National Institute for Health and Care Excellence

Final

Fertility problems: assessment and treatment

[Q] Immune therapies as a treatment add-on

NICE guideline number NG257

Evidence report underpinning recommendation 1.42.1 in the NICE guideline

March 2026

Final

Developed by NICE

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Review question

What is the clinical and cost effectiveness of immune therapies 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.

Immune therapies are sometimes offered to fertility patients whose cause of infertility is unclear, as it has been suggested that suppressing a patient's immune system may prevent the fetus being 'rejected' by it. However, the scientific rationale for this theory has not been established, and it is unclear whether immune treatments such as steroids, intralipids or intravenous immunoglobulins are effective at increasing patients' chances at having a live birth.

The aim of this review is to determine the effectiveness of immune treatments as a fertility-treatment add-on.

Summary of the protocol

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

Table 1: Summary of the protocol (PICO table)

Population	Inclusion: • People undergoing treatment for a health-related fertility problem In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination. Exclusion: • The management of recurrent miscarriage • The medical or surgical management of endometriosis

Intervention	Immunological treatments as a treatment add-on to standard fertility treatment (IVF/ICSI), including:
	• Steroids, also called corticosteroids, including:
	  ○ Prednisolone
	  ○ Methylprednisolone
	  ○ Dexamethasone
	• Intravenous intralipids
	• Intravenous immunoglobulin (IVIG)
	• TNF-alpha blocking agents (TNF-α inhibitors), including:
	  ○ Infliximab
	  ○ Adalimumab

	○ Etanercept
Comparison	• Standard fertility treatment (IVF/ICSI) without immunological treatments • Standard fertility treatment (IVF/ICSI) with placebo • Head to head comparisons of different immunological treatment add-ons (listed above)
Outcome	**Critical** • Live birth (as defined by study, risk of bias assessments will reflect where this is not defined as a live birth to include a gestational age of ≥ 20 weeks) • Clinical pregnancy (as defined by study, risk of bias assessments will reflect where this is not defined as an ultrasound scan that has shown at least one fetal heart rate) The primary unit of analysis will be cumulative rates (of each outcome) per woman randomised **Important** • Pregnancy loss (including miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy) • Number of participants with any adverse event • Number of participants with serious adverse events

ICSI: intracytoplasmic sperm injection; IVF: in-vitro fertilisation; TNF: tumour necrosis factor

Methods and process

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

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

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

During the development of this guideline, 2 published Cochrane reviews were identified investigating the effectiveness of glucocorticoid supplementation during ART. One investigated glucocorticoids during ovarian stimulation (Kalampokas 2017) and the other looked at peri-implantation glucocorticoid administration (Boomsma 2022), however only 1 of these reviews matched the committee's intended PICO, comparing the effectiveness of peri-implantation glucocorticoid administration versus no glucocorticoids (Boomsma 2022). In order to be consistent with the HFEA's approach and the intended approach as specified by the committee for this guideline, only this review was considered by the committee. No Cochrane reviews on any of the other immune therapies of interest (intralipids, intravenous immunoglobulin (IVIG), or TNF-alpha blocking agents) were identified.

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 2022, 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 immunological tests and treatments 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" (pp13-15, 21-22 and PDF pp43-45 and 51-54 for immune therapies evidence). The SCAAC decision making on the ratings is described in the document "SCAAC Minutes July 2023 - Treatment Add-Ons" (pp8-10).

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
Immunological tests and treatments for fertility: Steroids (glucocorticoids)	Rated red for increasing chances of having a baby and for reducing the chances of miscarriage, for most fertility patients and for patients undergoing immunological testing: • There are potential safety concerns and/or, on balance, the findings from moderate/high quality evidence shows that this add-on may reduce treatment effectiveness
Immunological tests and treatments for fertility: intralipids	Rated grey for increasing chances of having a baby and for reducing the chances of miscarriage, for most fertility patients and for patients undergoing immunological testing:

Treatment add-on	HFEA ratings
	• Effectiveness cannot be rated due to insufficient moderate/high quality evidence of effectiveness
Immunological tests and treatments for fertility: IVIG	Rated red for increasing chances of having a baby and for reducing the chances of miscarriage, for most fertility patients and for patients undergoing immunological testing: • There are potential safety concerns and/or, on balance, the findings from moderate/high quality evidence shows that this add-on may reduce treatment effectiveness
Immunological tests and treatments for fertility: TNF-alpha blocking agents	No evidence was identified and so a treatment rating was not made.

IVIG: intravenous immunoglobulins; TNF: tumour necrosis factor

HFEA treatment ratings

Three relevant immunological treatment interventions were given a HFEA treatment rating: steroids (glucocorticoids), intralipids, and intravenous immunoglobulin (IVIG).

Steroids (glucocorticoids) were overall given a red rating because of significant safety concerns associated with their use, including: an increased risk of minor to very serious infections, which can cause considerable harm to both the patient and the baby; common minor to rare serious side effects with increased likelihood and severity associated with higher doses of steroids; the risk of allergic reactions which range from minor rashes to serious anaphylaxis with facial swelling and difficulty breathing; the risk of serious and life-threatening withdrawal symptoms when stopped suddenly. There was no evidence considered to be of moderate or high quality that showed effectiveness of this intervention either in most fertility patients or in people undergoing immunological testing, and the HFEA committee agreed there is no scientific rationale for the use of steroids in fertility treatment.

Intralipids were overall given a grey rating for insufficient evidence of effectiveness, indicating that the effectiveness of the add-on at improving the treatment outcome could not be rated because no evidence considered to be of moderate or high quality was found. Two RCTs contributed to the rating for 'most fertility patients', which were both considered to be at high risk of bias, and reported conflicting results as to whether intralipids increased live birth rate. Only 1 of these studies reported on miscarriage and found no difference between groups. Three studies were considered for the sub-group of people undergoing immunological testing and the evidence was consistent with the findings for the general population but the populations for all these studies were people with recurrent miscarriage, who are out of scope of this guideline. The HFEA discussed safety concerns associated with the use of intralipids and agreed the safety issues existed but were not significant enough to justify a red rating. Instead, the safety concerns are highlighted on the treatment rating page, including the risk of severe allergic reactions which range from minor rashes to serious anaphylaxis with facial swelling and difficulty breathing, and the usual infection risks associated with IV infusions.

IVIG was overall given a red rating because of potential safety concerns related to their use, as well as imprecision in the evidence base on their effectiveness. The included studies for this intervention were considered to be well-designed but were small and showed no important difference between groups for live birth or miscarriage rates, with all outcomes having very wide confidence intervals. Additionally, all the studies were conducted with people who had a history of recurrent miscarriage, who were not considered to be representative of the general population, and who are out of scope of this guideline. The HFEA agreed IVIG is an intrusive treatment with patients having to be injected regularly over a long period. There were additional safety risks noted, including the risk of severe allergic reactions which range from minor rashes to serious anaphylaxis with facial swelling and

difficulty breathing, and the usual safety risks associated with blood products. The HFEA also noted the very high cost of the treatment.

TNF-alpha blocking agents were included as an intervention in the HFEA's literature search but no evidence was identified and so the HFEA decided not to make a statement regarding this treatment.

Further information about the HFEA ratings for immune therapies can be found on their website: https://www.hfea.gov.uk/treatments/treatment-add-ons/immunological-tests-and-treatments-for-fertility/

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 peri-implantation glucocorticoid administration versus no glucocorticoids (Boomsma 2022) including 16 RCTs (Ando 1996; Bider 1996-1; Bider 1996-2; Botti 1998; Catt 1994; Duvan 2006; Ezzeldin 2003; Kemeter 1986; Kim 1997; Moffitt 1995; Mohammadi 2018; Mottla 1996; Nanbakhsh 2014; Salah Edeen 2009; Tan 1992; Ubaldi 2002) was considered in this report. This Cochrane review had a different protocol to the HFEA's review, with stricter inclusion criteria (for example restricting included studies to RCTs only, excluding studies of people undergoing types of ART other than IVF/ICSI or spontaneous conception, and excluding specific subgroups of people with suggested immunological disorders such as positive antibodies, or a high number of uterine natural killer cells) and implementation of data synthesis. There was no overlap between Cochrane and the HFEA, primarily because only studies published since 2007 were reviewed by the HFEA. Cochrane excluded the RCTs included by the HFEA either due to the study type or included population. 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 (Boomsma 2022) including methods are available, as linked.

Economic evidence

A total of 735 studies were identified in the health economic search for this review question. After duplicates were removed, 558 studies were screened on title and abstract of which all were excluded at this stage.

Included studies

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

Also see the literature search strategy in appendix A 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.

Unit costs

Table 3: Unit costs

Resource	Unit costs	Source
Corticosteroids (steroids)		
Prednisolone	3p per day	British National Formulary (BNF) 5mg tablet per day – cost of 73p for 28 tablets
Methylprednisolone	21p per day	British National Formulary (BNF) 4mg tablet per day – cost of £6.19 for 30 tablets
Dexamethasone	7p per day	British National Formulary (BNF) 500mcg tablet per day – cost of £1.96 for 28 tablets
Intravenous intralipids		
Etanercept	£357.50 a week	British National Formulary (BNF) Assuming a dose of 25mg, four times a week prior to conception
Intravenous immunoglobulin (IVIG)		
Intravenous immunoglobulin (IVIG)	£321 for one dose	British National Formulary (BNF) Assuming a dose of 4g, administered prior to embryo transfer
TNF-alpha blocking agents (TNF-α inhibitors), including		
Infliximab	£377.66 for one dose	British National Formulary (BNF) 100mg powder for concentrate for solution for infusion vials
Adalimumab	£633.60	British National Formulary (BNF) Assuming a 40mg dose is given twice (2 weeks apart). Cost per dose is £316.80

The committee's discussion and interpretation of the evidence

The outcomes that matter most

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

The committee originally considered pregnancy loss, any adverse event, and serious adverse events as important outcomes. The HFEA review reported on miscarriage or other pregnancy loss as reported by the included studies, but did not report on adverse events. The Cochrane review reported on miscarriage and adverse events.

The quality of the evidence statements

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

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

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

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

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

The score for applicability was 6%. There is no discussion of barriers and facilitators of application and no information is given about feedback from key stakeholders, or whether this type of feedback was sought. There is no advice on how the evidence statements can be put into practice because the intention of the evidence statements is not to provide advice on how practice should be influenced. The cost of each add-on and resource implications are

described for add-ons in order to aid decision-making. No monitoring and/ or auditing criteria have been reported.

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

See Appendix B for the AGREE II reviewer scoring tables.

Benefits and harms

The committee discussed the HFEA treatment rating for intralipids and its underpinning evidence, and agreed there was insufficient evidence of an effect on live birth or miscarriage rates to justify its use. Although 1 RCT showed an increase in live birth rate in the intralipids arm, the other showed no important difference between groups either for live birth or for miscarriage rates. Additionally, the RCTs considered by the HFEA were all at high risk of bias. During consultation of the draft guideline, the committee were made aware that 2 of the studies included in the HFEA's underpinning evidence review had either been retracted (Al-Zebeidi 2019) or had trustworthiness issues related to the authorship group having retraction watch notices for other articles (El-Khayat 2015). However, the HFEA's treatment rating was reflective of an insufficient evidence base, and the committee agreed the exclusion of these 2 studies would reduce the evidence base further. The committee also discussed the risks of intralipid use, including the potential for congenital malformations as highlighted by the HFEA, and other side-effects associated with their use, including common minor side-effects such as headache and nausea, and rarer, more serious side effects such as bone pain and muscle weakness. The HFEA ratings for the sub-group of people undergoing immunological testing were consistent with those for the general population for all immune therapies; for intralipids, the 3 studies considered in this population were all conducted with people with recurrent miscarriage, which is out of scope of this guideline. As a result, the committee agreed there was insufficient evidence for the use of intralipids in people undergoing immunological testing either.

The HFEA's red rating for intravenous immunoglobulins (IVIG) was discussed by the committee, who agreed there were safety concerns associated with their use, in particular because IVIG carry the serious risks associated with being a blood product as well as other side-effects, including common adverse events such as headache and muscle pain, and more serious side-effects including thrombosis and kidney failure. The committee noted that IVIG is an invasive and expensive treatment, and agreed the existing evidence did not justify its use, because the studies considered by the HFEA were small and showed no important difference between groups for live birth or miscarriage rates, with all outcomes having very wide confidence intervals. The studies were also primarily conducted with people who had a history of recurrent miscarriage, who were not considered to be representative of the general population and who have also excluded from the scope of this guideline.

Steroids (glucocorticoids) were also given a red rating by the HFEA because of safety concerns associated with their use as well as a lack of convincing evidence of effectiveness. The HFEA noted a lack of evidence from moderate or high quality studies, and where there was evidence it was mostly conflicting. Some studies showed a benefit of steroids for live birth and miscarriage rates, while others showed no difference between groups who received steroids or no steroids for either outcome. During consultation of the draft guideline, the committee were made aware that 3 of the studies included in the HFEA's underpinning evidence review either had an expression of concern due to concerns about the reporting of the study (Fawzy 2008) or had trustworthiness issues related to the authorship group having retraction watch notices for other articles (Fawzy 2013, Gomaa 2014). Fawzy 2008 and Gomaa 2014 investigated the effect of steroids on women with a history of recurrent

miscarriage, which is an excluded population in the NICE fertility guideline. The committee had therefore already taken this into account when reviewing the HFEA's evidence review to ensure studies with an excluded population did not influence recommendations. Additionally, the HFEA's treatment rating was reflective of an insufficient evidence base, and the committee agreed the exclusion of the studies with trustworthiness concerns would reduce the evidence base further. The committee also discussed the Cochrane review (Boomsma 2022), which found low or very low quality evidence showing no important difference between groups receiving glucocorticoid supplementation or no glucocorticoids for any of the reported outcomes, including live birth, multiple pregnancy, clinical pregnancy, or miscarriage rate. The HFEA additionally stated there was no scientific rationale for the use of steroids, which the committee agreed with. The committee discussed the significant safety concerns associated with the use of steroids as highlighted by the HFEA, including the fact they inhibit the immune system and so put patients at increased risk of minor to very serious infections, which can cause considerable harm to both the patient and the baby. There is also the risk of allergic reactions which range from minor rashes to serious anaphylaxis with facial swelling and difficulty breathing, and steroids additionally carry the risk of serious and life-threatening withdrawal symptoms when stopped suddenly. Additionally, the committee discussed the fact that higher-than-normal doses of steroids tend to be used in IVF clinics, and the likelihood and severity of the side effects associated with steroid use increase with longer courses of more than two months or many repeated short courses.

The committee noted the HFEA had previously searched for evidence regarding the effectiveness of TNF-alpha blocking agents in October 2020 and found none.

As a result of the poor evidence base, lack of evidence of effect on live birth rates or miscarriage, and the safety concerns associated with the majority of immune therapies, the committee agreed none should be used as part of fertility treatment for any patients.

Cost effectiveness and resource use

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

The committee discussed the clinical evidence, noting the red rating from the HFEA for both steroids and intravenous immunoglobulins (IVIG). The committee also acknowledged that both these interventions have a cost over and above IVF and IVF with ICSI as these are treatment add-ons – noting the high cost of IVIG. The committee therefore concluded that steroids and IVIG should not be recommended.

The committee noted that there was a general lack of evidence of clinical effectiveness for the other interventions included in the protocol. Due to the high costs of these treatments the committee therefore concluded that immune therapies could not be considered as a cost-effective use of NHS resources at this time.

The guideline committee made recommendations reflective of current practice and therefore there will be no significant resource impact associated with the recommendations made for this review question.

Other factors the committee took into account

The committee were also aware of the recommendation made on immunomodulating treatments (including steroids, intralipids, IVIG, and anti-TNF agents) by the European Society of Human Reproduction and Embryology (ESHRE; Good practice recommendations on add-ons in reproductive medicine). This recommendation was based on existing RCTs and systematic reviews, as well as consideration of any safety concerns (ESHRE Add-ons working group 2023). The committee agreed the NICE recommendation aligns with ESHRE's findings that immunomodulating treatments could not be recommended.

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

Recommendations supported by this evidence review

This evidence review supports recommendation 1.42.1.

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Appendices

Appendix A Review protocols

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

Table 4: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42023466267
1.	Review title	Clinical and cost effectiveness of immune therapies as a treatment add-on for people undergoing fertility treatment
2.	Review question	What is the clinical and cost effectiveness of immune therapies as a treatment add-on for people undergoing fertility treatment?
3.	Objective	To determine the clinical and cost effectiveness of immune therapies as a treatment add-on for people undergoing fertility treatment. This will also inform decisions about whether immunological tests should be offered to people with fertility problems
4.	Searches	The following databases will be searched (with no date limit): Clinical searches • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE ALL • Epistemonikos Searches will be restricted by: • English language

		• Human studies The guideline committee will decide whether and when to re-run the searches before final submission of the review to retrieve further studies for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Fertility treatment add-ons
6.	Population	Inclusion: • People undergoing treatment for a health-related fertility problem. In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination. Exclusion: • The management of recurrent miscarriage • The medical or surgical management of endometriosis

7.	Interventions	Immunological treatments as a treatment add-on to standard fertility treatment (IVF/ICSI), including:
		• Steroids, also called corticosteroids, including:
		  ○ Prednisolone
		  ○ Methylprednisolone
		  ○ Dexamethasone
		• Intravenous intralipids
		• Intravenous immunoglobulin
		• TNF-alpha blocking agents (TNF-α inhibitors), including:
		  ○ Infliximab
		  ○ Adalimumab
		  ○ Etanercept

8.	Comparators	• Standard fertility treatment (IVF/ICSI) without immunological treatments

		• Standard fertility treatment (IVF/ICSI) with placebo • Head to head comparisons of different immunological treatment add-ons (listed above)
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) *Cross-over RCTs will be included but only where data can be extracted for the end of the first phase
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) The primary unit of analysis will be cumulative rates (of each outcome) per woman randomised
13.	Secondary outcomes (important outcomes)	• Pregnancy loss (including miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy) • Number of participants with any adverse event • Number of participants with serious adverse events
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary.

		Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies included after full-text review. The following data will be extracted: study details, participant characteristics, inclusion and exclusion criteria, details of the interventions, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs (and quasi-RCTs, if no RCT evidence identified) The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where there is available data, meta-analyses will be conducted using Cochrane Review Manager software, and data will be presented as risk ratios or odds ratios (all included outcomes are dichotomous outcomes). It is considered likely that a random-effects model will be used for meta-analyses (based on assumptions about methodological diversity of studies). Funnel plot asymmetry (relationship between the magnitude of the effect estimate and study size) will be considered (for meta-analyses that include at least 10 studies), and where asymmetry is indicated a fixed-effects model will be conducted (and both random-effects and fixed-effects analyses will be presented) or sensitivity analyses excluding small studies will be considered. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Importance and imprecision of findings will be assessed against minimally important differences (MIDs). The following MIDs will be used: • Live birth: statistical significance • All other outcomes: 0.8 and 1.25 for all relative dichotomous outcomes
17.	Analysis of sub-groups	Evidence will be sub-grouped by the following: • Female age (based on the mean age in the study): ○ <35 years

		○ 35-39 years ○ ≥39 years Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes: • Previous implantation failure ○ First embryo transfer ○ After previous failed embryo transfer • Timing/duration of treatment: ○ Pre-pregnancy only ○ Pre-pregnancy and continued into pregnancy 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	September 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=CRD42023466267	
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, immunotherapy, immunological, immunomodulation	
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 immune therapies as a treatment add-on for people undergoing fertility treatment?

Table 5: AGREE II quality assessment of HFEA evidence statements

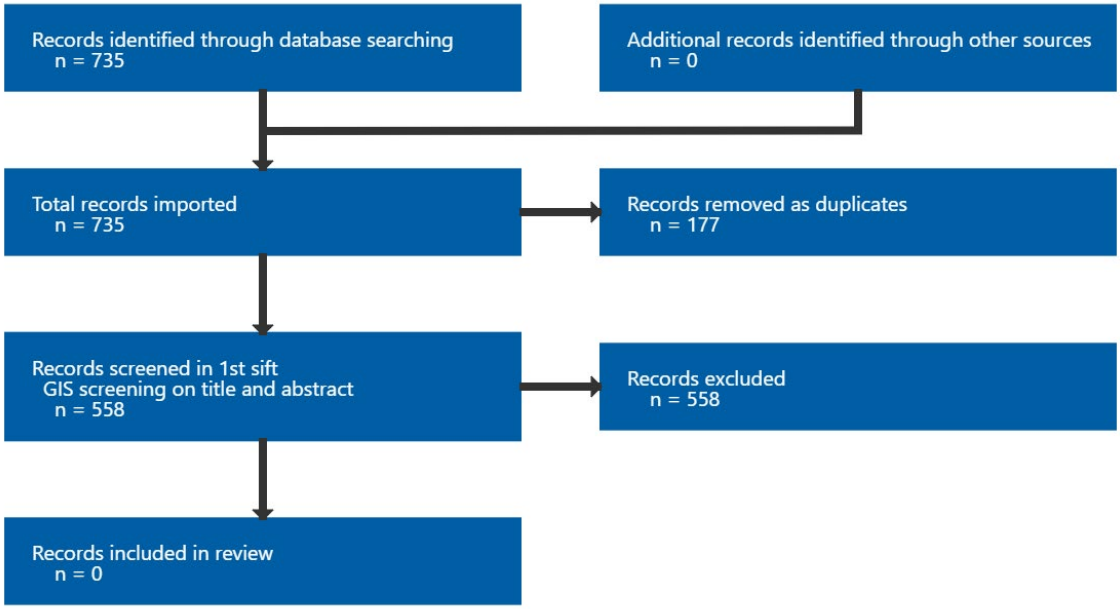
	1. Scope and purpose				2. Stakeholder involvement				3. Rigour of development									4. Clarity of presentation				5. Applicability					6. Editorial independence		
Reviewer	Objectives	Question	Population	Totals and **scores%**	Group membership	Target population	Target users	Totals and **scores%**	Search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

Appendix C Economic evidence study selection

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

No research recommendations were made for this review question.

Appendix H Literature search strategies

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

Database: Medline

Date of last search: 30/04/2024

#	Searches
1	exp Embryo Transfer/
2	((embryo* or blastocyst* or blastomer*) adj2 (transfer* or transplant*)).tw.
3	exp Fertilization in Vitro/
4	((invitro or vitro) adj5 fertili*).tw.
5	((intracytoplas* or intra-cytoplas*) adj5 sperm*).tw.
6	Reproductive Techniques, Assisted/
7	(assisted adj2 (reproducti* or conception)).tw.
8	exp Insemination, Artificial/
9	((artificial* or intrauterine) adj2 inseminat*).tw.
10	(ivf or icsi or art or iui).tw.
11	exp Abortion, Spontaneous/
12	(pregnan* adj3 (failure* or loss*)).tw.
13	(abortion* adj2 (habitual or recurrent or threaten* or spontaneous)).tw.
14	miscarriage*.tw.
15	((foetal or fetal or foetus* or fetus* or embryo*) adj3 (death* or die or died or dead or decease*)).tw.
16	exp Ovulation Induction/
17	((ovulat* or ovar*) adj5 (induc* or stimulat* or response* or hyperstimulat*)).tw.
18	superovulat*.tw.
19	(follic* adj5 phase*).tw.
20	COH.tw.
21	or/1-20
22	Adrenal Cortex Hormones/
23	(adrenal adj2 (cortex or cortical) adj2 hormone*).tw,kf.
24	(((adrenocortical or adreno* or adrenal) adj2 (steroid? or hormone*)) or adrenocorticosteroid? or corticosteroid? or cortical steroid? or cortico steroid? or corticoid*).tw,kf.
25	exp Glucocorticoids/
26	exp Dexamethasone/
27	(glucocorticoid* or glucocorticosteroid* or glucocortoid* or glycocorticoid* or glycocorticosteroid* or dexamethasone* or glensoludex* or decaject* or decameth* or decaspray* or dexasone* or dexpak* or hexadecadrol* or hexadrol* or maxidex* or methylfluorprednisolone* or millicorten* or oradexon* or auxison* or tobraDex* or "Tobramycin-Dexamethasone Drug Combination").tw,kf.
28	exp Betamethasone/
29	(betamethasone* or betadexamethasone* or celeston* or cellestoderm* or flubenisolone* or betnovate* or flubenisolonvalerate*).tw,kf.
30	exp Prednisolone/
31	(methylprednisolone* or medrol* or metipred* or urbason* or prednisolone* or "Di-Adreson-F" or predate* or predonine* or dilacort* or fluprednisolone*v or "Leo-1031" or stere?cyt*).tw,kf.
32	exp Hydrocortisone/
33	(hydrocortisone* or cortef* or cortifair* or cortisol* or cortril* or epicortisol* or fludrocortisone* or "9 alpha fludrohydrocortisone*" or "9 alpha-Fluoro-17-Hydroxycorticosterone*" or "9 alpha-Fluorohydrocortisone*" or "9-Fluoro-17-Hydroxycortisone*" or 9-Fluorocortisol* or 9-Fluorohydrocortisone* or astonin* or FCOL).tw,kf.
34	(dexol* or deltacortisol*).tw,kf.
35	Adrenocorticotropic Hormone/
36	(adrenocorticotrop* or corticotrop?in* or ACTH).tw,kf.
37	Steroids/

#	Searches
38	steroid*.tw,kf.
39	Cortisone/
40	(cortisone* or adreson*).tw,kf.
41	Immunoglobulins, Intravenous/
42	(alphaglobin* or endobulin* or "flebogamma DIF" or gamim?une* or gammagard* or gammonativ* or gamunex* or globulin-N or "IV Immunoglobulin*" or IVIG or intraglobin* or iveegam* or privigen* or sandoglobulin* or venimmune* or venoglobulin*).tw,kf.
43	(intravenous* adj2 (immunoglobulin* or globulin* or antibod* or IG)).tw,kf.
44	"Modified Immune Globulin".tw,kf.
45	(((lipid or fat or oil) adj2 emulsion*) or intralipid* or intra-lipid*).tw,kf.
46	exp Tumor Necrosis Factor Inhibitors/
47	((tumo?r* necrosis factor* or tnf) adj2 (antagonist* or inhibitor* or blocker*)).tw,kf.
48	tnf receptor type ii igg fusion protein.tw,kf.
49	(infliximab* or inflectra* or "mab ca2*" or (monoclonal antibody adj2 ca2*) or remicade* or renflexis* or remsima* or flixabi* or zessly*).tw,kf.
50	(adalimumab* or am?evita* or (antibody adj2 d2e7*) or cyltezo* or humira* or hyrimoz* or idacio* or imraldi* or yuflyma*).tw,kf.
51	(certolizumab pegol* or cimzia* or cdp 870).tw,kf.
52	Etanercept/
53	(etanercept* or enbrel* or erelzi* or (fusion protein adj2 (tnfr-fc or tnf or tnr or tnt)) or "tnr 001" or tntr-fc or benepali*).tw,kf.
54	or/22-53
55	21 and 54
56	letter/
57	editorial/
58	news/
59	exp historical article/
60	Anecdotes as topic/
61	comment/
62	case reports/
63	(letter or comment*).ti.
64	or/56-63
65	randomized controlled trial/ or random*.ti,ab.
66	64 not 65
67	animals/ not humans/
68	exp Animals, Laboratory/
69	exp Animal Experimentation/
70	exp Models, Animal/
71	exp Rodentia/
72	(rat or rats or rodent* or mouse or mice).ti.
73	or/66-72
74	55 not 73
75	limit 74 to English language
76	Economics/
77	Value of life/
78	exp "Costs and Cost Analysis"/
79	exp Economics, Hospital/
80	exp Economics, Medical/
81	exp Resource Allocation/
82	Economics, Nursing/
83	Economics, Pharmaceutical/
84	exp "Fees and Charges"/
85	exp Budgets/
86	budget*.ti,ab.

#	Searches
87	cost*.ti,ab.
88	(economic* or pharmaco?economic*).ti,ab.
89	(price* or pricing*).ti,ab.
90	(financ* or fee or fees or expenditure* or saving*).ti,ab.
91	(value adj2 (money or monetary)).ti,ab.
92	resourc* allocat*.ti,ab.
93	(fund or funds or funding* or funded).ti,ab.
94	(ration or rations or rationing* or rationed).ti,ab.
95	ec.fs.
96	or/76-95
97	quality-adjusted life years/
98	sickness impact profile/
99	(quality adj2 (wellbeing or well being)).ti,ab.
100	sickness impact profile.ti,ab.
101	disability adjusted life.ti,ab.
102	(qal* or qtime* or qwb* or daly*).ti,ab.
103	(euroqol* or eq5d* or eq 5*).ti,ab.
104	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
105	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
106	(hui or hui1 or hui2 or hui3).ti,ab.
107	(health* year* equivalent* or hye or hyes).ti,ab.
108	discrete choice*.ti,ab.
109	rosser.ti,ab.
110	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
111	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
112	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
113	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
114	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
115	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
116	or/97-115
117	75 and (96 or 116)

Database: Embase

Date of last search: 30/04/2024

#	Searches
1	exp in vitro fertilization/
2	((embryo* or blastocyst* or blastomer*) adj2 (transfer* or transplant*)).tw.
3	((invitro or vitro) adj5 fertili*).tw.
4	((intracytoplas* or intra-cytoplas*) adj5 sperm*).tw.
5	infertility therapy/
6	(assisted adj2 (reproducti* or conception)).tw.
7	exp artificial insemination/
8	((artificial* or intrauterine) adj2 inseminat*).tw.
9	(ivf or icsi or art or iui).tw.
10	exp spontaneous abortion/
11	(pregnan* adj3 (failure* or loss*)).tw.
12	(abortion* adj2 (habitual or recurrent or threaten* or spontaneous)).tw.
13	miscarriage*.tw.
14	((foetal or fetal or foetus* or fetus* or embryo*) adj3 (death* or die or died or dead or decease*)).tw.
15	ovulation induction/
16	superovulation/

#	Searches
17	((ovulat* or ovar*) adj5 (induc* or stimulat* or response* or hyperstimulat*)).tw.
18	superovulat*.tw.
19	(follic* adj5 phase*).tw.
20	COH.tw.
21	or/1-20
22	corticosteroid/
23	(adrenal adj2 (cortex or cortical) adj2 hormone*).tw,kf.
24	(((adrenocortical or adreno* or adrenal) adj2 (steroid? or hormone*)) or adrenocorticosteroid? or corticosteroid? or cortical steroid? or cortico steroid? or corticoid*).tw,kf.
25	glucocorticoid/
26	dexamethasone/
27	dexamethasone isonicotinate/
28	dexamethasone plus tobramycin/
29	(glucocorticoid* or glucocorticosteroid* or glucocortoid* or glycocorticoid* or glycocorticosteroid* or dexamethasone* or glensoludex* or decaject* or decameth* or decaspray* or dexasone* or dexpak* or hexadecadrol* or hexadrol* or maxidex* or methylfluorprednisolone* or millicorten* or oradexon* or auxison* or tobraDex* or "Tobramycin-Dexamethasone Drug Combination").tw,kf.
30	betamethasone valerate/ or betamethasone/
31	(betamethasone* or betadexamethasone* or celeston* or cellestoderm* or flubenisolone* or betnovate* or flubenisolonvalerate*).tw,kf.
32	prednisolone/
33	fluprednisolone/
34	methylprednisolone/
35	prednimustine/
36	(methylprednisolone* or medrol* or metipred* or urbason* or prednisolone* or "Di-Adreson-F" or predate* or predonine* or dilacort* or fluprednisolone*v or "Leo-1031" or stere?cyt*).tw,kf.
37	hydrocortisone/
38	fludrocortisone/
39	(hydrocortisone* or cortef* or cortifair* or cortisol* or cortril* or epicortisol* or fludrocortisone* or "9 alpha fludrohydrocortisone*" or "9 alpha-Fluoro-17-Hydroxycorticosterone*" or "9 alpha-Fluorohydrocortisone*" or "9-Fluoro-17-Hydroxycortisone*" or 9-Fluorocortisol* or 9-Fluorohydrocortisone* or astonin* or FCOL).tw,kf.
40	(dexol* or deltacortisol*).tw,kf.
41	corticotropin/
42	(adrenocorticotrop* or corticotrop?in* or ACTH).tw,kf.
43	steroid/
44	steroid*.tw,kf.
45	cortisone/
46	(cortisone* or adreson*).tw,kf.
47	immunoglobulin/
48	(alphaglobin* or endobulin* or "flebogamma DIF" or gamim?une* or gammagard* or gammonativ* or gamunex* or globulin-N or "IV Immunoglobulin*" or IVIG or intraglobin* or iveegam* or privigen* or sandoglobulin* or venimmune* or venoglobulin*).tw,kf.
49	(intravenous* adj2 (immunoglobulin* or globulin* or antibod* or IG)).tw,kf.
50	"Modified Immune Globulin".tw,kf.
51	lipid emulsion/ or intralipid/
52	(((lipid or fat or oil) adj2 emulsion*) or intralipid* or intra-lipid*).tw,kf.
53	exp tumor necrosis factor inhibitor/
54	((tumo?r* necrosis factor* or tnf) adj2 (antagonist* or inhibitor* or blocker*)).tw,kf.
55	tnf receptor type ii igg fusion protein.tw,kf.
56	(infliximab* or inflectra* or "mab ca2*" or (monoclonal antibody adj2 ca2*) or remicade* or renflexis* or remsima* or flixabi* or zessly*).tw,kf.
57	(adalimumab* or am?evita* or (antibody adj2 d2e7*) or cyltezo* or humira* or hyrimoz* or idacio* or imraldi* or yuflyma*).tw,kf.
58	(certolizumab pegol* or cimzia* or cdp 870).tw,kf.
59	(etanercept* or enbrel* or erelzi* or (fusion protein adj2 (tnfr-fc or tnf or tnr or tnt)) or "tnr 001" or tntr-fc or benepali*).tw,kf.

#	Searches
60	or/22-59
61	21 and 60
62	letter.pt. or letter/
63	note.pt.
64	editorial.pt.
65	case report/ or case study/
66	(letter or comment*).ti.
67	or/62-66
68	randomized controlled trial/ or random*.ti,ab.
69	67 not 68
70	animal/ not human/
71	nonhuman/
72	exp Animal Experiment/
73	exp Experimental Animal/
74	animal model/
75	exp Rodent/
76	(rat or rats or rodent* or mouse or mice).ti.
77	or/69-76
78	61 not 77
79	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
80	78 not 79
81	limit 80 to English language
82	health economics/
83	exp economic evaluation/
84	exp health care cost/
85	exp fee/
86	budget/
87	funding/
88	resource allocation/
89	budget*.ti,ab.
90	cost*.ti,ab.
91	(economic* or pharmaco?economic*).ti,ab.
92	(price* or pricing*).ti,ab.
93	(financ* or fee or fees or expenditure* or saving*).ti,ab.
94	(value adj2 (money or monetary)).ti,ab.
95	resourc* allocat*.ti,ab.
96	(fund or funds or funding* or funded).ti,ab.
97	(ration or rations or rationing* or rationed).ti,ab.
98	or/82-97
99	quality adjusted life year/
100	"quality of life index"/
101	short form 12/ or short form 20/ or short form 36/ or short form 8/
102	sickness impact profile/
103	(quality adj2 (wellbeing or well being)).ti,ab.
104	sickness impact profile.ti,ab.
105	disability adjusted life.ti,ab.
106	(qal* or qtime* or qwb* or daly*).ti,ab.
107	(euroqol* or eq5d* or eq 5*).ti,ab.
108	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
109	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
110	(hui or hui1 or hui2 or hui3).ti,ab.
111	(health* year* equivalent* or hye or hyes).ti,ab.

#	Searches
112	discrete choice*.ti,ab.
113	rosser.ti,ab.
114	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
115	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
116	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
117	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
118	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
119	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
120	or/99-119
121	81 and (98 or 120)

Database: INAHTA International HTA Database

Date of last search: 30/04/2024

#	Searches
1	"Embryo Transfer"[mhe]
2	((embryo* or blastocyst* or blastomer*) AND (transfer* or transplant*))
3	"Fertilization in Vitro"[mhe]
4	((invitro or vitro) AND fertili*)
5	((intracytoplasm* or"intra-cytoplasmic" or "intra-cytoplasm") AND sperm*)
6	"Reproductive Techniques, Assisted"[mh]
7	(assisted AND (reproducti* or conception))
8	"Insemination, Artificial"[mhe]
9	((artificial* or intrauterine) AND inseminat*)
10	(ivf or icsi or art or iui)
11	"Abortion, Spontaneous"[mhe]
12	(pregnan* AND (failure* or loss*))
13	(abortion* AND (habitual or recurrent or threaten* or spontaneous))
14	(miscarriage*)
15	((foetal or fetal or foetus* or fetus* or embryo*) AND (death* or die or died or dead or decease*))
16	"Ovulation Induction"[mhe]
17	((ovulat* or ovar*) AND (induc* or stimulat* or response* or hyperstimulat*))
18	(superovulat*)
19	(follic* AND phase*)
20	(COH)
21	#20 OR #19 OR #18 OR #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
22	((adrenal AND (cortex or cortical) AND hormone*)
23	((adrenocortical or adreno* or adrenal) AND (steroid or steroids or hormone*))
24	(adrenocorticosteroid or adrenocorticosteroids or corticosteroid or corticosteroids or "cortical steroid" or "cortical steroids" or "cortico steroid" or "cortico steroids" or corticoid*)
25	(glucocorticoid* or glucocorticosteroid* or glucocortoid* or glycocorticoid* or glycocorticosteroid* or dexamethasone* or glensoludex* or decaject* or decameth* or decaspray* or dexasone* or dexpak* or hexadecadrol* or hexadrol* or maxidex* or methylfluorprednisolone* or millicorten* or oradexon* or auxison* or tobraDex* or "Tobramycin-Dexamethasone Drug Combination")
26	(betamethasone* or betadexamethasone* or celeston* or cellestoderm* or flubenisolone* or betnovate* or flubenisolonvalerate*)
27	(methylprednisolone* or medrol* or metipred* or urbason* or prednisolone* or "Di-Adreson-F" or predate* or predonine* or dilacort* or fluprednisolone* or "Leo-1031" or sterecyt* or stereocyt*)
28	(hydrocortisone* or cortef* or cortifair* or cortisol* or cortril* or epicortisol* or fludrocortisone* or "9 alpha fludrohydrocortisone" or "9 alpha-Fluoro-17-Hydroxycorticosterone" or "9 alpha-Fluorohydrocortisone" or "9-Fluoro-17-Hydroxycortisone" or "9-Fluorocortisol" or "9-Fluorohydrocortisone" or astonin* or FCOL)
29	(dexol* or deltacortisol*)
30	(adrenocorticotrop* or corticotrop* or ACTH)
31	(steroid*)

#	Searches
32	(cortisone* or adreson*)
33	(alphaglobin* or endobulin* or "flebogamma DIF" or gamimune* Or gamimmune* or gammagard* or gammonativ* or gamunex* or "globulin-N" or "IV Immunoglobulin" or "IV Immunoglobulins" or IVIG or intraglobin* or iveegam* or privigen* or sandoglobulin* or venimmune* or venoglobulin*)
34	(intravenous* AND (immunoglobulin* or globulin* or antibod* or IG))
35	("Modified Immune Globulin")
36	((lipid or fat or oil) AND emulsion*))
37	(intralipid* or "intra-lipid" or "intra-lipids")
38	(("tumor necrosis factor" or "tumour necrosis factor" or "tumor necrosis factors" or "tumour necrosis factors" or tnf) AND (antagonist* or inhibitor* or blocker*))
39	("tnf receptor type ii igg fusion protein")
40	(monoclonal antibody AND ca2*)
41	(infliximab* or inflectra* or "mab ca2" or remicade* or renflexis* or remsima* or flixabi* or zessly*)
42	(antibody AND d2e7*)
43	(adalimumab* or amgevita* or amjevita* or cyltezo* or humira* or hyrimoz* or idacio* or imraldi* or yuflyma*)
44	(certolizumab pegol* or cimzia* or "cdp 870")
45	(etanercept* or enbrel* or erelzi* or "tnr 001" or "tntr-fc" or benepali*)
46	(fusion protein AND ("tnfr-fc" or tnf or tnr or tnt))
47	#46 OR #45 OR #44 OR #43 OR #42 OR #41 OR #40 OR #39 OR #38 OR #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22
48	#47 AND #21

Database: CRD HTA (last updated 31st March 2018)

Date of last search: 30/04/24

#	Searches
1	MeSH DESCRIPTOR Embryo Transfer EXPLODE ALL TREES
2	(((embryo* or blastocyst* or blastomer*) adj2 (transfer* or transplant*)))
3	MeSH DESCRIPTOR Fertilization in Vitro EXPLODE ALL TREES
4	(((invitro or vitro) adj5 fertili*))
5	MeSH DESCRIPTOR Reproductive Techniques, Assisted
6	((assisted adj2 (reproducti* or conception)))
7	MeSH DESCRIPTOR Insemination, Artificial EXPLODE ALL TREES
8	(((artificial* or intrauterine) adj2 inseminat*))
9	((ivf or icsi or art or iui))
10	MeSH DESCRIPTOR Abortion, Spontaneous EXPLODE ALL TREES
11	((pregnan* adj3 (failure* or loss*)))
12	((abortion* adj2 (habitual or recurrent or threaten* or spontaneous)))
13	(miscarriage*)
14	(((foetal or fetal or foetus* or fetus* or embryo*) adj3 (death* or die or died or dead or decease*)))
15	MeSH DESCRIPTOR Ovulation Induction EXPLODE ALL TREES
16	(((ovulat* or ovar*) adj5 (induc* or stimulat* or response* or hyperstimulat*)))
17	(superovulat*)
18	((follic* adj5 phase*))
19	(COH)
20	(((intracytoplas* or intra-cytoplas*) adj5 sperm*))
21	#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 OR #18 OR #19 OR #20
22	MeSH DESCRIPTOR Adrenal Cortex Hormones
23	((adrenal adj2 (cortex or cortical) adj2 hormone*))
24	((adrenocorticosteroid or adrenocorticosteroids or corticosteroid or corticosteroids or "cortical steroid" or "cortical steroids" or "cortico steroid" or "cortico steroids" or corticoid*))
25	MeSH DESCRIPTOR Glucocorticoids EXPLODE ALL TREES
26	MeSH DESCRIPTOR Dexamethasone EXPLODE ALL TREES

#	Searches
27	((glucocorticoid* or glucocorticosteroid* or glucocortoid* or glycocorticoid* or glycocorticosteroid* or dexamethasone* or glensoludex* or decaject* or decameth* or decaspray* or dexasone* or dexpak* or hexadecadrol* or hexadrol* or maxidex* or methylfluorprednisolone* or millicorten* or oradexon* or auxison* or tobraDex* or "Tobramycin-Dexamethasone Drug Combination"))
28	MeSH DESCRIPTOR Betamethasone EXPLODE ALL TREES
29	((betamethasone* or betadexamethasone* or celeston* or cellestoderm* or flubenisolone* or betnovate* or flubenisolonvalerate*))
30	MeSH DESCRIPTOR Prednisolone EXPLODE ALL TREES
31	((methylprednisolone* or medrol* or metipred* or urbason* or prednisolone* or "Di-Adreson-F" or predate* or predonine* or dilacort* or fluprednisolone*v or "Leo-1031" or sterecyt* or stereocyt*))
32	MeSH DESCRIPTOR Hydrocortisone EXPLODE ALL TREES
33	((hydrocortisone* or cortef* or cortifair* or cortisol* or cortril* or epicortisol* or fludrocortisone* or "9 alpha fludrohydrocortisone" or "9 alpha-Fluoro-17-Hydroxycorticosterone" or "9 alpha-Fluorohydrocortisone" or "9-Fluoro-17-Hydroxycortisone" or "9-Fluorocortisol" or"9-Fluorohydrocortisone" or astonin* or FCOL))
34	((dexol* or deltacortisol*))
35	MeSH DESCRIPTOR Adrenocorticotropic Hormone EXPLODE ALL TREES
36	((adrenocorticotrop* or corticotrop* or ACTH))
37	MeSH DESCRIPTOR Steroids
38	(steroid*)
39	MeSH DESCRIPTOR Cortisone
40	((cortisone* or adreson*))
41	MeSH DESCRIPTOR Immunoglobulins, Intravenous
42	((alphaglobin* or endobulin* or "flebogamma DIF" or gamimune* or gamimmune* or gammagard* or gammonativ* or gamunex* or "globulin-N" or "IV Immunoglobulin*" or IVIG or intraglobin* or iveegam* or privigen* or sandoglobulin* or venimmune* or venoglobulin*))
43	((intravenous* adj2 (immunoglobulin* or globulin* or antibod* or IG)))
44	("Modified Immune Globulin")
45	(((lipid or fat or oil) adj2 emulsion*))
46	((intralipid* or "intra-lipid" or "intra-lipids"))
47	MeSH DESCRIPTOR Tumor Necrosis Factor Inhibitors EXPLODE ALL TREES
48	((("tumor necrosis factor" or "tumour necrosis factor" or "tumor necrosis factors" or "tumour necrosis factors" or tnf) ADJ2 (antagonist* or inhibitor* or blocker*)))
49	("tnf receptor type ii igg fusion protein")
50	((monoclonal antibody adj2 ca2*))
51	((infliximab* or inflectra* or "mab ca2" or remicade* or renflexis* or remsima* or flixabi* or zessly*))
52	((adalimumab* or amgevita* or amjevita* or cyltezo* or humira* or hyrimoz* or idacio* or imraldi* or yuflyma*))
53	((certolizumab pegol* or cimzia* or "cdp 870"))
54	MeSH DESCRIPTOR Etanercept
55	((etanercept* or enbrel* or erelzi* or "tnr 001" or "tntr-fc" or benepali*))
56	((fusion protein ADJ2 ("tnfr-fc" or tnf or tnr or tnt)))
57	#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56
58	#21 AND #57
59	#21 AND #57 in HTA