Scientific and Clinical Advances Advisory Committee (SCAAC) - agenda

Monday 06 June 2022, 12:00pm – 4:00pm
Teleconference via Zoom

Agenda item	Time
1. Welcome, apologies, declarations of interest	12:00pm (5')
2. Matters arising Ana Hallgarten (HFEA)	12:05pm (5')
3. Chair's business	12:10pm (5')
4. Monitoring the effects of COVID on fertility, assisted conception and early pregnancy	12:15pm (15')
5. Impact of Stress Victoria Askew (HFEA)	12:30pm (30')
Lunch Break	*1:00pm (45')*
6. Application form – Androgen supplementation Ana Hallgarten (HFEA)	1:45pm (20')
7. Treatment add-ons – Expansion of the evidence base Sonia Macleod (HFEA)	2:05pm (40')
Break	*2:45pm (15')*
8. Treatment add-ons – Expansion of the evidence base Sonia Macleod (HFEA)	3:00pm (50')
9. Any other business	3:50pm (5')
10. Meeting summary and close	3:55pm (5')

Scientific and Clinical Advances Advisory Committee (SCAAC) – Matters arising

Monday 6 June 2022

Date	Action	Responsibility	Due date	Progress to date
06/06/2020	The Committee agreed to monitor research into the effects of COVID-19 on reproduction or early pregnancy and to discuss this research in a standing agenda item.	All SCAAC members	Ongoing	The Committee were reminded to highlight relevant papers ahead of the meeting. An agenda item will be scheduled at SCAAC meetings for this discussion.
11/10/2021	Consider androgen supplementation as a separate treatment add-on from immunological tests and treatments.	Victoria Askew Policy Manager	Ongoing	Treatment add-on application for androgen supplementation to be discussed during agenda item six of this meeting.
31/01/2022	SCAAC members who are part of ARCS and the BFS to discuss relevant COVID papers at ARCS and BFS meetings to give feedback to SCAAC.	Relevant SCAAC members	Ongoing	To be discussed at this and future SCAAC meetings.
31/01/2022	Amend committee workplan according to the feedback from SCAAC members.	Policy team	Complete	Updated work plan included as Annex A to this paper.
31/01/2022	Assess whether further outputs are required in the topic of the impact of the microbiome, and whether it needs to be considered as a treatment add-on.	Policy team	Ongoing	This will be assessed as part of an agenda item at the October 2022 SCAAC meeting, as per committee workplan in Annex A.
31/01/2022	SCAAC members make recommendations for external experts to discuss	All SCAAC members	Ongoing	SCAAC members were asked to send through suggested experts following January

	high priority topics at future meetings.		minutes. If there are any suggestions throughout the year, SCAAC members should highlight these to the Scientific Policy Team.

Annex A – updated work plan

Priority topic	Item	Possible speaker(s)	Meeting
Add-ons – expansion of the evidence base	External speakers	External experts	June 2022
Add-ons – androgen supplementation	Literature review	Internal	June 2022
The impact of stress	Literature review	Internal	June 2022
The impact of the microbiome	Literature review	Internal	October 2022
Extension of 14-day rule	Literature review and external speaker	Academic	October 2022
Artificial Intelligence	Literature review	Internal	October 2022
Synthetic embryo like entities	Literature review	Internal	February 2023
Add-ons – evidence review	Literature review and external speaker	Expert reviewer	February 2023
In vitro derived gametes	Literature review	Academic	June 2023
Health outcomes (inc. culture media)	Literature review	Internal	June 2023

Impact of stress on fertility treatment outcomes.

Details about this paper

Area(s) of strategy this paper relates to:	The best care
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	5
Paper number:	HFEA (06/06/2022) 005
Meeting date:	06 June 2022
Author:	Victoria Askew, Policy Manager
Annexes	Annex 1: References

Output from this paper

For information or recommendation?	For information
Recommendation:	Members are asked to: • Consider the development in research into the impacts of stress on fertility treatment outcomes, including whether a clear link has been established; • Advise the Executive if they are aware of any other recent developments, and; • Review whether any outputs from the HFEA are required addressing the impacts of stress on fertility treatment outcomes.
Resource implications:	NA
Implementation date:	NA
Communication(s):	Minutes of committee discussion circulated via Clinic Focus
Organisational risk:	Low

1. Introduction

1.1. Patients undergoing fertility treatment frequently report high levels of stress and anxiety. This could be due to several factors such as the distressing nature of experiencing difficulties in conceiving, the physical and emotional impacts of undergoing fertility treatment, and the uncertainty of treatment outcomes. Patient may also experience feelings of isolation, anger or frustration, impacts on relationships, financial strains, and lack of support from employers, friends, or family.

1.2. Anecdotally, some patients have suggested that stress could play a role in their chances of having a successful treatment outcome. Patients may be told stories of people who have become pregnant spontaneously after having relief from the stress of trying to conceive, for example, after having decided to end their fertility treatment journey.

1.3. Regardless of any impact on treatment outcomes, the HFEA is committed to improving the emotional experience of care before, during, and after treatment or donation. On inspection clinics are required to demonstrate an effective patient support policy, in line with the requirements in the HFEA's **Code of Practice**. Patient support can include counselling but can also encompass other forms of formal and informal psychological support, such as patient support groups or forums.

1.4. Researchers have shown an interest in investigating a possible association between increased levels of stress and poor fertility treatment outcomes. If a link between stress and fertility treatment outcomes is established the HFEA may be able to help by providing more evidence-based information, guidance, and advice both to clinics and patients.

1.5. This relationship between stress and fertility treatment outcomes is particularly relevant as high levels of stress have been reported after the delays and interruptions to treatment caused by the COVID-19 pandemic (Jaiswal et al., 2022; Lawson et al., 2023; Marom Haham et al., 2021; Wedner-Ross et al., 2022).

1.6. As a medium priority topic, this was last discussed by the committee in **February 2018**. It was found that previous research results were mixed, and it was unclear how stress may impact a couple's chance of having a successful treatment cycle. A study by Massey et al., 2016, suggested that lower levels of cortisol in the months before fertility treatment could benefit patient outcomes. However, the Committee concluded that the objective study on stress in patients in relation to fertility can be difficult because of confounding factors.

1.7. This review highlights key developments in our understanding of the impact of stress on fertility treatment outcomes with a focus on developments since February 2018.

2. Research outcomes

Impact found on fertility treatment outcomes

2.1. A meta-analysis conducted by Zhou et al., 2021 included 29 studies investigating the effects of psychological interventions on psychological distress (for example stress, anxiety and depression) and pregnancy outcomes in infertile couples. Ten of these studies, with a total of 1318 patients, included patient pregnancy outcomes. Compared with results from the placebo groups, infertile patients who received psychotherapy were more likely to fall pregnant (either spontaneously or using assisted reproduction) than those who received the placebo (risk ratio

(RR)=1.43,95% confidence interval (CI) (1.07, 1.93)). In a subgroup analysis based on assisted reproduction, there was a statistically significant difference in the pregnancy rate between the placebo group and patients using assisted reproduction (RR=1.18, 95% CI (1.002, 1.40)). When analysing specific types of psychotherapy, cognitive behavioral therapy (CBT) (RR=2.00, 95% CI (1.44, 2.77)) and the integrative body-mind-spirit intervention (BMS) (RR=1.49, 95% CI (1.04, 2.13)) were found to significant increase pregnancy rates in patients experiencing infertility. The meta-analysis concluded that psychotherapy, especially CBT and BMS, could be beneficial to increase the pregnancy rate for patients undergoing assisted reproduction.

2.2. A prospective cohort study by Aimagambetova et al., 2020 measured psychological stress in 304 female fertility patients in Kazakhstan using self-reporting questionnaires. Depression was measured using the Centre for Epidemiological Studies Depression Scale (CES-D). Fertility related stress was measured using the Fertility Problem Inventory (FPI) which assessed social, sexual and relationship concerns, rejection of child free lifestyles, and need for parenthood. Anxiety was measured using Spielberger State-Trait Anxiety Inventory (STAI). No association was found between reported levels of anxiety and depression, and clinical pregnancy rate. However, within the FPI, higher stress related to sexual concern, need for parenthood, rejection of children lifestyle and global stress were negatively associated with clinical pregnancy rate at a significant level.

2.3. The same group from Nazarbayev University School of Medicine outlined in point 2.2 conducted another prospective cohort study in 2021 (Bapayeva et al., 2021). 304 women undergoing IVF treatment were assessed for depression, anxiety and fertility related stress using the CES-D, STAI and FPI respectively. No statistically significant association was found between depression or fertility related stress and IVF outcomes. However, after adjusting for confounding variables higher STAI scores were negatively associated with clinical pregnancy rate.

2.4. A pilot randomised control trail (RCT) by Raad et al., 2020 found that women (n=29) allocated to a stress management programme (SMP) at the start of their intra cytoplasmic sperm injection (ICSI) cycle had a significantly lower perceived stress scale (PSS) score at the end of treatment compared to the start of treatment ($p < 0.001$; effect size, ES = 0.5). The SMP group also had a significantly lower PSS score at the end of treatment compared to women (n=30) in the treatment as usual (TAU) group ($p = 0.02$; ES = 0.09). The study measured characteristics of embryo development and found that mtDNA levels were significantly lower in luteal granulosa cells of the SMP group than the TAU group ($p = 0.02$). An earlier time of pronuclei appearance ($p = 0.03$) and time to two cells ($p = 0.015$) and a faster time to full compaction ($p = 0.045$) were detected in the embryos of the SMP group compared with the TAU group.

2.5. Zhou et al., 2019 conducted a prospective cohort study in 457 couples undergoing their first cycle of IVF. The group collected saliva samples from patients on the morning of their first day of treatment. Increased salivary alpha-amylase (SAA) levels in males (>149 µmol/L), females (>136µmol/L) and couples (>288 µmol/L) were associated with an increased risk in pregnancy failure than those with low SAA. SAA levels were found to be directly correlated with follicle stimulating hormone (FSH) levels, and inversely proportional to anti-Mullerian hormone (AMH) levels and endometrial thickness. In male patients increase SAA levels were associated with several factors of poorer semen quality. Couples with a combined high SAA level were also found to have fewer transferable and high-quality embryos.

No or conflicting impact found on fertility treatment outcomes

2.6. A prospective study by Cesta et al., 2018 collected data from 485 women who underwent IVF or ICSI in central Sweden. The investigation included self-reported stress levels through the completion of an online questionnaire, the cortisol levels in morning and evening saliva samples, and the analysis of clinically relevant data. They found no association between self-reported stress or cortisol measures and IVF outcomes, including whether the cycle progressed to egg aspiration, embryo transfer or resulted in a clinical pregnancy. Additionally, there were no significant associations between stress and indicators of egg and embryo quality except between evening cortisol and average integrated morphology cleavage (IMC) embryo score.

2.7. Barrett et al., 2018 used a secondary data analysis from participants of a previous RCT, "Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation (AMIGOS)". This study calculated the allostatic load (AL) scores (the cumulative burden of chronic stress and life events) of 836 ovulatory women with unexplained infertility. The women went on to receive up to four cycles of ovarian stimulation and were followed through any resulting pregnancy. There was no significant link found between AL and fertility treatment outcomes (clinical pregnancy, miscarriage, or live birth rates). However, increase AL was associated with poor pregnancy outcomes (increase in odds for pre-eclampsia, pre-term birth and low birth weight).

2.8. In a study by Miller et al., 2019 salivary cortisol measurements were taken for 72 patients before treatment began, before egg collection, and before embryo transfer. Emotional stress was also calculated at these time points through the State-Trait Anxiety Inventory and a one to ten Visual Analogue Scale. Cortisol levels and emotional stress were found to peak before egg collection. However, both the physiological and psychological stress measures were not associated with results of embryo transfer, fertilisation rate, embryo quality or clinical pregnancy rate. Follicular cortisol concentrations were positively correlated with fertilisation rate ($r = 0.4$, $P = 0.004$).

2.9. Cheung et al., 2019 undertook a prospective observational study to analyse the impacts of psychological and physiological stress on 197 women undergoing fresh or frozen IVF or ICSI cycles. Psychological stress was measured using a questionnaire given to the patients at embryo transfer and pregnancy testing. Physiological stress was measuring using saliva samples before and after embryo transfer and at pregnancy testing. They found significant differences in psychological or physiological stress levels between those who had a clinical pregnancy and those who did not, or those who went on to have a miscarriage or an ongoing pregnancy.

2.10. A systematic review by Paraskevi et al., 2021 of 14 previously published systematic reviews and meta-analyses conducted looked at the impact of stress, anxiety, or depression on the treatment outcomes for males, females and couples undergoing assisted reproduction. These included studies assessing the relationship between stress and anxiety in couples undergoing fertility treatment and the outcome of the treatment, and the psychological state and psychological adjustment of the couples after a negative result. Studies also considered the impact of interventional methods for reducing stress, anxiety, or depression on the psychological state of the couples undergoing treatment and on their pregnancy outcomes. The group reported that the included studies had conflicting results for the impact of stress on treatment outcomes. However, they found that couples who had received psychological support were more likely to adjust better to the treatment procedure and outcomes.

2.11. Koumparou et al., 2021 conducted a pilot RCT in 144 women undergoing IVF. The 74 patients that were allocated to the intervention group underwent eight weekly session of stress management techniques including biofeedback, diaphragmatic respiration, muscular relaxation, diet, and cognitive restructuring. It is not clear from the paper at what stage of treatment the patients underwent this course. Both the control and intervention arms completed questionnaires on week one and week eight of the course, including the Depression, Anxiety and Stress Scale 21 (DSS-21), the Perceived Stress Scale 14 (PSS-14) and the FPI. The study found that the total reported stress of those in the intervention arm significant decreased during the eight-week stress management course ($P<0.001$). There was also a significant lower level of total reported stress in the intervention arm compared to the control arm at the end of the course ($P<0.001$).

2.12. Participants that did not go on to have a positive clinical pregnancy result had, on average, a lower PSS-14 scale score during the measurement taken on week one ($P=0.29$). This same significant difference was not found with the results of the DSS-21 or FPI questionnaires. However, this does not indicate whether the intervention had an impact on the clinical pregnancy rate and the group conclude that evaluating the direct effect of the intervention on IVF outcome was not possible due to the independent variables that were pivotal for the result. This included the participants' age ($p=0.046$), which was negatively correlated to IVF success, and the spouses' medical history of cryptorchidism (undescended testicles) ($p=0.05$).

2.13. Liu et al., 2021 measured the level of perceived anxiety and depression in 247 couples undergoing IVF in China. Participants completed two questionnaires for anxiety and depression scales respectively on the day they started treatment, the day that human chorionic gonadotropin (hCG) was administered, and four days after embryo transfer. The group found that anxiety and depression scores were not correlated with pregnancy rates.

2.14. Peng et al., 2021 undertook a case control study in 150 couples who did not achieve a clinical pregnancy after their first cycle of fresh IVF or ICSI and 300 age matched controls that did have a positive clinical pregnancy. Anxiety and depression before treatment were measured using a self-rating anxiety scale and CES-D respectively. No significant differences were identified in anxiety, depression or perceived stress between patients that did or did not have a positive clinical pregnancy, or their partners. Adjusted odds ratios of logistic regression were 1.00 (95% CI 0.97-1.03) for anxiety, 0.98 (95% CI 0.95-1.02) for depression, and 0.98 (95% CI 0.95-1.01) for perceived stress.

2.15. In a study by Sallem et al., 2021 79 women undergoing IVF completed a questionnaire (Beck anxiety inventory (BAI)) on the day of egg collection and were subsequently categorised as having very low anxiety ($BAI>21$), moderate anxiety ($22\leq BAI\leq 35$) or severe anxiety ($BAI\geq 36$). Blood samples were also collected on the day of egg collection and embryo transfer to test for free cortisol levels. A lower implantation rate was found in severely anxious patients compared with moderately anxious women ($p= 0.03$) and those having low levels of anxiety ($p= 0.001$) and was negatively correlated to BAI score ($r= -0.65$; $p= 0.001$). However, there were no statistically significant differences in clinical pregnancy and livebirth rates between the three groups.

2.16. Trikoilis et al., 2022 conducted a case control study to investigate the link between different stress biomarkers and IVF or ICSI treatment outcomes. 109 women in their first fresh IVF or ICSI treatment cycle were allocated according to the outcome of their treatment, either group A (positive pregnancy test) or group B (negative pregnancy test). Spielberger State-Trait Anxiety

Inventory (STAI) questionnaires (Marteau and Bekker modification) were used to measure state anxiety on the days of egg retrieval and embryo transfer. Serum stress biomarkers (cortisol, adrenaline, noradrenaline, α-amylase, and prolactin) were measured at the same time points. Women in both groups showed comparable levels of state anxiety, which were unlikely to influence the chance of pregnancy. Noradrenaline levels were higher in the non-pregnant group, with significant cardiovascular changes. Other stress biomarkers did not reflect the different treatment outcomes between the groups.

3. Conclusions

3.1. It is widely acknowledged that patients undergoing assisted reproduction are at risk of experiencing high levels of psychological and physiological stress both before and during their treatment. Some studies suggest that differences in levels of social support, personality traits and resilience can impact the degree of distress a patient may experience during infertility treatment.

3.2. Despite the clear high levels of stress and anxiety in fertility patients, the research to date is inconclusive on whether these increased stress levels have a negative impact on fertility treatment outcomes. Study samples tend to be small, and psychological stress can be difficult to measure with many studies using self-reporting questionnaires. This subjective data collection could contribute to the conflicting results that are seen in the research on this topic. More high-quality research is needed to determine whether stress is a cause or a consequence of infertility.

3.3. Although a clear relationship between stress and fertility treatment outcomes has not yet been established, offering emotional support to patients when it is needed during their fertility treatment continues to be an important role of fertility clinics.

4. Recommendations

4.1. Members are asked to:

- Consider the progress in research into the impacts of stress on fertility treatment outcomes, including whether a clear link has been established;
- Advise the Executive if they are aware of any other recent developments, and;
- Review whether any outputs from the HFEA are required addressing the impacts of stress on fertility treatment outcomes.

Annex A - References

Aimagambetova, G., Issanov, A., Terzic, S., Bapayeva, G., Ukybassova, T., Baikoshkarova, S., Aldiyarova, A., Shauyen, F., Terzic, M., 2020. The effect of psychological distress on IVF outcomes: Reality or speculations? PLoS One 15. https://doi.org/10.1371/JOURNAL.PONE.0242024

Bapayeva, G., Aimagambetova, G., Issanov, A., Terzic, S., Ukybassova, T., Aldiyarova, A., Utepova, G., Daribay, Z., Bekbossinova, G., Balykov, A., Laganà, A.S., Terzic, M., 2021. The Effect of Stress, Anxiety and Depression on In Vitro Fertilization Outcome in Kazakhstani Public Clinical Setting: A Cross-Sectional Study. Journal of Clinical Medicine 10, 937. https://doi.org/10.3390/jcm10050937

Barrett, E.S., Vitek, W., Mbowe, O., Thurston, S.W., Legro, R.S., Alvero, R., Baker, V., Wright Bates, G., Casson, P., Coutifaris, C., Eisenberg, E., Hansen, K., Krawetz, S., Robinson, R., Rosen, M., Usadi, R., Zhang, H., Santoro, N., Diamond, M., 2018. Allostatic load, a measure of chronic physiological stress, is associated with pregnancy outcomes, but not fertility, among women with unexplained infertility. Hum Reprod 33, 1757–1766. https://doi.org/10.1093/HUMREP/DEY261

Cesta, C.E., Johansson, A.L.V., Hreinsson, J., Rodriguez-Wallberg, K.A., Olofsson, J.I., Holte, J., Wramsby, H., Wramsby, M., Cnattingius, S., Skalkidou, A., Nyman Iliadou, A., 2018. A prospective investigation of perceived stress, infertility-related stress, and cortisol levels in women undergoing in vitro fertilization: influence on embryo quality and clinical pregnancy rate. Acta Obstetricia et Gynecologica Scandinavica 97, 258–268. https://doi.org/10.1111/aogs.13280

Cheung, C.W.C., Saravelos, S.H., Chan, T.Y.A., Sahota, D.S., Wang, C.C., Chung, P.W., Li, T.C., 2019. A prospective observational study on the stress levels at the time of embryo transfer and pregnancy testing following in vitro fertilisation treatment: a comparison between women with different treatment outcomes. BJOG 126, 271–279. https://doi.org/10.1111/1471-0528.15434

Jaiswal, P., Mahey, R., Singh, S., Vanamail, P., Gupta, M., Cheluvaraju, R., Sharma, J.B., Bhatla, N., 2022. Psychological impact of suspension/postponement of fertility treatments on infertile women waiting during COVID pandemic. Obstet Gynecol Sci 65, 197–206. https://doi.org/10.5468/OGS.21254

Koumparou, M., Bakas, P., Pantos, K., Economou, M., Chrousos, G., 2021. Stress management and In Vitro Fertilization (IVF): A pilot randomized controlled trial. Psychiatriki. https://doi.org/10.22365/jpsych.2021.029

Lawson, A.K., Mcqueen, D.B., Swanson, A.C., Confino, R., Feinberg, E.C., Pavone, M.E., 2023. Psychological distress and postponed fertility care during the COVID-19 pandemic. https://doi.org/10.1007/s10815-020-02023-x/Published

Liu, Y.-F., Fu, Z., Chen, S.-W., He, X.-P., Fan, L.-Y., 2021. The Analysis of Anxiety and Depression in Different Stages of in vitro Fertilization-Embryo Transfer in Couples in China. Neuropsychiatric Disease and Treatment Volume 17, 649–657. https://doi.org/10.2147/NDT.S287198

Marom Haham, L., Youngster, M., Kuperman Shani, A., Yee, S., Ben-Kimhy, R., Medina-Artom, T.R., Hourvitz, A., Kedem, A., Librach, C., 2021. Suspension of fertility treatment during the COVID-19 pandemic: views, emotional reactions and psychological distress among women undergoing fertility treatment. Reproductive Biomedicine Online 42, 849. https://doi.org/10.1016/J.RBMO.2021.01.007

Massey, A.J., Campbell, B.K., Raine-Fenning, N., Pincott-Allen, C., Perry, J., Vedhara, K., 2016. Relationship between hair and salivary cortisol and pregnancy in women undergoing IVF. Psychoneuroendocrinology 74, 397–405. https://doi.org/10.1016/J.PSYNEUEN.2016.08.027

Miller, N., Herzberger, E.H., Pasternak, Y., Klement, A.H., Shavit, T., Yaniv, R.T., Ghetler, Y., Neumark, E., Eisenberg, M.M., Berkovitz, A., Shulman, A., Wiser, A., 2019. Does stress affect IVF outcomes?

A prospective study of physiological and psychological stress in women undergoing IVF. Reprod Biomed Online 39, 93–101. https://doi.org/10.1016/J.RBMO.2019.01.012

Paraskevi, L., Antigoni, S., Kleanthi, G., 2021. Stress and Anxiety Levels in Couples who Undergo Fertility Treatment: a Review of Systematic Reviews. Materia Socio Medica 33, 60. https://doi.org/10.5455/msm.2021.33.60-64

Peng, M., Wen, M., Jiang, T., Jiang, Y., Lv, H., Chen, T., Ling, X., Li, H., Meng, Q., Huang, B., Tao, S., Huang, L., Liu, C., Xu, X., Lu, Q., Liu, X., Xu, B., Han, X., Zhou, K., Chen, J., Lin, Y., Ma, H., Xia, Y., Shen, H., Hu, Z., Chen, F., Du, J., Jin, G., 2021. Stress, anxiety, and depression in infertile couples are not associated with a first IVF or ICSI treatment outcome. BMC Pregnancy Childbirth 21, 725. https://doi.org/10.1186/s12884-021-04202-9

Raad, G., Tanios, J., Kerbaj, S., Mourad, Y., Fakih, F., Shamas, F., Azouri, J., Fakih, C., 2020. Stress Management during the Intracytoplasmic Sperm Injection Cycle May Slow Down First Embryo Cleavage and Accelerate Embryo Compaction: A Pilot Randomized Controlled Trial. Psychotherapy and Psychosomatics 1–8. https://doi.org/10.1159/000512530

Sallem, A., Essoussi, H., Mustapha, H. ben, Zaouali, M., Ajina, M., 2021. Impact of psychological stress on the outcomes of assisted reproduction in Tunisian infertile women. Pan African Medical Journal 40. https://doi.org/10.11604/pamj.2021.40.250.32207

Trikoilis, N., Mavromatidis, G., Tzafetas, M., Deligeoroglou, E., Tzafetta, M., Loufopoulos, A., Dafoulis, V., Tziomalos, K., Goulis Dimitrios, G., 2022. The association of in vitro fertilization/intracytoplasmic sperm injection results with anxiety levels and stress biomarkers: An observational, case-control study. Journal of Gynecology Obstetrics and Human Reproduction 51, 102254. https://doi.org/10.1016/j.jogoh.2021.102254

Wedner-Ross, S., Schippert, C., von Versen-Höynck, F., 2022. The impact of the COVID-19 pandemic on women seeking fertility treatment: the patient's perspective. Arch Gynecol Obstet. https://doi.org/10.1007/S00404-021-06379-Y

Zhou, F. jing, Cai, Y. na, Dong, Y. zhi, 2019. Stress increases the risk of pregnancy failure in couples undergoing IVF. Stress 22, 414–420. https://doi.org/10.1080/10253890.2019.1584181

Zhou, R., Cao, Y.-M., Liu, D., Xiao, J.-S., 2021. Pregnancy or Psychological Outcomes of Psychotherapy Interventions for Infertility: A Meta-Analysis. Frontiers in Psychology 12. https://doi.org/10.3389/fpsyg.2021.643395

Application to include a new add-on on the HFEA traffic list

1. Background

Treatment add-ons **are often non-essential treatments that are commonly offered in fertility clinics in addition to routine treatment with the claim that they can improve a patient's chance of having a baby for most fertility patients**. As with all new treatments or technologies being introduced into reproductive medicine, we expect the introduction of treatment add-ons into clinics to be preceded by good quality scientific research into the effectiveness and safety of these interventions. However, some treatment add-ons are being offered to patients without this evidence base either for their effectiveness at increasing live birth rate or for their safety. They are frequently offered outside of a research setting and may be charged for as an additional cost.

This form can be used to propose that we review the evidence for a treatment add-on if they are concerned that it is being offered to patients in a UK licensed clinic:

- with the claim that it will increase the live birth rate
- without conclusive evidence of its effectiveness at improving the live birth rate;
- it is not already listed in our the HFEA's traffic-light rated list of add-ons
- there is evidence that an add-on treatment is ineffective.

We will use the information given on this form to help us consider whether to include the proposed add-on(s) as part of our traffic-light rated list of add-ons, which are reviewed annually for evidence of their effectiveness for increasing the live birth rate for most fertility patients.

Your submitted information could be used to inform other webpages, outside of the HFEA's traffic-light rated list of add-ons.

2. Guidance

The purpose of this guidance is to assist you in completing the treatment add-ons application form. Add-ons could include tests, drugs, equipment, and surgical interventions.

Do not use this form to send information about treatment add-ons that are already on the HFEA's traffic-light rated list of add-ons.

Please use plain unabbreviated language (understandable to non-specialists) in your application.

SCAAC review

The HFEA Scientific and Clinical Advances Advisory Committee (SCAAC) considers advances in science and clinical practice which are relevant to the Authority's work. The SCAAC will review the

current published evidence base for the treatment, alongside this application, and determine its suitability to be part of the HFEA's traffic-light rated list of add-ons. The SCAAC review will consider:

- whether the treatment is an additional, non-essential treatment
- if patients undergoing fertility treatment are currently being offered, or are requesting, the treatment on a regular basis and/or are being charged for its use in their treatment;
- the likelihood that the treatment is unable to increase pregnancy or live birth rates compared to using established ART techniques without the treatment;
- whether there is a lack of standardised procedure between different laboratories and the lack of potential for this treatment to be implemented by other centres; and
- whether patients need information about the risks or safety of the procedure, for both patients and children born as a result of treatment.

Your application should be completed comprehensively to enable the committee to assess all areas.

A decision tree for SCAAC to use to determine what does and does not classify as a treatment add-on can be found in Annex A of the application form.

Submitted applications will be reviewed at the next available SCAAC meeting, which take place three times a year in February, June and October. If an application for this treatment has already been received and is currently under consideration, then we will let you know. If, after submitting your application, you wish to withdraw it from consideration, then please contact us as soon as possible.

If SCAAC recommends that this treatment is not suitable for inclusion in **the HFEA's traffic-light rated list of add-ons**, then we will notify you of this outcome by email. If, in the future, more evidence is published that supports this treatment as an add-on, i.e. conflicting evidence to show it can increase live birth rate, then you will be able to re-apply.

Assignment of a 'traffic light' rating

If SCAAC gives a recommendation that the treatment you told us about is suitable for inclusion in the annually-updated **HFEA's traffic-light rated list of add-ons**, then the published randomised control trials investigating the treatment will be reviewed for the outcome of live birth or pregnancy rate to allow SCAAC to assign a traffic light rating.

Once a traffic light rating has been assigned **the HFEA's traffic-light rated list of add-ons** will be updated accordingly and reviewed annually.

Thank you for taking the time to submit the application form and sharing your information.

3. Applicant information

Name	
Occupation and institution	
Email address	
Declaration of any financial or personal interest in relation to this treatment	

4. Proposed treatment add-on

4.1 What is the name of the treatment?

Androgen supplementation

Most commonly either dehydroepiandrosterone (DHEA) or testosterone.

4.2 Please provide some background about the treatment and include how the treatment is used and how it claims to improve live birth rate. (max. 600 words)

DHEA and testosterone are steroid hormones used in assisted reproduction (they are used within standard treatment for those with poor ovarian response (POR) or diminished ovarian reserve (DOR)), due to their suggested role in improving pregnancy rates and increasing live birth rates.

Testosterone is administered transdermally, through either patches or gel, or orally. DHEA is ingested as a 75mg pill once per day, up to 12 weeks prior to ovarian stimulation and during ovarian stimulation. DHEA is an androgen pre-hormone and a precursor to multiple hormones (including testosterone), which decreases as a women's age increases (Nagels et al., 2015).

Animal studies and human studies have demonstrated that androgens have an essential role in the regulation of ovarian function (Walters & Handelsman 2018) in particular in pre-antral and small antral follicular health (Sunkara et al., 2012). Other suggestions for the role of androgens includes their acting as ligands for androgen receptors, also promoting follicular growth (Fouany & Sharah 2013, Nagels et al., 2015). High levels of androgens are observed in the development of polycystic ovarian syndrome (PCOS) (Walters, 2015).

Studies have investigated the role of androgens in increasing the effect of FSH on follicular growth (Vendola et al., 1999, Weil 1998), and animal models have been used to investigate the method by which androgens regulate 'follicle health, development and ovulation' (Anderson et al., 2012 and Walters, 2015). However, much of the scientific mechanism of androgens continues to be 'elusive' (Nagels et al., 2015), and the mechanism of androgens for increasing the follicular pool in patients with POR is still being investigated (Montoya-Botero, 2019, Founay & Sharara 2013).

Research into androgens has investigated their role in increasing the expression of androgen receptors (Hu et al., 2017), their positive effect in ovarian follicular development, recruitment, and growth (Polyzos et al., 2018, Vendola et al., 1998 & 1999, Weil 1998), and their role in increasing the number of primary and pre-antral follicles (Triantafyllidou, 2017). Animal and human research has shown that the use of androgen supplementation can increase the number of oocytes produced, which in turn could assist in increasing pregnancy rates (Barad 2007, Gleicher 2011, Nagels et al., 2015)

Androgen supplementation has been suggested as beneficial for women with DOR or POR (that is, not for all patient groups) due to the improvement in ovarian function due to an increase in: ovarian response to stimulation, ovarian reserve, and follicular development and recruitment (Kim C H 2013, Fanchin et al., 2011, Lossl et al., 2020, Noventa et al., 2019, Nagels et al., 2015). Androgen supplementation has also been suggested to reduce aneuploidy rates, thereby decreasing miscarriages in older women resulting in higher live birth rates (Gleicher et al., 2009, 2010, 2015, Fouany & Sharara 2013).

A large number of RCTs and meta-analyses call for further RCTs and studies to continue to further establish the role of androgen supplementation in IVF.

4.3 Please demonstrate that this treatment is being offered to or requested by patients in a UK fertility clinic with the claim that this treatment increases live birth rate or chances of success. This could be contained in patient information leaflets, website content or anonymised conversations between patients and fertility clinic staff. (max. 300 words)

DHEA and Testosterone are available in the UK with a prescription. In the USA they are available as an over-the-counter supplement.

Academic papers have claimed that approximately a quarter to one-third of fertility clinics use DHEA to improve pregnancy chances (Gleicher & Barad, 2011, Fouany & Sharara 2013).

Androgen supplementation is not discussed on many HFEA licenced clinic websites, nor is there extensive discussion of the topic on UK fertility forums.

The HFEA has not received any recent enquiries regarding the use of androgen supplementation.

DHEA and testosterone are listed in the fee lists of several fertility clinics. However, DHEA and testosterone are offered within standard treatment plans for some subsets of patients, including patients with diminished ovarian reserve or patients who are poor responders.

There is no indication that, in the UK, androgen supplementation is being offered outside of these patient groups to increase clinical pregnancy or live birth rates.

4.4 Please provide any recommendations made by professional bodies, eg NICE, ESHRE, RCOG, BFS or ASRM, for or against the use of this treatment in fertility patients. (max. 500 words)

ESHRE published recommendations in 2019 in which the use of either DHEA or testosterone in IVF was not recommended for use in poor responders.

As regards to DHEA, in this report they stated that the evidence for its use is 'inconsistent' for improving live birth rate and ongoing pregnancy rate. The studies they considered used varying durations of DHEA treatment, which may have contributed to the inconsistencies in the results.

Similarly, ESHRE stated that the evidence for testosterone pre-treatment is currently 'inconsistent'.

Due to this, ESHRE recommended that large RCTs should take place for DHEA supplementation and testosterone supplementation in order to establish further information on dosage, administration duration, and safety.

NICE added recommendations about DHEA to their 'Fertility problems: assessment and treatment' clinical guidelines in 2013. In this they stated that DHEA should not be used as an adjuvant treatment for controlled ovarian stimulation in IVF. There are no recommendations on the use of testosterone.

5. Current evidence base

Effectiveness

5.1 To be included in the HFEA add-on review list, a treatment needs to lack published evidence about its effectiveness. Please provide peer-reviewed published evidence that this treatment add-on **is or is not effective at increasing live birth rate**, i.e. the extent to which this treatment is or is not able to deliver the promised benefits. Please include references to any relevant

published and/or unpublished data as appendices to this form. For example, you may wish to include references to data from animal studies, large data studies, research on human embryos, or clinical trial data. Study outcomes should include live birth rate as a primary or secondary outcome. (max. 500 words)

There is limited research in androgen supplementation for women who are not poor responders or who do not have diminished ovarian reserve.

Live birth rates

A 2015 **Cochrane review** analysed 17 RCTs reporting on DHEA or testosterone supplementation in IVF (12 DHEA, 5 testosterone) (Nagels et al., 2015). It included 1496 participants with most trials focussing on '"poor responders"' to standard IVF protocols' (Nagels et al., 2015). Pre-treatment with DHEA was associated with higher live birth rates. However, when trials with a risk of performance bias were removed, the results no longer reached significance. Similarly, pre-treatment with testosterone was only associated with higher live birth rates when studies at a high risk of performance bias were included in the analysis. Reasons for defining the evidence from these RCTs as 'moderate' included low sample sizes, lack of blinding, and the imprecise/poor reporting of study methods (Nagels et al., 2015).

Two further RCT meta-analyses found that women with POR receiving testosterone showed higher live birth rates (Noventa et al., 2019, Bosdou et al., 2012) as did patients with POR and DOR receiving DHEA (Xu et al, 2019). However, Sunkara et al., 2011, found that androgen supplementation did not show significant differences in live-birth rates.

Zhang et al., 2021, investigated DHEA use in women with endometriosis and found that live birth rate was higher in the DHEA supplementation group. However, there were only 44 study participants. Another RCT investigating DHEA supplementation in women (52 participants) with POR undergoing IVF found that pre-treatment DHEA supplementation did not improve live birth rates (Narkwichean et al., 2017).

Other outcomes

One RCT found that DHEA slightly increased the number of oocytes retrieved and increased the fertilization rate in women with DOR (Kara et al., 2018). However, two RCTs investigating testosterone supplementation in women with POR found that testosterone did not increase the number of mature oocytes retrieved (Subirá et al., 2021, Hoang et al., 2021). Hoang et al., 2021, reported pre-treatment of testosterone for 4 or 6 weeks increased clinical pregnancy rates.

Further trials have also noted increased clinical pregnancy rates and functional ovarian reserves through the use of DHEA (Singh et al., 2013, Barad et al., 2014, Li et al., 2015). Clinical trials have reported the effectiveness of DHEA for women with DOR or POR varies by age and FMR1 genotypes (Gleicher, 2013 and Weghofer et al., 2012).

One meta-analysis found that DHEA improves pregnancy rates in young women with DOR, and reduces miscarriage rates in older women with DOR as it decreases age-related aneuploidy (Fouany & Sharara 2013).

In their 2021 meta-analysis Richard & Jayaprakasan found that DHEA conferred no benefit to women with DOR on IVF outcome. They also reported testosterone use in women with DOR or POR improved IVF outcomes, but only when including low quality studies with a high risk of bias.

Other meta-analyses found that DHEA treatment did not result in a significant difference in clinical pregnancy rates in women with DOR or POR (Narkwichean et al., 2013). Qin et al.,

2017 noted that DHEA only increased clinical pregnancy rates for women with DOR when non-RCT studies were included within their meta-analysis.

Safety

5.2 If there is evidence that this treatment is **not** safe or there is risk of harm, for either the patients or the children born after the use of this treatment, please outline it here. Please include references to any relevant published and/or unpublished data as appendices to this form. For example, you may wish to include references to data from animal studies, large data studies, research on human embryos, or clinical trials data. (max. 500 words)

Studies have shown little discussion and research into the safety of DHEA and testosterone.

As noted in Polyzos et al., 2018, an excess of testosterone is likely to 'induce adverse events' and could be either 'ineffective' or 'detrimental'. Additionally, as excess androgens show a key role in the polycystic ovary syndrome, further research is required (Walters et al., 2019).

A meta-analysis by Xu et al., 2019, found that DHEA supplementation did not cause any adverse effects and that miscarriage rates did not differ between control and DHEA groups.

Side effects in women undergoing DHEA treatment have included acne, hair loss, excess hair growth, dizziness and voice deepening (Tartagni et al., 2015, Wiser et al., 2010, Zhang et al., 2014). Limiting treatment at 75mg/day of DHEA reduces these effects (Kroboth et al., 1999, Artini et al., 2012). The Cochrane review has noted that patient's medical history, administration methods, and dosage of both DHEA and testosterone require further research and studies (Nagels et al., 2015). Additionally, further research is needed into the effect of androgen supplementation on the embryo (Sir-Petermann et al., 2002, Nagels et al., 2015) to establish whether any risk of harm exists for children born after use of this treatment.

6. Declaration

The information provided on this form is to the best of my knowledge true and accurate

Check the box to confirm acceptance of the above statement ☐

Signature: Completed by the HFEA

Date: _____26/05/2022_____

This form should be submitted, with any associated papers and information, to **enquiriesteam@hfea.gov.uk**.

Annex A – References

Anderson, E., Lee, M. -T and Lee, G. Y. (1992) 'Cystogenesis of the ovarian antral follicle of the rat: ultrastructural changes and hormonal profile following the administration of dehydroepiandrosterone', The Anatomical record. Anat Rec, 234(3), pp. 359–382. doi: 10.1002/AR.1092340307.

Artini, P. G. et al. (2012) 'DHEA supplementation improves follicular microenviroment in poor responder patients', https://doi.org/10.3109/09513590.2012.705386. Taylor & Francis, 28(9), pp. 669–673. doi: 10.3109/09513590.2012.705386.

Barad, D. H. et al. (2014) 'Effect of inter-cycle interval on oocyte production in humans in the presence of the weak androgen DHEA and follicle stimulating hormone: a case-control study', Reproductive biology and endocrinology : RB&E. Reprod Biol Endocrinol, 12(1). doi: 10.1186/1477-7827-12-68.

Bosdou, J. K. et al. (2012) 'The use of androgens or androgen-modulating agents in poor responders undergoing in vitro fertilization: A systematic review and meta-analysis', Human Reproduction Update, 18(2), pp. 127–145. doi: 10.1093/humupd/dmr051.

Casson, P. R. et al. (2000) 'Dehydroepiandrosterone supplementation augments ovarian stimulation in poor responders: a case series', Human reproduction (Oxford, England). Hum Reprod, 15(10), pp. 2129–2132. doi: 10.1093/HUMREP/15.10.2129.

Chen, Z. et al. (2021) 'A Proper Increasing in the Testosterone Level May Be Associated With Better Pregnancy Outcomes for Patients With Tubal or Male Infertility During in vitro Fertilization/Intracytoplasmic Sperm Injection.', Frontiers in physiology. Frontiers Media S.A., 12, p. 696854. doi: 10.3389/fphys.2021.696854.

Drakopoulos, P. et al. (2021) 'Androgens and Anti-Müllerian Hormone in Infertile Patients', Reproductive sciences (Thousand Oaks, Calif.). Reprod Sci, 28(10), pp. 2816–2821. doi: 10.1007/S43032-021-00539-W.

Fanchin, R. et al. (2011) 'Androgens and poor responders: are we ready to take the plunge into clinical therapy?', Fertility and sterility. Elsevier Inc., 96(5), pp. 1062–5. doi: 10.1016/j.fertnstert.2011.09.050.

Fouany, M. R. and Sharara, F. I. (2013) 'Is there a role for DHEA supplementation in women with diminished ovarian reserve?', Journal of Assisted Reproduction and Genetics, 30(9), pp. 1239–1244. doi: 10.1007/s10815-013-0018-x.

Gleicher, N. et al. (2013) 'Starting and resulting testosterone levels after androgen supplementation determine at all ages in vitro fertilization (IVF) pregnancy rates in women with diminished ovarian reserve (DOR)', Journal of Assisted Reproduction and Genetics, 30(1), pp. 49–62. doi: 10.1007/s10815-012-9890-z.

Gleicher, N. et al. (2015) 'Is there an androgen level threshold for aneuploidy risk in infertile women?', Reproductive biology and endocrinology : RB&E. Reprod Biol Endocrinol, 13(1). doi: 10.1186/S12958-015-0034-Z.

Gleicher, N., Weghofer, A. and Barad, D. H. (2010) 'Dehydroepiandrosterone (DHEA) reduces embryo aneuploidy: Direct evidence from preimplantation genetic screening (PGS)', Reproductive Biology and Endocrinology. BioMed Central, 8(1), pp. 1–5. doi: 10.1186/1477-7827-8-140/FIGURES/1.

Gleicher, N. and Barad, D. H. (2011) 'Dehydroepiandrosterone (DHEA) supplementation in diminished ovarian reserve (DOR)', Reproductive biology and endocrinology : RB&E. Reprod Biol Endocrinol, 9. doi: 10.1186/1477-7827-9-67.

Gleicher, N. et al. (2009) ‘Miscarriage rates after dehydroepiandrosterone (DHEA) supplementation in women with diminished ovarian reserve: A case control study’, Reproductive Biology and Endocrinology, 7, p. 108. doi: 10.1186/1477-7827-7-108.

Hu, Q. et al. (2017) ‘The effect of dehydroepiandrosterone supplementation on ovarian response is associated with androgen receptor in diminished ovarian reserve women’, Journal of Ovarian Research. BioMed Central Ltd., 10(1). doi: 10.1186/s13048-017-0326-3.

Kara, M. et al. (2014) ‘Does dehydroepiandrosterone supplementation really affect IVF-ICSI outcome in women with poor ovarian reserve?’, European Journal of Obstetrics and Gynecology and Reproductive Biology. Elsevier Ireland Ltd, 173(1), pp. 63–65. doi: 10.1016/j.ejogrb.2013.11.008.

Kim C H (no date) Androgen supplementation in IVF - Minerva Ginecologica 2013 October;65(5):497-504 - Minerva Medica - Journals. Available at: https://www.minervamedica.it/en/journals/minerva-obstetrics-gynecology/article.php?cod=R09Y2013N05A0497 (Accessed: 24 March 2022).

Kroboth, P. D. et al. (1999) ‘DHEA and DHEA-S: A Review’, The Journal of Clinical Pharmacology. John Wiley & Sons, Ltd, 39(4), pp. 327–348. doi: 10.1177/00912709922007903.

Li, J. et al. (2015) ‘A meta-analysis of dehydroepiandrosterone supplementation among women with diminished ovarian reserve undergoing in vitro fertilization or intracytoplasmic sperm injection’, International Journal of Gynecology and Obstetrics. Elsevier Ireland Ltd, 131(3), pp. 240–245. doi: 10.1016/j.ijgo.2015.06.028.

Løssl, K. et al. (2020) ‘Biological and Clinical Rationale for Androgen Priming in Ovarian Stimulation.’, Frontiers in endocrinology. Frontiers Media S.A., 11, p. 627. doi: 10.3389/fendo.2020.00627.

Montoya-Botero, P., Rodriguez-Purata, J. and Polyzos, N. P. (2019) ‘Androgen supplementation in assisted reproduction: where are we in 2019?’, Current opinion in obstetrics & gynecology. Curr Opin Obstet Gynecol, 31(3), pp. 188–194. doi: 10.1097/GCO.0000000000000532.

Nagels, H. E. et al. (2015) ‘Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction’, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd, 2015(11). doi: 10.1002/14651858.CD009749.pub2.

Narkwichean, A. et al. (2017) ‘Efficacy of Dehydroepiandrosterone (DHEA) to overcome the effect of ovarian ageing (DITTO): A proof of principle double blinded randomized placebo controlled trial’, European Journal of Obstetrics and Gynecology and Reproductive Biology. Elsevier Ireland Ltd, 218, pp. 39–48. doi: 10.1016/j.ejogrb.2017.09.006.

Narkwichean, A. et al. (2013) ‘Efficacy of dehydroepiandrosterone to improve ovarian response in women with diminished ovarian reserve: a meta-analysis.’, Reproductive biology and endocrinology : RB&E, 11. doi: 10.1186/1477-7827-11-44.

Neves, A. R., Montoya-Botero, P. and Polyzos, N. P. (2021) ‘The Role of Androgen Supplementation in Women With Diminished Ovarian Reserve: Time to Randomize, Not Meta-Analyze’, Frontiers in endocrinology. Front Endocrinol (Lausanne), 12. doi: 10.3389/FENDO.2021.653857.

Noventa, M. et al. (2019) ‘Testosterone therapy for women with poor ovarian response undergoing IVF: a meta-analysis of randomized controlled trials’, Journal of assisted reproduction and genetics. J Assist Reprod Genet, 36(4), pp. 673–683. doi: 10.1007/S10815-018-1383-2.

Polyzos, N. P. et al. (2018) ‘Testosterone for poor ovarian responders: Lessons from ovarian physiology’, Reproductive Sciences. SAGE Publications Inc., 25(7), pp. 980–982. doi: 10.1177/1933719116660849.

Qin, J. C., Fan, L. and Qin, A. P. (2017) 'The effect of dehydroepiandrosterone (DHEA) supplementation on women with diminished ovarian reserve (DOR) in IVF cycle: Evidence from a meta-analysis', Journal of Gynecology Obstetrics and Human Reproduction. Elsevier Masson SAS, 46(1), pp. 1–7. doi: 10.1016/j.jgyn.2016.01.002.

Richardson, A. and Jayaprakasan, K. (2021) 'The Use of Androgen Priming in Women with Reduced Ovarian Reserve Undergoing Assisted Reproductive Technology', Seminars in Reproductive Medicine. Thieme Medical Publishers, Inc., 39(5–6), pp. 207–219. doi: 10.1055/s-0041-1735646.

Singh, N. et al. (2013) 'A prospective study on role of dehydroepiandrosterone (DHEA) on improving the ovarian reserve markers in infertile patients with poor ovarian reserve', Gynecological Endocrinology, 29(11), pp. 989–992. doi: 10.3109/09513590.2013.824957.

Sir-Petermann, T. et al. (2002) 'Maternal serum androgens in pregnant women with polycystic ovarian syndrome: possible implications in prenatal androgenization', Human Reproduction. Oxford Academic, 17(10), pp. 2573–2579. doi: 10.1093/HUMREP/17.10.2573.

Subirá, J. et al. (2021) 'Testosterone does not improve ovarian response in Bologna poor responders: a randomized controlled trial (TESTOPRIM)', Reproductive biomedicine online. Reprod Biomed Online, 43(3), pp. 466–474. doi: 10.1016/J.RBMO.2021.05.021.

Sunkara, S. K., Pundir, J. and Khalaf, Y. (2011) 'Effect of androgen supplementation or modulation on ovarian stimulation outcome in poor responders: A meta-analysis', Reproductive BioMedicine Online, 22(6), pp. 545–555. doi: 10.1016/j.rbmo.2011.01.015.

Sunkara, S. K. et al. (2012) 'Should androgen supplementation be used for poor ovarian response in IVF?', Human reproduction (Oxford, England). Hum Reprod, 27(3), pp. 637–640. doi: 10.1093/HUMREP/DER464.

Tartagni, Massimo et al. (2015) 'Dehydroepiandrosterone decreases the age-related decline of the in vitro fertilization outcome in women younger than 40 years old', Reproductive Biology and Endocrinology : RB&E. BioMed Central, 13(1). doi: 10.1186/S12958-015-0014-3.

Triantafyllidou, O., Sigalos, G. and Vlahos, N. (2017) 'Dehydroepiandrosterone (DHEA) supplementation and IVF outcome in poor responders', Human fertility (Cambridge, England). Hum Fertil (Camb), 20(2), pp. 80–87. doi: 10.1080/14647273.2016.1262065.

Vendola, K. A. et al. (1998) 'Androgens stimulate early stages of follicular growth in the primate ovary', Journal of Clinical Investigation. American Society for Clinical Investigation, 101(12), pp. 2622–2629. doi: 10.1172/JCI2081.

Vendola, K. et al. (1999) 'Androgens promote oocyte insulin-like growth factor I expression and initiation of follicle development in the primate ovary', Biology of Reproduction, 61(2), pp. 353–357. doi: 10.1095/BIOLREPROD61.2.353.

Walters, K. A. and Handelsman, D. J. (2018) 'Role of androgens in the ovary', Molecular and Cellular Endocrinology. Elsevier Ireland Ltd, 465, pp. 36–47. doi: 10.1016/J.MCE.2017.06.026.

Wiser, A. et al. (2010) 'Addition of dehydroepiandrosterone (DHEA) for poor-responder patients before and during IVF treatment improves the pregnancy rate: A randomized prospective study', Human Reproduction. Oxford Academic, 25(10), pp. 2496–2500. doi: 10.1093/HUMREP/DEQ220.

Walters, K. A. (2015) 'Role of androgens in normal and pathological ovarian function', Reproduction. BioScientifica Ltd., 149(4), pp. R193–R218. doi: 10.1530/REP-14-0517.

Walters, K. A. et al. (2019) 'Androgens and ovarian function: Translation from basic discovery research to clinical impact', Journal of Endocrinology. BioScientifica Ltd., 242(2), pp. R23–R50. doi: 10.1530/JOE-19-0096.

Weghofer, A. et al. (2012) ‘The impact of androgen metabolism and FMR1 genotypes on pregnancy potential in women with dehydroepiandrosterone (DHEA) supplementation’, Human reproduction (Oxford, England). Hum Reprod, 27(11), pp. 3287–3293. doi: 10.1093/HUMREP/DES265.

Xu, L. et al. (2019) ‘The Effect of Dehydroepiandrosterone (DHEA) Supplementation on IVF or ICSI: A Meta-Analysis of Randomized Controlled Trials.’, Geburtshilfe und Frauenheilkunde. Georg Thieme Verlag, 79(7), pp. 705–712. doi: 10.1055/a-0882-3791.

Yeung, T. W. Y. et al. (2013) ‘A randomized double-blinded placebo-controlled trial on the effect of 16 weeks of dehydroepiandrosterone (DHEA) on ovarian reserve markers and IVF outcomes in poor responders’, Fertility and Sterility. Elsevier, 100(3), pp. S159–S160. doi: 10.1016/J.FERTNSTERT.2013.07.1521.

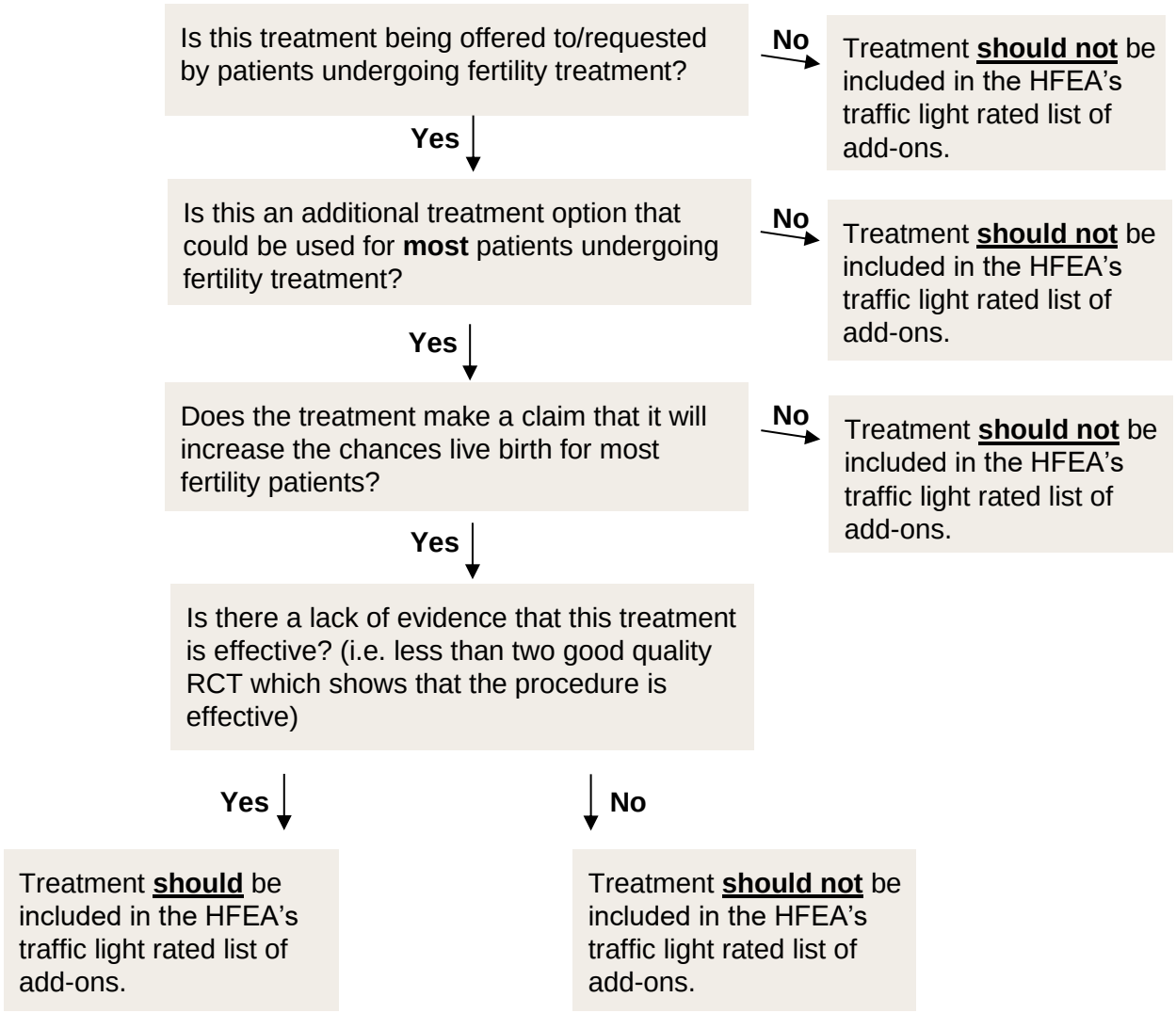
Zhang, H. et al. (2016) ‘Dehydroepiandrosterone plus climen supplementation shows better effects than dehydroepiandrosterone alone on infertility patients with diminished ovarian reserve of low-FSH level undergoing in-vitro fertilization cycles: A randomized controlled trial’, Reproductive Biology and Endocrinology. BioMed Central Ltd., 14(1). doi: 10.1186/s12958-016-0139-z.

Zhang, J. et al. (2015) ‘Dehydroepiandrosterone improves the ovarian reserve of women with diminished ovarian reserve and is a potential regulator of the immune response in the ovaries’, Bioscience trends. Biosci Trends, 9(6), pp. 350–359. doi: 10.5582/BST.2015.01154.

Zhang, Y. et al. (2021) ‘Randomized Controlled Study of the Effects of DHEA on the Outcome of IVF in Endometriosis.’, Evidence-based complementary and alternative medicine : eCAM. Hindawi Limited, 2021, p. 3569697. doi: 10.1155/2021/3569697.

Annex B

SCAAC treatment add-on application decision tree



Treatment add-ons rating evidence base review.

Details about this paper

Area(s) of strategy this paper relates to:	The best care/The right information
Meeting:	Scientific and Clinical Advances Advisory Committee (SCAAC)
Agenda item:	7 & 8
Paper number:	HFEA (06/06/2022) 007 & 008
Meeting date:	06 June 2022
Author:	Sonia Macleod, Scientific Policy Manager
Annexes	Annex A: Evidence base used by Cochrane, National Institute for Health and Care Excellence (NICE) and Medicines and Healthcare products Regulatory Agency (MHRA)

Output from this paper

For information or recommendation?	For recommendation
Recommendation:	Member are asked to: • recommend the types of evidence that should be used to determine ratings for treatment add-ons, and • define the circumstances in which it would be appropriate to use each of these evidence types
Resource implications:	Resource implications will be estimated based on the SCAAC's recommendation.
Implementation date:	NA
Communication(s):	NA
Organisational risk:	Medium

1. Introduction

1.1. At the Authority meeting in September 2021, it was agreed that we would undertake work to further evolve the rating system for treatment add-ons, specifically

- to evolve the presentation of the rating system for treatment add-ons,
- to consider broadening the range of data that the HFEA consider when assigning ratings to treatment add-ons, and
- for these issues to be brought back to a future Authority meeting

1.2. Work on the presentation of the rating system is underway. This paper addresses the consideration of broadening the evidence base used to generate treatment add-ons ratings.

2. Background

2.1. Traffic light ratings are allocated by SCAAC based on the evaluation of the evidence base in the form of randomised controlled trials (RCTs), and advice from an independent expert in systematic reviews and evidence assessment using the GRADE methodology[1]. **Currently only live birth rates are considered, but the scoping work indicates an appetite for rating additional outcomes, which should be considered when making recommendations on the ratings evidence base.**

2.2. When reviewing the effectiveness of treatments, well-designed RCTs provide the most reliable source of evidence. However, there are many situations where RCTs have not yet been carried out, and this is true for many treatment add-ons. The reasons for this are many and varied, including funding and the difficulty of sufficiently large sample sizes, but as things stand it is likely that many treatment add-ons will not have well-designed RCTs for the foreseeable future.

2.3. It has been raised that the HFEA should consider whether to continue to use only RCTs to determine the rating. It was suggested that maybe other types of evidence should be incorporated into the rating assessment (for example retrospective studies of large data). The issue is further complicated by an increasing proportion of the sector relying on their data and analysis of live birth rates and patient outcomes within their clinics, to make claims relating to the effectiveness of certain add-on treatments for patients.

2.4. The SCAAC considered broadening the evidence base that the HFEA consider when assigning traffic light ratings to add-ons in October 2019 and agreed that, with intelligent use, large data can complement RCTs but cannot replace them.

2.5. SCAAC are now being asked to re-evaluate whether the evidence base should be broadened as part of the larger review of the traffic lights rating systems for add-ons.

2.6. Continuing with a traffic light rating based on RCTs ensures that our assessment is based on the highest quality studies, but risks being overtaken by other publicly available research data.

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[1] GRADE is the most prominent framework for evaluating the effectiveness of systematic reviews is (**Grading quality of evidence and strength of recommendations).** GRADE is used to rate the certainty of evidence for a treatment efficacy from high to very low. The GRADE system takes in two types of studies: randomized controlled trials (RCTs) and observational studies (also including non-randomized trials)

However, accommodating data from other less robust sources risks diluting the objective quality of that assessment. It is therefore essential to consider the appropriateness of alternative evidence in these circumstances. To facilitate SCAAC making a recommendation we held a workshop with invited speakers to discuss the pros and cons of broadening the evidence base and we have carried out scoping work to consider the evidence bases used by other organisations.

2.7. The evidence bases used by the following organisations are further described in Annex A:

- Cochrane
- National Institute for Health and Care Excellence (NICE)
- Medicines and Healthcare Regulatory Agency (MHRA)

2.8. There are two factors which will need to be considered when discussing potentially expanding the evidence base used for add-on ratings. These are which types of evidence should be used, and when it would be appropriate to use them. These are set out in more detail below.

3. Types of evidence

3.1. Factors that SCAAC might be minded to consider when making this recommendation are:-

- Whether evidence is published or unpublished
- Whether the evidence has been peer-reviewed or not
- Whether only specified types of studies, e.g. RCTs, would be acceptable
- Whether specified types of studies would be unacceptable in any circumstances
- Whether specified types of studies would be acceptable if they met other quality control measures, for example GRADE scores, and if so, what these quality control measures are
- Any other points that SCAAC considers appropriate

4. When it would be appropriate to use different evidence types

4.1. RCTs are used in the current rating system. If the evidence base is to be expanded SCAAC need to recommend when it would be appropriate to use these different types of evidence.

4.2. Factors that SCAAC might be minded to consider when making this recommendation are:

- Whether other evidence types should be considered as equal to RCTs when developing treatment add-ons ratings
- Should other evidence types be secondary to RCTs
- Should other evidence types only be used when there are no RCTs available
- Should other evidence types be used when there a limited number of RCTs, if so, what constitutes a ‘limited number’
- What, if any, quality control measures, should be used for studies that the GRADE methodology would not be appropriate for
- Any other points that SCAAC considers appropriate

4.3. If the recommendation is to expand the evidence base then SCAAC should consider whether to follow the example of other organisations (see Annex A) and recommend a hierarchy of evidence types and/or decision trees.

5. Next Steps

5.1. We will take both the recommendation on presentational format, outcomes to be rated and SCAAC's recommendation on the evidence base to the Authority at the same time. As noted above, work on how best to present add-ons ratings and whether to include additional outcomes as well as live births has been undertaken. In summary, that work included a discussion with experts in risk communication/presentation of healthcare information, from which we created ten possible options. Those options were then presented to various stakeholders including the Licensed Clinics Panel, the Patient Organisations Stakeholder Group and to individual patients in interviews. The Authority then chose two options which formed the basis of surveys for patients/the public and for professionals. Focus groups of patients were also carried out to obtain more in-depth information on views of the two options.

5.2. Decisions made by the Authority at its July meeting might enable SCAAC to undertake their annual review of treatment add-ons at the October SCAAC meeting based on a modified rating system/evidence base. This is with the caveat that if either the rating system or the evidence base changes substantially then more time may be required for external reviewing before SCAAC can be asked to review each add-on, most likely at the February 2023 meeting.

5.3. In the longer term substantially expanding the evidence base could lead to longer intervals between ratings, and/or to reviewing the rating for different add-ons at different times of the year rather than the current system where all add-ons are reviewed together once a year. These options can be discussed at the October SCAAC meeting once there is clarity on the size of any changes to the evidence base.

5.4. Any changes to the RAG rating system will be subjected to user-acceptance testing, and published as part of a wider communications plan, including infographics for use on social media, social media posts and in Clinic Focus.

6. Recommendations

6.1. Members are asked to:

- recommend the types of evidence should be used to determine ratings for treatment add-ons, and
- define the circumstances in which it would be appropriate to use each of these evidence types

Annex A – Evidence base used by Cochrane, NICE and MHRA

Cochrane

Cochrane summary

Allow the use of non-randomised trials, but only in limited circumstances. They list five reasons where they accept the use of non-randomised trials:

1. Where available RCTs only address the question indirectly or are incomplete (e.g. Non randomised Studies of the intervention can be used to provide information on rare treatment outcomes, or very long term effects of treatments where the results may not be available for many years)
2. Where randomisation is not a realistic possibility (e.g. When considering the population effects of specific pieces of legislation or where participants would not agree to randomisation)
3. To provide the case for a RCT to be undertaken, by highlighting the faults with the non-randomised study
4. When an intervention effect is very large (clearly there are ethical concerns with randomisation if the intervention effect is large or if the effect is randomisation would not be desirable to participants, e.g., when one cohort would undergo surgery and the other would not)
5. When RCTs could be used, but very few RCTs are available

They emphasise that they consider the first two reasons as more valid than the third, and all three of these much more valid than the fourth and fifth.

They allow for the publication of an “empty review” when evidence is too limited, rather than including questionable studies.

Cochrane Full Description

Link

Chapter 24: Including non-randomized studies on intervention effects | Cochrane Training

Broadly, we consider that there are two main justifications for including NRSI in a systematic review, covered by the flow diagram shown in **Figure 24.1.a**:

1. To provide evidence of the effects (benefit or harm) of interventions that can feasibly be studied in randomized trials, but for which available randomized trials address the review question indirectly or incompletely (an element of the GRADE approach to assessing the certainty of the evidence, see **Chapter 14, Section 14.2**) (Schünemann et al 2013). Such non-randomized evidence might address, for example, long-term or rare outcomes, different populations or settings, or ways of delivering interventions that better match the review question.
2. To provide evidence of the effects (benefit or harm) of interventions that cannot be randomized, or that are extremely unlikely to be studied in randomized trials. Such non-randomized evidence might address, for example, population-level interventions (e.g. the effects of legislation; (Macpherson and Spinks 2008) or interventions about which prospective study participants are likely to have strong preferences, preventing randomization (Li et al 2016).

A third justification for including NRSI in a systematic review is reasonable, but is unlikely to be a strong reason in the context of a Cochrane Review:

1. To examine the case for undertaking a randomized trial by providing an explicit evaluation of the weaknesses of available NRSI. The findings of a review of NRSI may also be useful to inform the design of a subsequent randomized trial (e.g., through the identification of relevant subgroups).

Two other reasons sometimes described for including NRSI in systematic reviews are:

1. When an intervention effect is very large.
2. To provide evidence of the effects (benefit or harm) of interventions that can feasibly be studied in randomized trials, but for which only a small number of randomized trials is available (or likely to be available).

We urge caution in invoking either of these justifications. Reason 4, that an effect is large, is implicitly a result-driven or post-hoc argument, since some evidence or opinion would need to be available to inform the judgement about the likely size of the effect. Whilst it can be argued that large effects are less likely to be completely explained by bias than small effects (Glasziou et al 2007), clinical and economic decisions still need to be informed by unbiased estimates of the magnitude of these large effects (Reeves 2006). Randomized trials are the appropriate design to quantify large effects (and the trials need not be large if the effects are truly large). Of course, there may be ethical opposition to randomized trials of interventions already suspected to be associated with a large benefit, making it difficult to randomize participants, and interventions postulated to have large effects may also be difficult to randomize for other reasons (e.g., surgery versus no surgery). However, the justification for a systematic review including NRSI in these circumstances can be classified as reason 2 above (i.e., interventions that are unlikely to be randomized).

The appropriateness of reason 5 depends to a large extent on expectations of how the review will be used in practice. Most Cochrane Reviews seek to identify highly trustworthy evidence (typically only randomized trials) and if none is found then the review can be published as an ‘empty review’. However, as Cochrane Reviews also seek to inform clinical and policy decisions, it can be necessary to draw on the ‘best available’ evidence rather than the ‘highest tier’ of evidence for questions that have a high priority. While acknowledging the priority to inform decisions, it remains important that the challenges associated with appraising, synthesizing and interpreting evidence from NRSI, as discussed in the remainder of this chapter, are well-appreciated and addressed in this situation. See also **Section 24.2.1.3** for further discussion of these issues. Reason 5 is a less appropriate justification in a review that is not a priority topic where there is a paucity of evidence from randomized trials alone; in such instances, the potential of NRSI to inform the review question directly and without a critical risk of bias are paramount.

Review authors may need to apply different eligibility criteria in order to answer different review questions about harms as well as benefits (**Chapter 19, Section 19.2.2**). In some reviews the situation may be still more complex, since NRSI specified to answer questions about benefits may have different design features from NRSI specified to answer questions about harms (see **Section 24.2**). A further complexity arises in relation to the specification of eligible NRSI in the protocol and the desire to avoid an empty review (depending on the justification for including NRSI).

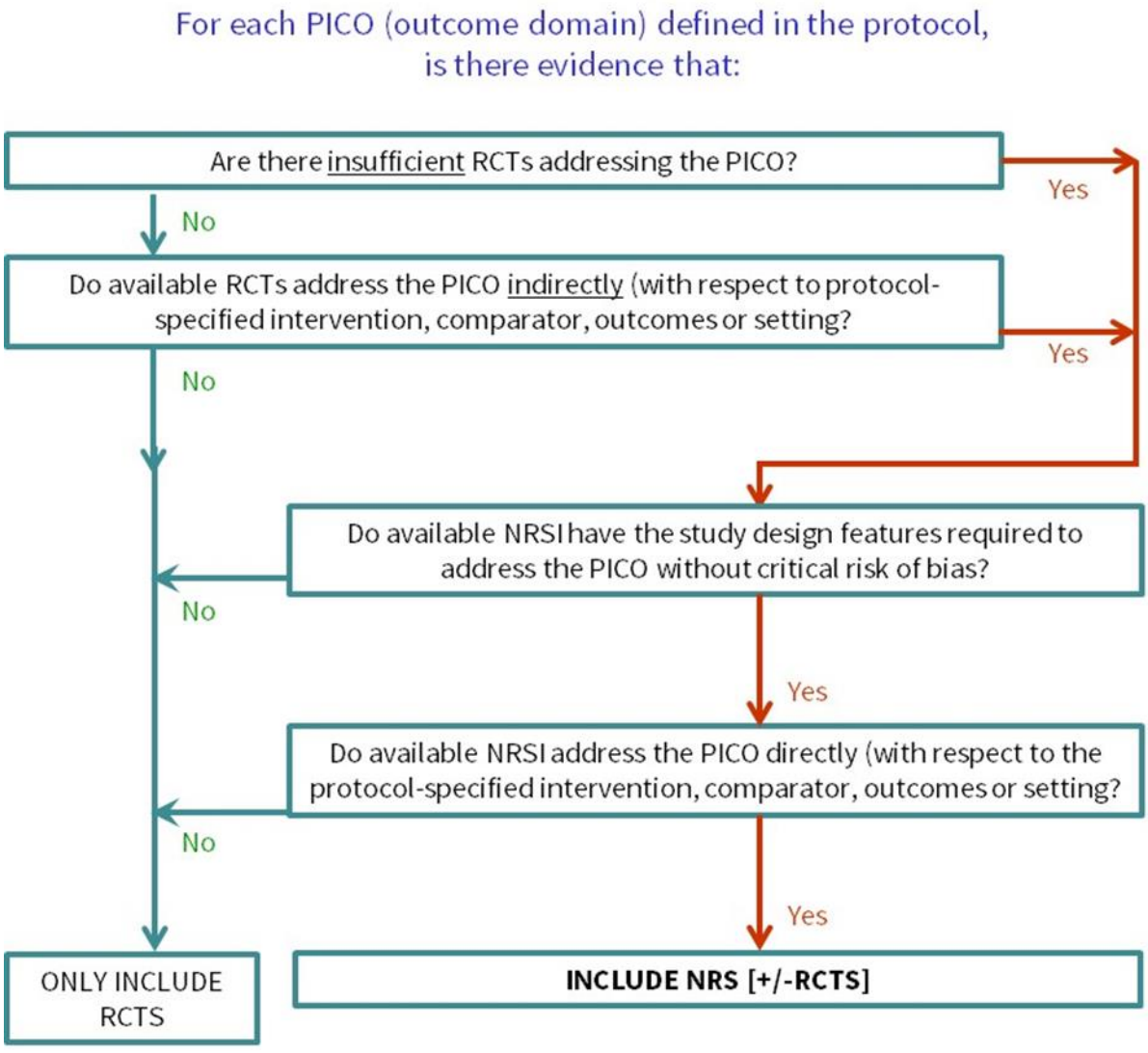
Whenever review authors decide that NRSI are required to answer one or more review questions, the review protocol must specify appropriate methods for reviewing NRSI. If a review aims to include both randomized trials and NRSI, the protocol must specify methods appropriate for both. Since methods for reviewing NRSI can be complex, **we recommend that review authors scope the available NRSI evidence**, after registering a title but in advance of writing a protocol, allowing review authors to check that relevant NRSI exist and to specify NRSI with the most appropriate study design features in the protocol (Reeves et al 2013). If the registered title is broadly conceived, this may require detailed review questions to be formulated in advance of scoping: these are the **PICOs for each synthesis** as discussed in **Chapter 3, Section 3.2**. Scoping also allows the directness of the available evidence to be assessed against specific review questions (see **Figure 24.1.a**). Basing protocol decisions on scoping creates a small risk that different kinds of studies are found to be necessary at a later stage to answer the review

questions. In such instances, we recommend completing the review as specified and including other studies in a planned update, to allow timelines for the completion of a review to be set.

An alternative approach is to write a protocol that describes the review methods to be used for both randomized trials and NRSI (and all types of NRSI) and to specify the study design features of eligible NRSI after carrying out searches for both types of study. We recommend against this approach in a Cochrane Review, largely to minimize the work required to write the protocol, carry out searches and examine study reports, and to allow timelines for the completion of a review to be set.

Their decision tree on the use of non-randomised trials is shown in figure 24.1.a below. Note the following abbreviations:

- RCTs = Randomised Control Trials
- NRS = Non-Randomised Studies
- NRSI = Non-Randomised Studies of Interventions
- PICO = Population, Intervention(s), Comparator(s), Outcomes



NICE (National Institute for Health and Care Excellence)

NICE summary

Largely only use published material. In exceptional circumstances, they allow for the use of pre-prints, but the example of exceptional circumstances they give is a “public health emergency”.

The possible pieces of evidence are gathered, the least relevant are filtered out, and then up to three pieces of evidence are selected using the following priority rankings:

1. Systematic reviews
2. Randomised control trials
3. Cohort/case-control/case series, ranked upon a combination of their size/publication date/clarity of data/inclusion of an “active comparator” (effectively, a placebo option)/how representative the study population is of the relevant UK population

If none of the above can be identified, the search criteria may be broadened

Note, studies ranked below RCTs are **only used if no RCTs are available**, or if they provide data on a specific outcome not discussed in an RCT

Worth noting, they include details in their report of the studies they shortlisted, and reasons for non-inclusion of studies on this list they didn’t use

NICE Full Description

Link

6 Developing the evidence summary | Evidence summaries: process guide | Guidance | NICE – Section (6.5 in particular)

6.5 Literature search

6.5.1 Searching for evidence

NICE's information services do a literature search according to the agreed scope and PICO. The aim is to find the best available evidence on the effectiveness, safety and resource impact of the medicine. In exceptional circumstances, the literature search may include preprints from medRxiv and bioRxiv, for example during a public health emergency.

The search strategy and quality assurance of the search process is included as an appendix in the evidence review.

6.5.2 Selecting the evidence

Evidence identified from the literature search is reviewed to find relevant primary research that addresses the use of the medicine within the defined indication and population under review. If robust systematic reviews of randomised controlled trials (RCTs) or RCTs are available, they form the basis of the review. However, the best available evidence may include evidence other than RCTs, such as observational studies.

First sift

The first sift reviews the title and abstract of the study against the scope and PICO and removes evidence of low relevance. This may include non-English language studies, or conference abstracts or studies that have not been published in full (because these cannot be critically appraised). Note that preprints may be considered for inclusion in exceptional circumstances.

Second sift

The second sift of full papers further excludes articles that do not meet the criteria in the scope.

When all relevant studies have been identified, the best available evidence is selected for inclusion in the evidence review. Usually no more than 3 studies are prioritised for inclusion, using these principles:

- systematic reviews of RCTs are prioritised first, followed by single RCTs
- if 1 or more systematic reviews or RCTs are included, lower-quality studies (for example cohort or case-control studies, or case series) would only be included if they provide additional data on outcomes not available from the higher-quality studies
- if further prioritisation is needed, other factors would be considered such as:
    - size of study (number of study participants)
    - date of publication
    - how well the data are reported
    - whether an active comparator was used, and whether this reflects usual UK practice
    - whether the population in the study reflects the typical UK population for which this medicine is likely to be used.

If no relevant evidence is identified, the development team will consider if broadening the search to include a wider population may provide useful information for decision making.

A summary of included studies and those studies excluded at second sift (with reasons for non-inclusion) are included as appendices in the evidence review.

Relevant regulatory information such as a European public assessment report (EPAR) or national public assessment report (if this has been published) are also reported to supplement the included studies, if needed.

6.5.3 Appraising the prioritised evidence

The development team appraises the included studies to assess risk of bias or quality of studies using a **NICE quality appraisal checklist** suitable for the type of evidence being reviewed. This quality assessment is included in an appendix in the evidence review.

MHRA (Medicines and Healthcare products Regulatory Agency)

MHRA summary

MHRA's role is to decide whether a treatment should be legal, rather than whether its use should be encouraged. In order to be licenced a medicine must demonstrate safety and efficacy.

The MHRA use different types of evidence at different stages.

Licensing

There are several **potential routes to licence a new medicine** in the UK, including national and international processes (which rely on mutual recognition). Regardless of the route chosen **the licensing of a new medicine relies on evidence from clinical trials,[2] almost exclusively RCTs.** All pre-authorisation clinical trials must be approved by the MHRA, who provide an **algorithm** to identify if a clinical trial is needed.

MHRA state that Clinical trials are used in a risk-proportionate way. There are processes for accelerated routes to the UK market such as the Innovative Licensing and Access Pathways and the Early Access to Medicines Scheme which aim to streamline/add flexibility to the licensing process to allow for earlier

[2] There are different requirements for generics and medicines which have been in widespread use for over a decade.

patient access to important medicines. However, in essence **medicines do not reach the wider market without clinical trials having been undertaking, usually RCTs, which demonstrate safety and efficacy.**

Post-marketing surveillance

The objective of post-marketing vigilance is to monitor safety in a real-world context and to detect rare adverse events that were not seen in clinical trials which have a more limited study population. There are two major types of post-marketing reporting, mandatory reporting and spontaneous reporting.

Reporting by Marketing Authorisation Holders (MAHs) is mandatory, with MAHs having to report adverse reactions to either the relevant notified body or the European Medicines Agency, depending on which procedure was used to license the medicine.

In addition to mandatory reporting by MAHs there is spontaneous reporting. MHRA have a section of their website (**Yellow Card | Making medicines and medical devices safer (mhra.gov.uk)**) where anyone can report an adverse event that they feel is a side effects of treatment. Such pharmacovigilance reports are shared with other international regulators to increase the size of the reporting pool. Spontaneous reporting has traditionally been considered the lowest level of the evidence pyramid, indicating that MHRA consider all forms of evidence about potential dangers of licenced medicines to be valid (though they are not necessarily weighted equally, for an example see Section 3 of **Review paper: Citrin-Diav O et al (publishing.service.gov.uk)**).

Post-marketing surveillance incorporates a wide range of evidence types and methodologies ranging from requirements on marketing authorisation holders to report suspected serious adverse events to the competent authority to spontaneous adverse event reports from individuals into their national ADR reporting scheme. Various different types of evidence can feed into post-market pharmacovigilance, including RCTs and meta-analysis, cohort or observational studies, linkage studies, prescription event monitoring, the use of registries and spontaneous reports.

When we approached them MHRA confirmed that they will use a variety of evidence types, stating

'If a new side effect is identified which may impact the balance of risks and benefits of a product, information from different data sources is carefully considered in the context of the overall side effect profile for the medicine, and how it compares with other medicines used to treat the same condition. A regulatory decision is made based on assessment of all relevant data and expert advice from the Commission on Human Medicines and/or its Expert Working Groups.'

MHRA Full Description

Links –

Clinical trials for medicines: apply for authorisation in the UK - GOV.UK (www.gov.uk)

Algorithm_Clean__1_.pdf (publishing.service.gov.uk)

Clinical trials for medicines: manage your authorisation, report safety issues

Innovative Licensing and Access Pathway - GOV.UK (www.gov.uk)

Apply for the early access to medicines scheme (EAMS) - GOV.UK (www.gov.uk)

Yellow Card | Making medicines and medical devices safer (mhra.gov.uk)

Notes:

Clinical trials

In their online guidance on **Clinical trials** MHRA set out the process for authorising a clinical trial, a selection of relevant sections are detailed below including:-

1. **When a clinical trial authorisation (CTA) is needed**.
2. **Risk Proportionate Approaches**, and
3. **Applications that need expert advice**

When a clinical trial authorisation (CTA) is needed

Use the online algorithm **Is it a clinical trial of a medicinal product?** (PDF, 68KB, 2 pages) to find out if your study needs MHRA authorisation.

The algorithm is a set of questions that determine:

- whether the substance you're testing counts as a medicinal product
- whether your trial counts as a clinical trial within the scope of the relevant legislation

You can also read the **Mock examples to assist with the question 'Is it a clinical trial of an investigational medicinal product?'** to help you decide if your study needs a CTA.

For further advice you may also wish to consult your local regulatory department or research governance team. From October 2021 the 'SCOPE' advice service will only be available via self-service using the guidance on this webpage.

Risk Proportionate Approaches

A risk proportionate approach to the initiation, management and monitoring of certain clinical trials is possible. The sponsor should carry out a risk assessment based on the potential risks associated with the IMP. View our guidance on **risk-adapted approaches to the management of clinical trials of investigational medicinal products**.

We will perform a risk adapted assessment of certain 'Type A' trials in which the risk to the patient from the IMP is considered to be no greater than that of standard medical care. These are trials involving medicinal products licensed in any EU Member State if:

- the trial relates to the licensed range of indications, dosage and form of the product, or;
- the trial involves off-label use (such as in paediatrics and oncology) that is established practice and supported by enough published evidence and/or guidelines.

Applications that need expert advice

For certain trials, we will seek advice from the Clinical Trials, Biologicals and Vaccines Expert Advisory Group (CTBVEAG) of the Commission on Human Medicines (CHM). The CHM will then discuss the trial at their meeting, which will take place later in the same week as the CTBVEAG meeting. We will make the decision to refer applications for expert advice based on an assessment of the risks and how the sponsor plans to mitigate them. Areas we look at when considering risk factors include:

- mode of action
- nature of the target
- relevance of animal species and models

We may refer other applications for expert advice if we identify issues during the assessment process. Examples of trials where expert advice may be needed include first-in-human (FIH) trials with novel compounds where the:

- mode of action involves a target that is connected to multiple signalling pathways (target with pleiotropic effects), e.g. leading to various physiological effects or targets that are ubiquitously expressed
- compound acts (directly or indirectly) via a cascade system where there may be an amplification effect which might not be sufficiently controlled by a physiological feedback mechanism
- compound acts (directly or indirectly) via the immune system with a target or mechanism of action which is novel or currently not well characterised
- is novelty in the structure of the active substance e.g. a new type of engineered structural format such as those with enhanced receptor interaction as compared with the parent compound
- level of expression and biological function of the target receptor may differ between healthy individuals and patients with the relevant disease
- is insufficient available knowledge of the structure, tissue distribution, cell specificity, disease specificity, regulation, level of expression and biological function of the human target, including down-stream effects
- compound acts via a possible or likely species specific mechanism or where animal data are unlikely to be predictive of activity in humans

If you are a sponsor of a FIH or early stage clinical trial you should read the **Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products**. You should use the document to help you identify risk factors and create mitigation strategies.

Sponsors should use the criteria above to decide if their trial needs expert advice. You can get pre-submission advice from us if you are unsure if your compound falls into the ‘higher-risk’ category.

To get advice you should send an email with ‘URGENT – EAG/CHM QUERY’ as the title to **clintrialhelpline@mhra.gov.uk** including:

- a summary of the nature of the compound
- its target/mechanism of action
- the relevance of the animal model(s)

We will send a response to this email within 14 days.

If we confirm that the application comes within the category of ‘higher risk’, or you have determined this yourself, you should **select the date of the CTBVEAG meeting** where you want your trial discussed.

You should prepare your complete submission package and submit it in the new part of IRAS as described above. At least 14 days prior to submission you should alert MHRA and HRA (**clintrialhelpline@mhra.gov.uk**; **approvals@hra.nhs.uk**) that the application is planned and it requires EAG/CHM review to ensure an appropriate REC meeting is scheduled. The submission should be made no later than 21 days before the date of the CTBVEAG meeting it will be discussed at, but ideally much earlier to enable a smooth review process. Applications that are received later will be assigned to the next available meeting.

The rest of the application process is as described above for all applications. The combined response letter will be sent to the sponsor as soon as possible after the REC meeting. Please refer to HRA website for further information regarding scheduling of the REC meeting.

Post-marketing surveillance – Spontaneous reporting

Spontaneous reporting has been important in detecting rare side effects which are not seen at a high enough level to be detected by the relatively small numbers of people taking part in clinical trials. Particular attention is paid to medicines which are under additional monitoring requirements, including those which are new to market and vaccines, these are also part of the black triangle scheme.

The **Yellow Card website** states:-

Yellow Card

The Yellow Card scheme is vital in helping the Medicines and Healthcare products Regulatory Agency (MHRA) monitor the safety of all healthcare products in the UK to ensure they are acceptably safe for patients and users.

Reports can be made for:

- suspected adverse drug reactions (ADRs) to all medicines including:
    - vaccines
    - blood factors and immunoglobulins
    - herbal medicines
    - homeopathic remedies
- all medical devices available on the UK market
- defective medicines (those that are not of an acceptable quality)
- fake or counterfeit medicines or medical devices
- nicotine-containing electronic cigarettes and refill containers (e-liquids)

It is important that problems with medicines and medical devices and other nicotine e-cigarette products are reported, as the reports help identify new problems with these products.

MHRA will review the product and if necessary and take action to minimise risk and maximise benefit to patients and the public.

MHRA is also able to investigate counterfeit medicines or devices and if necessary take action.

Black triangle scheme

New medicines and vaccines that are under additional monitoring have an inverted black triangle symbol (▼) displayed in their package leaflet and summary of product characteristic, together with a short sentence explaining what the triangle means – it does not mean the medicine is unsafe. You should report all suspected ADRs for these products.

For products with regards to Northern Ireland, the European Medicines Agency (EMA) is responsible for maintaining the list of black triangle products. For products with regards to the United Kingdom the MHRA is responsible for maintaining the list of black triangle products.

This symbol appears next to the name of a relevant product:

- in the British National Formulary (BNF)
- in the British National Formulary for Children (BNFC)
- in Monthly Index of Medical Specialties (MIMS)
- in the Association of the British Pharmaceutical Industry (ABPI) Medicines Compendium
- on advertising material

- in Drug Safety Update
- in summaries of product characteristics and patient information leaflets

See **the Black Triangle scheme - new medicines and vaccines subject to EU-wide additional monitoring** (PDF, 139KB, 4 pages).