

Fertility problems: assessment and treatment

[Q] Evidence report for immune therapies as a treatment add-on

NICE guideline number NGXXX

Evidence report underpinning recommendation 1.10.6 in the NICE guideline

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Draft for consultation

This evidence review was developed by NICE

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1 Immune therapies as a treatment add-on

2 Review question

3 What is the clinical and cost effectiveness of immune therapies as a treatment add-on for
4 people undergoing fertility treatment?

5 Introduction

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

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

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

19 Summary of the protocol

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

22 **Table 1: Summary of the protocol (PICO table)**

Population	<p>Inclusion:</p> <ul style="list-style-type: none"> • People undergoing treatment for a health-related fertility problem <p>In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy:</p> <ul style="list-style-type: none"> • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination. <p>Exclusion:</p> <ul style="list-style-type: none"> • The management of recurrent miscarriage • The medical or surgical management of endometriosis
Intervention	<p>Immunological treatments as a treatment add-on to standard fertility treatment (IVF/ICSI), including:</p> <ul style="list-style-type: none"> • Steroids, also called corticosteroids, including: <ul style="list-style-type: none"> ◦ Prednisolone ◦ Methylprednisolone ◦ Dexamethasone • Intravenous intralipids • Intravenous immunoglobulin (IVIG) • TNF-alpha blocking agents (TNF-α inhibitors), including: <ul style="list-style-type: none"> ◦ Infliximab ◦ Adalimumab

	o Etanercept
Comparison	<ul style="list-style-type: none"> • 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	<p>Critical</p> <ul style="list-style-type: none"> • Live birth (as defined by study, risk of bias assessments will reflect where this is not defined as a live birth to include a gestational age of ≥ 20 weeks) • Clinical pregnancy (as defined by study, risk of bias assessments will reflect where this is not defined as an ultrasound scan that has shown at least one fetal heart rate) <p>The primary unit of analysis will be cumulative rates (of each outcome) per woman randomised</p> <p>Important</p> <ul style="list-style-type: none"> • Pregnancy loss (including miscarriage, ectopic pregnancy, stillbirth, termination of pregnancy) • Number of participants with any adverse event • Number of participants with serious adverse events

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

2 Methods and process

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

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

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

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: <ul style="list-style-type: none"> 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
	<ul style="list-style-type: none"> Effectiveness cannot be rated due to insufficient moderate/high quality evidence of effectiveness
Immunological tests and treatments for fertility: IVIG	<p>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:</p> <ul style="list-style-type: none"> 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.

1 *IVIG: intravenous immunoglobulins; TNF: tumour necrosis factor*

2 HFEA treatment ratings

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

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

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

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

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

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

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

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

11 **Cochrane review**

12 One Cochrane review comparing the effectiveness of peri-implantation glucocorticoid
13 administration versus no glucocorticoids (Boomsma 2022) including 16 RCTs (Ando 1996;
14 Bider 1996-1; Bider 1996-2; Botti 1998; Catt 1994; Duvan 2006; Ezzeldin 2003; Kemeter
15 1986; Kim 1997; Moffitt 1995; Mohammadi 2018; Mottla 1996; Nanbakhsh 2014; Salah
16 Edeen 2009; Tan 1992; Ubaldi 2002) was considered in this report. This Cochrane review
17 had a different protocol to the HFEA's review, with stricter inclusion criteria (for example
18 restricting included studies to RCTs only, excluding studies of people undergoing types of
19 ART other than IVF/ICSI or spontaneous conception, and excluding specific subgroups of
20 people with suggested immunological disorders such as positive antibodies, or a high
21 number of uterine natural killer cells) and implementation of data synthesis. There was no
22 overlap between Cochrane and the HFEA, primarily because only studies published since
23 2007 were reviewed by the HFEA. Cochrane excluded the RCTs included by the HFEA
24 either due to the study type or included population. The Cochrane review was considered
25 sufficiently relevant, high quality and up to date, and therefore was additionally considered by
26 the committee to ensure all evidence had been reviewed, and used to supplement the HFEA
27 evidence statements to guide recommendation making by the committee. See the benefits
28 and harms section for the committee's discussion of the Cochrane evidence.

29 Full details of [the Cochrane review \(Boomsma 2022\)](#) including methods are available, as
30 linked.

31 **Economic evidence**

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

35 **Included studies**

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

38
39 Also see the literature search strategy in appendix A and the economic study selection flow
40 chart in appendix C.

41 **Excluded studies**

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

1 Economic model

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

4 Unit costs

5 **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

6

7 The committee's discussion and interpretation of the evidence

8 The outcomes that matter most

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

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

1 **The quality of the evidence statements**

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

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

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

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

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

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

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

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

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

9 **Benefits and harms**

10 The committee discussed the HFEA treatment rating for intralipids and its underpinning
11 evidence, and agreed there was insufficient evidence of an effect on live birth or miscarriage
12 rates to justify its use. Although 1 RCT showed an increase in live birth rate in the intralipids
13 arm, the other showed no important difference between groups either for live birth or for
14 miscarriage rates. Additionally, the RCTs considered by the HFEA were all at high risk of
15 bias. The committee also discussed the risks of intralipid use, including the potential for
16 congenital malformations as highlighted by the HFEA, and other side-effects associated with
17 their use, including common minor side-effects such as headache and nausea, and rarer,
18 more serious side effects such as bone pain and muscle weakness. The HFEA ratings for
19 the sub-group of people undergoing immunological testing were consistent with those for the
20 general population for all immune therapies; for intralipids, the 3 studies considered in this
21 population were all conducted with people with recurrent miscarriage, which is out of scope
22 of this guideline. As a result, the committee agreed there was insufficient evidence for the
23 use of intralipids in people undergoing immunological testing either.

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

35 Steroids (glucocorticoids) were also given a red rating by the HFEA because of safety
36 concerns associated with their use as well as a lack of convincing evidence of effectiveness.
37 The HFEA noted a lack of evidence from moderate or high quality studies, and where there
38 was evidence it was mostly conflicting. Some studies showed a benefit of steroids for live
39 birth and miscarriage rates, while others showed no difference between groups who received
40 steroids or no steroids for either outcome. The committee also discussed the Cochrane
41 review (Boomsma 2022), which found low or very low quality evidence showing no important
42 difference between groups receiving glucocorticoid supplementation or no glucocorticoids for
43 any of the reported outcomes, including live birth, multiple pregnancy, clinical pregnancy, or
44 miscarriage rate. The HFEA additionally stated there was no scientific rationale for the use of
45 steroids, which the committee agreed with. The committee discussed the significant safety
46 concerns associated with the use of steroids as highlighted by the HFEA, including the fact
47 they inhibit the immune system and so put patients at increased risk of minor to very serious
48 infections, which can cause considerable harm to both the patient and the baby. There is
49 also the risk of allergic reactions which range from minor rashes to serious anaphylaxis with
50 facial swelling and difficulty breathing, and steroids additionally carry the risk of serious and
51 life-threatening withdrawal symptoms when stopped suddenly. Additionally, the committee

1 discussed the fact that higher-than-normal doses of steroids tend to be used in IVF clinics,
2 and the likelihood and severity of the side effects associated with steroid use increase with
3 longer courses of more than two months or many repeated short courses.

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

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

9 **Cost effectiveness and resource use**

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

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

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

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

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

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

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

34 **Recommendations supported by this evidence review**

35 This evidence review supports recommendation 1.10.6.

36 **References**

37 **Boomsma 2022**

38 Boomsma CM, Kamath MS, Keay SD, Macklon NS. Peri-implantation glucocorticoid
39 administration for assisted reproductive technology cycles. Cochrane Database of
40 Systematic Reviews 2022, Issue 6. Art. No.: CD005996. DOI:
41 10.1002/14651858.CD005996.pub4. <accessed 04/04/2024>

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

1 ESHRE Add-ons working group, K Lundin, J G Bentzen, G Bozdag, T Ebner, J Harper, N Le
2 Clef, A Moffett, S Norcross, N P Polyzos, S Rautakallio-Hokkanen, I Sfontouris, K Sermon, N
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4 medicine, Human Reproduction, Volume 38, Issue 11, November 2023, Pages 2062–2104,
5 <https://doi.org/10.1093/humrep/dead184>

6 **HFEA**

7 HFEA, Immunological tests and treatments for fertility, October 2023,
8 [https://www.hfea.gov.uk/treatments/treatment-add-ons/immunological-tests-and-treatments-](https://www.hfea.gov.uk/treatments/treatment-add-ons/immunological-tests-and-treatments-for-fertility/)
9 [for-fertility/](https://www.hfea.gov.uk/treatments/treatment-add-ons/immunological-tests-and-treatments-for-fertility/) <accessed 04/04/2024>

10 **HFEA**

11 HFEA, Scientific and Clinical Advances Advisory Committee (SCAAC) – Agenda (Hybrid),
12 July 2023, available at [https://www.hfea.gov.uk/about-us/our-authority-committees-and-](https://www.hfea.gov.uk/about-us/our-authority-committees-and-panels/scientific-and-clinical-advances-advisory-committee-scaac/)
13 [panels/scientific-and-clinical-advances-advisory-committee-scaac/](https://www.hfea.gov.uk/about-us/our-authority-committees-and-panels/scientific-and-clinical-advances-advisory-committee-scaac/) <accessed 04/04/2024>

14 **HFEA**

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

19

1 Appendices

2 Appendix A Review protocols

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

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

		<ul style="list-style-type: none"> Human studies <p>The guideline committee will decide whether and when to re-run the searches before final submission of the review to retrieve further studies for inclusion.</p> <p>The full search strategies for MEDLINE database will be published in the final review.</p>
5.	Condition or domain being studied	Fertility treatment add-ons
6.	Population	<p>Inclusion:</p> <ul style="list-style-type: none"> People undergoing treatment for a health-related fertility problem. <p>In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy:</p> <ul style="list-style-type: none"> after 12 months of regular unprotected sexual intercourse or after 6 cycles of artificial insemination. <p>Exclusion:</p> <ul style="list-style-type: none"> The management of recurrent miscarriage The medical or surgical management of endometriosis
7.	Interventions	<p>Immunological treatments as a treatment add-on to standard fertility treatment (IVF/ICSI), including:</p> <ul style="list-style-type: none"> Steroids, also called corticosteroids, including: <ul style="list-style-type: none"> Prednisolone Methylprednisolone Dexamethasone Intravenous intralipids Intravenous immunoglobulin TNF-alpha blocking agents (TNF-α inhibitors), including: <ul style="list-style-type: none"> Infliximab Adalimumab Etanercept
8.	Comparators	<ul style="list-style-type: none"> Standard fertility treatment (IVF/ICSI) without immunological treatments

		<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Systematic reviews of RCTs • RCTs* (individual or cluster) • If no RCT evidence: <ul style="list-style-type: none"> ◦ Quasi-randomised controlled trials (experimental studies using a non-randomly assigned control group design with matched comparison or another method of controlling for confounding variables) <p>*Cross-over RCTs will be included but only where data can be extracted for the end of the first phase</p>
10.	Other exclusion criteria	<p>Other exclusion criteria:</p> <ul style="list-style-type: none"> • Language limitations: non-English-language papers will be excluded (unless data can be obtained, and risk of bias assessed, from an existing systematic review) • Conference abstracts, dissertations and unpublished data will not be included unless the data can be extracted (and risk of bias assessed) from elsewhere (for instance, from an existing systematic review)
11.	Context	This guidance will fully update the following NICE guideline: Fertility problems: assessment and treatment (last updated 2017; CG156)
12.	Primary outcomes (critical outcomes)	<ul style="list-style-type: none"> • Live birth (as defined by study, risk of bias assessments will reflect where this is not defined as a live birth to include a gestational age of ≥ 20 weeks) • Clinical pregnancy (as defined by study, risk of bias assessments will reflect where this is not defined as an ultrasound scan that has shown at least one fetal heart rate) <p>The primary unit of analysis will be cumulative rates (of each outcome) per woman randomised</p>
13.	Secondary outcomes (important outcomes)	<ul style="list-style-type: none"> • 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)	<p>All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol.</p> <p>Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary.</p>

		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	<p>Quality assessment of individual studies will be performed using the following checklists:</p> <ul style="list-style-type: none"> • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs (and quasi-RCTs, if no RCT evidence identified) <p>The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.</p>
16.	Strategy for data synthesis	<p>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.</p> <p>Heterogeneity in the effect estimates of the individual studies will be assessed using the I² statistic. Alongside visual inspection of the point estimates and confidence intervals, I² values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses.</p> <p>The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/</p> <p>Importance and imprecision of findings will be assessed against minimally important differences (MIDs). The following MIDs will be used:</p> <ul style="list-style-type: none"> • Live birth: statistical significance • All other outcomes: 0.8 and 1.25 for all relative dichotomous outcomes
17.	Analysis of sub-groups	<p>Evidence will be sub-grouped by the following:</p> <ul style="list-style-type: none"> • Female age (based on the mean age in the study): <ul style="list-style-type: none"> ◦ <35 years

		<ul style="list-style-type: none"> ○ 35-39 years ○ ≥39 years <p>Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes:</p> <ul style="list-style-type: none"> ● Previous implantation failure <ul style="list-style-type: none"> ○ First embryo transfer ○ After previous failed embryo transfer ● Timing/duration of treatment: <ul style="list-style-type: none"> ○ Pre-pregnancy only ○ Pre-pregnancy and continued into pregnancy <p>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.</p>	
18.	Type and method of review	<input checked="" type="checkbox"/> Intervention <input type="checkbox"/> Diagnostic <input type="checkbox"/> Prognostic <input type="checkbox"/> Qualitative <input type="checkbox"/> Epidemiologic <input type="checkbox"/> Service Delivery <input type="checkbox"/> Other (please specify)	
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	September 2023	

22.	Anticipated completion date	November 2024		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	<input type="checkbox"/>	<input type="checkbox"/>
		Piloting of the study selection process	<input type="checkbox"/>	<input type="checkbox"/>
		Formal screening of search results against eligibility criteria	<input type="checkbox"/>	<input type="checkbox"/>
		Data extraction	<input type="checkbox"/>	<input type="checkbox"/>
		Risk of bias (quality) assessment	<input type="checkbox"/>	<input type="checkbox"/>
		Data analysis	<input type="checkbox"/>	<input type="checkbox"/>
24.	Named contact	<p>5a. Named contact Guideline development team A</p> <p>5b. Named contact e-mail FertilityProblems@nice.org.uk</p> <p>5c. Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)</p>		
25.	Review team members	<p>Senior Technical Analyst</p> <p>Technical Analyst</p>		
26.	Funding sources/sponsor	This systematic review is being completed by NICE.		
27.	Conflicts of interest	<p>All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.</p>		

28.	Collaborators	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: <ul style="list-style-type: none"> • 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	<input type="checkbox"/>	Ongoing
		<input type="checkbox"/>	Completed but not published
		<input type="checkbox"/>	Completed and published
		<input type="checkbox"/>	Completed, published and being updated
		<input checked="" type="checkbox"/>	Discontinued
35..	Additional information	None	
36.	Details of final publication	www.nice.org.uk	

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

1 Appendix B Quality assessment (AGREE II)

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

4 **Table 5: AGREE II quality assessment of HFEA evidence statements**

Table 6: AGREE II quality assessment of the EA 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%

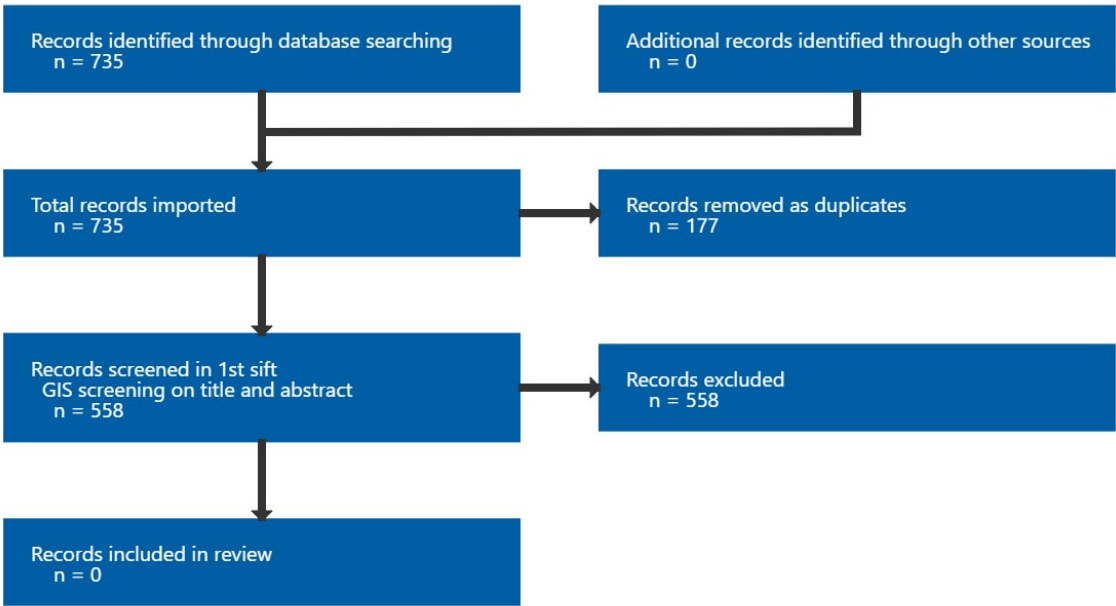
5

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



1 **Appendix D Economic evidence tables**

2 **Economic evidence tables for review question: What is the clinical and cost**
3 **effectiveness of immune therapies as a treatment add-on for people**
4 **undergoing fertility treatment?**

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

6

1 **Appendix E Economic model**

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

5 No economic analysis was conducted for this review question.

6

7

8

1 **Appendix F Excluded studies**

2 **Excluded studies for review question: What is the clinical and cost**
3 **effectiveness of immune therapies as a treatment add-on for people**
4 **undergoing fertility treatment?**

5 **Excluded effectiveness studies**

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

7 **Excluded economic studies**

8 No economic evidence was identified for this review.

9

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

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

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

1 Appendix H Literature search strategies

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

5 Database: Medline

6 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 glyco corticoid* or glyco corticosteroid* 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	Adrenocorticotrophic 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?* 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 hqi* 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)

1 Database: Embase

2 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 glyocorticoid* or glyocorticosteroid* 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?* 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 hqol* 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)

1 Database: INAHTA International HTA Database

2 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 glyocorticoid* or glyocorticosteroid* or dexamethasone* or glensoludex* or decaject* or decameth* or decaspray* or dexasone* or dexpak* or hexadecadrol* or hexadrol* or maxidex* or methylfluprednisolone* 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 flubenisonvalerate*)
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 gamimmune* Or gammimmune* 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

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

2 **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 flubenisonvalerate*))
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 Adrenocorticotrophic 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 cyletzo* 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

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