous time-lapse monitoring versus standard embryo selection. Therefore, studies in which both arms used standard embryo selection to compare the environment for embryo development were not of relevance and were not considered by the committee.

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 time-lapse systems (TLS) versus conventional embryo incubation and

assessment (Armstrong 2019). The Cochrane protocol differed from the committee's intended intervention in that Three comparisons were made: TLS with conventional morphological assessment of still TLS images versus conventional incubation and assessment; TLS utilising embryo selection software versus TLS with conventional morphological assessment of still TLS images; TLS utilising embryo selection software versus conventional incubation and assessment. However, in order to be consistent with the intended approach as specified by the committee for this guideline, the comparison of TLS with conventional morphological assessment of still TLS images versus conventional incubation and assessment was not 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 2019, 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. One randomised controlled trial (RCT; Bhide 2024) was acknowledged and considered by the committee. See the benefits and harms sections for the committee's discussion of this study.

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 time lapse imaging and incubation 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" (pp16, 22-23 and PDF pp54-57 for time lapse imaging and incubation evidence). The SCAAC decision making on the ratings is described in the document "SCAAC Minutes July 2023 - Treatment Add-Ons" (p5), and in the document "SCAAC Minutes February 2023" (p6).

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

Table 2: Summary of HFEA ratings

Treatment add-on	HFEA ratings
Time-lapse imaging and incubation	Rated black for improving the chances of having a baby for most fertility patients when using automated analyses of embryos and for improving the chances of having a baby for most fertility patients when using manual analyses of embryos: • On balance, the evidence from moderate/high quality evidence shows that this add-on has no effect on the treatment outcome

HFEA treatment ratings

Time-lapse imaging and incubation was overall given a black rating, indicating on balance, the evidence from studies considered to be of moderate or high quality shows that this add-on has no effect on the treatment outcome.

Time-lapse monitoring was rated black regardless of whether analyses of embryos were automated (using algorithms or AI) or manual (by an embryologist). This was based on the findings of 5 studies considered to be of moderate or high quality with consistent results showing no improvements in live birth rate for most fertility patients when using automated or manual annotation. Four of these studies compared embryo selection guided by time-lapse monitoring with standard embryo selection (guided by morphological criteria). Of these, 2 compared a single embryo transfer based on either Eeva classification (Kaser 2017) or KIDScore (Ahlstrom 2022) versus conventional morphology and found no important difference between groups for ongoing pregnancy, clinical pregnancy rate or early pregnancy loss. The other 2 studies compared time lapse incubation with embryo selection guided by either 'Geri assess' or KIDScore versus conventional incubation and morphology: 1 study found live birth to be lower in the time-lapse arm (Meng 2022) and the other found no important difference between groups for live birth rate or cumulative live birth (Zhang 2022).

The HFEA did note some benefits of using time-lapse imaging not covered by the review, including observation of late pro nuclei appearance, patients knowing how their embryos are developing and potentially feeling reassured and informed by this. Overall, no additional known safety concerns were noted related to using time-lapse imaging and incubation for the person undergoing fertility treatment or any child born as a result of fertility treatment.

Further information about the HFEA rating for time-lapse imaging can be found on their website: https://www.hfea.gov.uk/treatments/treatment-add-ons/time-lapse-imaging-and-incubation/

Further information about the HFEA's rating system can be found on their website: https://www.hfea.gov.uk/treatments/treatment-add-ons/

Cochrane review

One Cochrane review comparing the effectiveness of TLS utilising embryo selection software versus TLS with conventional morphological assessment of still TLS images, and TLS utilising embryo selection software versus conventional incubation and assessment (Armstrong 2019) was considered in this report. The review included 2 RCTs in the comparison between TLS utilising embryo selection software versus TLS with conventional morphological assessment of still TLS images (Goodman 2016; Kaser 2017), and 3 RCTs in the comparison between TLS utilising embryo selection software versus conventional incubation and assessment (Kovacs 2019; Rubio 2014; Yang 2018). 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. There was overlap between Cochrane and the HFEA, as all the 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 (Armstrong 2019) including methods are available, as linked.

Economic evidence

A total of 456 studies were identified in the health economic literature search for this review question. After duplicates were removed, 296 studies were screened on title and abstract of which were excluded at this stage.

Included studies

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

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

Excluded studies

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

Economic model

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

The committee's discussion and interpretation of the evidence

The outcomes that matter most

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

The committee originally considered miscarriage, number of cycles without an embryo transfer, and embryo utilisation rate as important outcomes. The HFEA review reported on miscarriage, but did not report on number of cycles without an embryo transfer or embryo utilisation rate. The Cochrane review reported on miscarriage but not number of cycles without an embryo transfer or embryo utilisation rate.

The quality of the evidence statements

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

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

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

The score for rigour of development was 40%. A literature search was performed but there is no publicly available information on the search strategy and searches which are therefore not replicable. The committee also noted the review was not systematic and only one database was searched for relevant studies, although they agreed it was unlikely that any critical evidence was missed. The criteria for selecting the evidence are partially described including detailed information about study selection, but an explicit list of inclusion/exclusion criteria, excluded studies lists and protocols are not reported. Detailed descriptions of the evidence are provided narratively but GRADE tables were not reported. There was also no synthesis of the evidence reported. The committee therefore agreed to use the Cochrane reviews to supplement their understanding of the evidence base, and to ensure any synthesised evidence was considered where possible. The risk of bias domains assessed are described but it is unclear whether an appropriate, certified checklist was used for each study type. Details on the methodology used by the HFEA to arrive at each evidence rating are provided, including a decision tree and descriptions of each rating. There is detailed information about specific discussions the committee had about the evidence, benefits, harms, risks, and, where appropriate, costs of each add-on. There are limited descriptions of how the evidence was interpreted to influence the statements, though it is usually unclear what evidence contributes to each statement and there is some inconsistency in how the evidence has been used to inform evidence statements between add-ons. There is no information about an external review of the evidence statements 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 discussed the HFEA treatment rating for time-lapse imaging and its underpinning evidence, and also noted the Cochrane review referred to by the HFEA, which

compared the effectiveness of time-lapse systems versus conventional embryo incubation and assessment (Armstrong 2019). In the Cochrane review, the effectiveness of the 3 interventions considered by the HFEA were assessed (the effects of the time-lapse incubation environment for embryo development; the effects of the embryo selection process based on time-lapse imaging; the combined effect of both the incubation environment and the embryo selection process). In order to be consistent with the agreed approach for this review, the committee only considered evidence on embryo selection guided by continuous time-lapse monitoring (with or without artificial intelligence algorithms), and did not review the comparison that examined the effects of only the incubation environment. The committee noted that the evidence showed no clinically important benefit of time-lapse imaging on live birth, ongoing pregnancy, or clinical pregnancy rates. There was some evidence of lower miscarriage rates with time-lapse systems using both embryo selection software and the stable incubation environment relative to standard embryo selection (guided by morphological criteria alone) and conventional incubation. However, this evidence was very low quality. The committee also discussed that the effect on miscarriage may be due to the stable incubation environment and noted that in the comparison that controlled for this there was no clinically important benefit on miscarriage. The committee agreed not to recommend the use of time-lapse imaging given the uncertainties about benefits relative to conventional embryo selection. However, the committee did not want to preclude the use of time-lapse imaging because these systems are widely used within the NHS and may have benefits in terms of incubation even if benefits in terms of embryo selection are less clear.

During the development of this guideline the committee became aware of a trial that was published after the HFEA and Cochrane reviews (Bhide 2024). The findings of this RCT were consistent with not recommending time-lapse imaging because no important difference in live birth rates was shown for time-lapse imaging compared to standard care. The committee discussed that this was a pragmatic trial and as such was designed to reflect current practice, in that each centre used their own time-lapse imaging system and algorithm. The committee highlighted that there might be future potential for embryo selection guided by continuous time-lapse monitoring, given that it is likely that artificial intelligence (AI) algorithms will improve with the development of big data analytics. The committee agreed that further research would be needed to develop and to test these algorithms but that it would be premature to draft a fully specified and implementable research recommendation that would be able to deliver conclusive results about the potential benefits of time-lapse imaging for embryo selection.

Cost effectiveness and resource use

No health economic evidence was identified for this review question. The clinical evidence was uncertain and showed no clinical benefit. Therefore, the committee agreed not to recommend the use of time-lapse imaging for embryo selection – noting that this recommendation is reflective of current practice.

Because the clinical evidence for time-lapse imaging for embryo selection showed no clinical benefit, it can be inferred that, based on current knowledge, time-lapse imaging for embryo selection would not be a cost-effective use of NHS resources.

This review question assessed the clinical and cost effectiveness for embryo selection. However the committee noted that time-lapse imaging is widely used in the NHS and may be cost-effective for embryo incubation. Embryo incubation was not within the scope for this review question, and therefore clinical and health economic literature about embryo incubation was not systematically searched for. To determine the cost effectiveness of time-lapse imaging for embryo incubation, a systematic review of the health economic literature is required, with potential further need for economic modelling – dependent on the clinical and health economic evidence base.

Other factors the committee took into account

The committee also considered the recommendation made on time-lapse imaging by ESHRE when drafting their recommendations, which was based on existing RCTs and systematic reviews (including the Cochrane review referred to by the HFEA: Armstrong 2019), as well as consideration of any safety concerns associated with the use of time-lapse imaging. ESHRE recommended against using time-lapse imaging as a tool to improve live birth rates, but noted they found evidence of no difference in safety between time-lapse imaging and embryo culture in conventional benchtop incubators. The committee agreed with ESHRE's findings that time-lapse imaging should not be used as a tool to improve live birth rates but felt it was important not to make a recommendation in order to avoid dissuading the use of time-lapse imaging in embryo culture.

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

No recommendations were made from this evidence review.

References

Armstrong 2019

Armstrong S, Bhide P, Jordan V, Pacey A, Marjoribanks J, Farquhar C. Time-lapse systems for embryo incubation and assessment in assisted reproduction. Cochrane Database of Systematic Reviews 2019, Issue 5. Art. No.: CD011320. DOI: 10.1002/14651858.CD011320.pub4. <accessed 22/04/2024>

Bhide 2024

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ESHRE Add-ons working group 2023

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Appendices

Appendix A Review protocols

Review protocol for review question: What is the clinical and cost effectiveness of embryo selection guided by continuous time-lapse monitoring (with or without artificial intelligence algorithms) as a treatment add-on for people undergoing fertility treatment?

Table 3: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42023451318
1.	Review title	Clinical and cost effectiveness of embryo selection guided by continuous time-lapse monitoring (with or without artificial intelligence algorithms) as a treatment add-on for people undergoing fertility treatment
2.	Review question	What is the clinical and cost effectiveness of embryo selection guided by continuous time-lapse monitoring (with or without artificial intelligence algorithms) as a treatment add-on for people undergoing fertility treatment?
3.	Objective	To determine the clinical and cost effectiveness of embryo selection guided by continuous time-lapse monitoring (with or without artificial intelligence algorithms) 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 IVF 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	• Embryo selection guided by the use of continuous time-lapse monitoring, with or without artificial intelligence algorithms Exclusion: Comparisons of closed embryo culture incubation versus standard incubation only, with standard embryo selection (guided by morphological criteria alone) across arms, were not included
8.	Comparators	Standard embryo selection (guided by morphological criteria alone), with standard incubation or closed embryo culture incubation
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) • Cycles without embryo transfer • Embryo utilisation rate (number of embryos that are used or frozen)
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 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 for dichotomous outcomes, and mean differences or standardised mean differences for continuous 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, 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 • Continuous outcomes: +/- 0.5x pooled control group SD for mean difference and SMD -0.5/0.5 for standardised mean difference • Dichotomous outcomes (other than live birth): 0.8 and 1.25 for all relative dichotomous outcomes
17.	Analysis of sub-groups	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 • Artificial intelligence algorithms ○ Embryo selection guided by continuous time-lapse monitoring (TLM) with artificial intelligence (AI) algorithm ○ Embryo selection guided by continuous TLM without AI algorithm Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes: • Incubation in control arm ○ Standard incubation ○ Closed embryo culture incubation

		Where evidence is sub grouped the committee will consider on a case-by-case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.			
18.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	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=CRD42023451318
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, time-lapse monitoring, time-lapse imaging and incubation, embryo selection	
33.	Details of existing review of same topic by same authors	None	
34.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☒	Discontinued
35..	Additional information	None	
36.	Details of final publication	www.nice.org.uk	

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

Appendix B Quality assessment (AGREE II)

AGREE II reviewer scoring tables for review question: What is the clinical and cost effectiveness of embryo selection guided by continuous time-lapse monitoring (with or without artificial intelligence algorithms) as a treatment add-on for people undergoing fertility treatment?

Table 4: AGREE II quality assessment of HFEA evidence statements

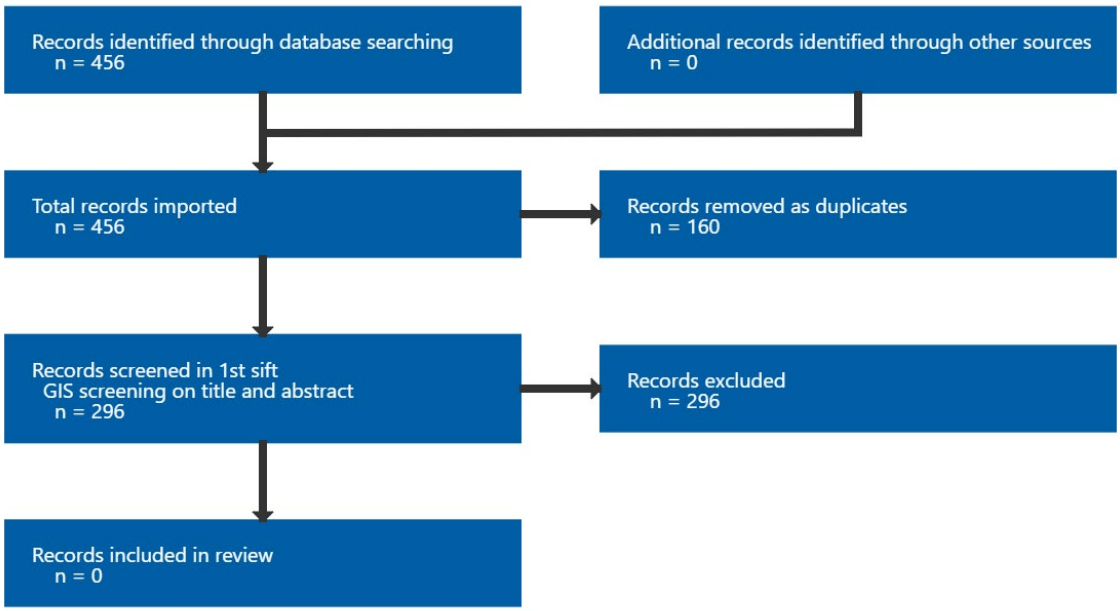
	1. Scope and purpose				2. Stakeholder involvement				3. Rigour of development									4. Clarity of presentation				5. Applicability					6. Editorial independence		
Reviewer	Objectives	Question	Population	Totals and **scores%**	Group membership	Target population	Target users	Totals and **scores%**	Search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

Appendix C Economic evidence study selection

Study selection for review question: What is the clinical and cost effectiveness of embryo selection guided by continuous time-lapse monitoring (with or without artificial intelligence algorithms) as a treatment add-on for people undergoing fertility treatment?

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

Figure 1: Study selection flow chart



Appendix D Economic evidence tables

Economic evidence tables for review question: What is the clinical and cost effectiveness of embryo selection guided by continuous time-lapse monitoring (with or without artificial intelligence algorithms) as a treatment add-on for people undergoing fertility treatment?

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

Appendix E Economic model

Economic model for review question: What is the clinical and cost effectiveness of embryo selection guided by continuous time-lapse monitoring (with or without artificial intelligence algorithms) as a treatment add-on for people undergoing fertility treatment?

No economic analysis was conducted for this review question.

Appendix F Excluded studies

Excluded studies for review question: What is the clinical and cost effectiveness of embryo selection guided by continuous time-lapse monitoring (with or without artificial intelligence algorithms) as a treatment add-on for people undergoing fertility treatment?

Excluded effectiveness studies

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

Excluded economic studies

No economic evidence was identified for this review.

Appendix G Research recommendations – full details

Research recommendations for review question: What is the clinical and cost effectiveness of embryo selection guided by continuous time-lapse monitoring (with or without artificial intelligence algorithms) as a treatment add-on for

No research recommendations were made for this review question.

Appendix H Health economic literature search strategies

Health economic literature search strategies for review question: What is the clinical and cost effectiveness of pre-implantation genetic testing for aneuploidy (PGT-A; with blastocyst stage biopsy and genome-wide analysis) as a treatment add-on for people undergoing fertility treatment?

Database: Ovid MEDLINE(R) ALL <1946 to May 28, 2024>

Date of last search: 29/05/2024

#	Searches
1	exp Fertilization in Vitro/
2	exp Embryo Transfer/ or Embryo Implantation/
3	Blastocyst/
4	(embryo* or blastocyst* or blastomer*).tw.
5	(vitro adj1 fertili*).tw.
6	(ivf or ICSI).tw.
7	((intracytoplas* or intra-cytoplas*) adj2 (sperm or injection*)).tw.
8	exp Reproductive Techniques, Assisted/
9	(assisted adj1 (reproduct* or conception)).tw.
10	ectogenesis/ or exp embryonic development/
11	(ectogenes* or ectogestat*).tw.
12	(artificial adj2 gestation*).tw.
13	or/1-12
14	Time-Lapse Imaging/
15	((time adj1 lapse*) or timelapse*).tw.
16	Fetoscopes/ or Fetoscopy/
17	(fetoscop* or amnioscop* or embryoscop*).tw.
18	(embryoviewer* or embryo-viewer*).tw.
19	(Eeva* or Primo vision* or kitazato* or cryotop* or rapid-i).tw.
20	(embryo* adj2 (scor* or assess* or grade* or grading* or rank*)).tw.
21	(live adj1 cell adj1 (imag* or microscop*)).tw.
22	Oocytes/ and Vitrification/
23	((closed or vitrificat*) adj4 system*).tw.
24	or/14-23
25	13 and 24
26	limit 25 to english language
27	letter/
28	editorial/
29	news/
30	exp historical article/
31	Anecdotes as topic/
32	comment/
33	case reports/
34	(letter or comment*).ti.
35	or/27-34
36	randomized controlled trial/ or random*.ti,ab.
37	35 not 36
38	animals/ not humans/
39	exp Animals, Laboratory/
40	exp Animal Experimentation/
41	exp Models, Animal/

#	Searches
42	exp Rodentia/
43	(rat or rats or rodent* or mouse or mice).ti.
44	or/37-43
45	26 not 44
46	Economics/
47	Value of life/
48	exp "Costs and Cost Analysis"/
49	exp Economics, Hospital/
50	exp Economics, Medical/
51	exp Resource Allocation/
52	Economics, Nursing/
53	Economics, Pharmaceutical/
54	exp "Fees and Charges"/
55	exp Budgets/
56	budget*.ti,ab.
57	cost*.ti,ab.
58	(economic* or pharmaco?economic*).ti,ab.
59	(price* or pricing*).ti,ab.
60	(financ* or fee or fees or expenditure* or saving*).ti,ab.
61	(value adj2 (money or monetary)).ti,ab.
62	resourc* allocat*.ti,ab.
63	(fund or funds or funding* or funded).ti,ab.
64	(ration or rations or rationing* or rationed).ti,ab.
65	ec.fs.
66	or/46-65
67	quality-adjusted life years/
68	sickness impact profile/
69	(quality adj2 (wellbeing or well being)).ti,ab.
70	sickness impact profile.ti,ab.
71	disability adjusted life.ti,ab.
72	(qal* or qtime* or qwb* or daly*).ti,ab.
73	(euroqol* or eq5d* or eq 5*).ti,ab.
74	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
75	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
76	(hui or hui1 or hui2 or hui3).ti,ab.
77	(health* year* equivalent* or hye or hyes).ti,ab.
78	discrete choice*.ti,ab.
79	rosser.ti,ab.
80	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
81	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
82	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
83	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
84	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
85	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
86	or/67-85
87	45 and (66 or 86)

1 **Database: Embase <1974 to 2024 May 28>**

2 **Date of last search: 29/05/2024**

#	Searches
1	exp in vitro fertilization/

#	Searches
2	exp embryo transfer/
3	blastocyst/
4	(embryo* or blastocyst* or blastomer*).tw.
5	(vitro adj1 fertili*).tw.
6	(ivf or ICSI).tw.
7	((intracytoplas* or intra-cytoplas*) adj2 (sperm or injection*)).tw.
8	exp infertility therapy/
9	(assisted adj1 (reproduct* or conception)).tw.
10	exp embryo development/
11	(ectogenes* or ectogestat*).tw.
12	(artificial adj2 gestation*).tw.
13	or/1-12
14	exp time lapse imaging/
15	((time adj1 lapse*) or timelapse*).tw.
16	amnioscopy/ or amnioscope/ or fetoscopy/
17	(fetoscop* or amnioscop* or embryoscop*).tw.
18	(embryoviewer* or embryo-viewer*).tw.
19	(Eeva* or Primo vision* or kitazato* or cryotop* or rapid-i).tw.
20	(embryo* adj2 (scor* or assess* or grade* or grading* or rank*)).tw.
21	(live adj1 cell adj1 (imag* or microscop*)).tw.
22	oocyte vitrification/
23	((closed or vitrificat*) adj4 system*).tw.
24	or/14-23
25	13 and 24
26	limit 25 to english language
27	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
28	26 not 27
29	letter.pt. or letter/
30	note.pt.
31	editorial.pt.
32	case report/ or case study/
33	(letter or comment*).ti.
34	or/29-33
35	randomized controlled trial/ or random*.ti,ab.
36	34 not 35
37	animal/ not human/
38	nonhuman/
39	exp Animal Experiment/
40	exp Experimental Animal/
41	animal model/
42	exp Rodent/
43	(rat or rats or rodent* or mouse or mice).ti.
44	or/36-43
45	28 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.

#	Searches
54	cost*.ti,ab.
55	(economic* or pharmaco?economic*).ti,ab.
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: 29/05/2024

#	Searches
1	"Fertilization in Vitro"[mhe]
2	"Embryo Transfer"[mhe]
3	"Embryo Implantation"[mh]
4	"Blastocyst"[mh]
5	(embryo* or blastocyst* or blastomer*)
6	(vitro and fertili*)
7	(ivf or ICSI)
8	((intracytoplas* or "intra-cytoplasm" or "intra-cytoplasmic" or "intra cytoplasm" or "intra cytoplasmic") and (sperm or injection*))
9	"Reproductive Techniques, Assisted"[mhe]
10	(assisted and (reproduct* or conception))
11	"Ectogenesis"[mh]
12	"Embryonic Development"[mhe]
13	(ectogenes* or ectogestat*)
14	(artificial and gestation*)

#	Searches
15	#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
16	"Time-Lapse Imaging"[mh]
17	((time and lapse*) or timelapse*)
18	"Fetoscopes"[mh]
19	"Fetoscopy"[mh]
20	(fetoscop* or amnioscop* or embryoscop*)
21	(embryoviewer* or "embryo-viewer" or "embryo-viewers" or "embryo viewer" or "embryo viewers")
22	(Eeva* or "Primo vision" or kitazato* or cryotop* or "rapid-i" or "rapid i")
23	(embryo* and (scor* or assess* or grade* or grading* or rank*))
24	(live and cell and (imag* or microscop*))
25	"Oocytes"[mh]
26	"Vitrification"[mh]
27	#26 AND #25
28	((closed or vitrificat*) and system*)
29	#28 OR #27 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16
30	#29 AND #15

1 **Database: HTA via CRD**

2 **Date of last search: 29/05/2024**

#	Searches
1	MESH DESCRIPTOR Fertilization in Vitro EXPLODE ALL TREES
2	MESH DESCRIPTOR Embryo Transfer EXPLODE ALL TREES
3	MESH DESCRIPTOR Embryo Implantation
4	MESH DESCRIPTOR Blastocyst
5	(embryo* or blastocyst* or blastomer*)
6	(vitro near1 fertili*)
7	(ivf or ICSI)
8	((intracytoplas* or (intra next cytoplas*)) near2 (sperm or injection*))
9	MESH DESCRIPTOR Reproductive Techniques, Assisted EXPLODE ALL TREES
10	(assisted near1 (reproduct* or conception))
11	MESH DESCRIPTOR Ectogenesis
12	MESH DESCRIPTOR Embryonic Development
13	(ectogenes* or ectogestat*)
14	(artificial near2 gestation*)
15	#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
16	MESH DESCRIPTOR Time-Lapse Imaging
17	((time near1 lapse*) or timelapse*)
18	MESH DESCRIPTOR Fetoscopes
19	MESH DESCRIPTOR Fetoscopy
20	(fetoscop* or amnioscop* or embryoscop*)
21	(embryoviewer* or (embryo next viewer*))
22	(Eeva* or (Primo next vision*) or kitazato* or cryotop* or "rapid-i" or "rapid i")
23	(embryo* near2 (scor* or assess* or grade* or grading* or rank*))
24	(live near1 cell near1 (imag* or microscop*))
25	#16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26	MESH DESCRIPTOR Oocytes
27	MESH DESCRIPTOR Vitrification
28	#26 and #27
29	((closed or vitrificat*) near4 system*)
30	#25 or #28 or #29
31	#15 and #30

#	Searches
32	(#15 and #30) IN HTA