Fertility problems assessment and treatment

Consultation on draft guideline - Stakeholder comments table
10/09/2025 – 21/10/2025

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Anthony Nolan	Guideline	General	General	**Fertility testing** – There is currently no provision for **NHS-funded fertility testing** in the guidance. Many people who have undergone cellular therapy face uncertainty about their fertility post-treatment. Everyone's fertility is affected differently: while some individuals experience minimal impact, others face permanent infertility or early menopause. This uncertainty can cause patients to feel anxious, depressed, and struggling with their sense of identity, future plans, and family life. One patient shared that "*it impacts you psychologically, emotionally, and in regard to your identity, the future you might have had or you imagined for yourself*". Another questioned "*Will I still be the same person I imagined myself to be if I can't have children?*". A third patient described being told she may never have children and how she "*got really depressed, as I always wanted to be a mum*", only to find out later that she could get pregnant. In addition to the emotional impact, uncertainty about fertility can also impact patients physically and affect their ability to make informed decisions about their (sexual) health. One young person shared that she was unsure whether she needed contraception or how hormonal contraception may affect her post-transplant. Another	Thank you for your comment. This was not within the scope of the guideline update, so no comment has been made on this.

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				explained that she was not offered fertility testing until she presented with pregnancy symptoms, as her medical team had simply assumed she was infertile and experiencing menopause. We therefore recommend that **NHS-funded fertility testing** be made available to all patients who received NHS-funded treatment that may have affected their fertility. This could reduce stressors to the physical and mental wellbeing of patients and allow them to make more informed decisions about their care and own bodies.	
Anthony Nolan	Guideline	General	General	**Education and follow-up** – We would like to see **stronger and more explicit provisions for education and long-term follow-up on fertility and sexual health** for all individuals who undergo medical treatment that may affect their fertility, regardless of whether they pursued preservation. Many patients preparing for cellular therapy have to process information about their fertility (of which often there is no written record) at the same time as information about their diagnosis, prognosis and complex treatment regimen. As one patient explained "*[The fertility aspect of pre-transplant care] was a very quick process, even though it was a big part of this cancer journey. It was*	Thank you for your comment. This was not within the scope of the guideline update, so no comment has been made on this.

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				explored and wrapped up quickly, but it's probably the longest standing aspect of treatment." The lack of attention paid to fertility and sexual health before, during and after treatment can lead to unnecessary distress for patients in their recovery and relationships. One patient shared how a private gynaecologist "*sorted a problem out within a month*" that had been repeatedly raised with their transplant consultant. The patient reflected, *"I felt very bitter about this — it was an unnecessary thing that was taken away from me, seeing how quickly it was fixed."* Fertility and sexual health issues are some of the most enduring and life-altering effects of treatment, so while it's encouraging to see preservation and IVF offered to those whose fertility may be affected by medical treatment, **age-appropriate education for patients and parents of young patients, and careful follow-up must continue** beyond initial preservation decisions and be regularly revisited.	
Anthony Nolan	Guideline	002	General	**Would it be challenging to implement of any of the draft recommendations? Please say why and for whom. Please include any suggestions that could help users overcome these challenges (for example, existing practical resources or national initiatives.**	Thank you for your comment. We recognise the difficult decisions ICBs must make on the allocation of scarce resources, and the committee did discuss implementation. However, the committee

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				Rec 1.9.4 & 1.14.7 – While we commend the recommendation of three full IVF cycles and needs-based cryopreservation periods for those whose fertility was affected by medical treatment, these may not translate into practice. As these guidelines are not binding for ICBs, funded preservation periods and number of funded IVF cycles (if any) have become a postcode lottery and created significant inequalities in access to fertility services. In regions where Trusts aren't following NICE best practice guidelines, some patients who underwent fertility-affecting treatment have had to turn to private providers, which carries a significant financial burden. As one patient put it: "*You think the financial aspect of transplant is over after transplant, but this will be a big expense every year until I want a child.*" We are particularly concerned about rec 1.14.7. Replacing a clearly defined storage period without providing a minimum standard may lead ICBs to reduce already inconsistent and inadequate funded storage periods, potentially resulting in a 'race to the bottom'. Having a low funded storage period can be particularly distressing to patients, as they may feel they have no choice but to pay. Therefore, whilst we welcome the introduction of needs-based storage periods for	considered that the recommendations they made were in line with the best available clinical and cost-effectiveness evidence. The recommendation about offering initial 3 cycles is based on evidence that showed it to be cost-effective. We additionally state in the guideline that the evidence for this recommendation is now stronger than before. The recommendation about offering needs-based fertility preservation was based on evidence from evidence review R, which showed that preservation of different material was feasible and effective for multiple populations. The committee were aware that by law, consent to store cryopreserved material must be renewed every 10 years with the person for NHS-funded storage to lawfully continue and agreed that this period was too long. Although a wide range of follow-up times was reported in the evidence, the committee agreed that a follow-up at minimum every 5 years is reasonable but often more frequent follow-ups could be warranted. The committee agreed that the recommendation could be potentially cost-saving to the NHS given the low return rates shown in the evidence review and that continued NHS-funded storage could be unnecessary for those whose fertility has not been impaired by treatment. The

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				cryopreserved reproductive materials for those who have undergone fertility-impacting treatment, we would still like to see a commitment to a **minimum timeframe** that storage is funded across all ICBs, e.g. ten years, after which needs-based storage would take effect. This would ensure consistent and extended funding for storage across all ICBs, rather than leaving the guidance open to interpretations that could weaken access and inadvertently limit patient choice. **Rec 1.1.9** – We welcome the recommendation that all individuals should have access to a fertility specialist. However, implementation must ensure that **fertility teams work in close collaboration with a patient's multi-disciplinary team (MDT)**. Cellular therapy patients often have complex needs, meaning fertility specialists can only provide effective care and advice if they work alongside the treating MDT. Without this collaboration, patients may not only experience poorer care but are forced to advocate for themselves. This places an undue burden on individuals, particularly those who may be less able to self-advocate for cultural, personal, or educational reasons. **Rec 1.14.2** – Current NHS-funded preservation is limited to individuals who received NHS-funded treatment.	committee agreed there is an indicative minimum period of five years, and subsequently in five-year blocks. Principles of care for people receiving fertility treatment, including advice on generalist and specialist care, were not within the scope of the guideline update, so no comment has been made on this. The recommendation on NHS-funded fertility preservation is intended to prevent eligibility criteria for conventional fertility treatment being used for access to NHS-funded fertility preservation, and this recommendation does not comment on who should be able to access fertility preservation in general. A separate recommendation has been added to this section of the guideline giving guidance on when to consider fertility preservation. Education on fertility preservation, including for those transitioning between paediatric and adult services, was not within the scope of the guideline update, so no comment has been made on this.

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				However, cellular therapies are unique in that they are rapidly evolving; treatments that are initially only available privately or in comparable countries often become available on the NHS shortly afterward. As a result, patients' survival and fertility prospects can be tied to market availability rather than medical need. In such a fast-changing field, fertility preservation should be **NHS-funded for all cell and gene therapy patients**, regardless of where they initially received treatment. Many patients who access private care do so out of necessity, not choice, and often return to NHS care for post-treatment care, at which point their fertility needs re-enter the NHS system. **Transition to adult services** – Education around preservation and fertility more broadly must be significantly improved for paediatric patients, particularly during their transition into adult services. Many young people reported moving from structured paediatric fertility pathways to limited fertility support in adult settings. Fertility conversations often stop altogether, even though these are crucial years for understanding long-term implications and options. One person reflected that "*these are big decisions to make at such a young age, and you're never going to know how you'll feel in years to*	

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				come." Another explained: "*I'd need someone talking to me about this, I can't keep googling".* Several individuals who underwent cellular therapy as paediatric patients reported learning about the impact of their treatment on fertility years later in unsupportive settings, such as school, or experiencing perimenopause without preparation. Many parents also reported not being prepared for these conversations. This is particularly important for young individuals who had their fertility materials stored while in paediatric settings. One young patient shared that they "*had no idea what documents [they were] signing*" when agreeing to cryopreservation and how they still don't know when their funded storage may run out or how to access materials if needed. As such, **clear transition and age-appropriate education pathways** should be put in place to ensure young patients whose fertility is affected by treatment receive support into adulthood. Young people must have access to age-appropriate information about their fertility post-treatment, so they can take ownership of their care and future decisions.	

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Anthony Nolan	Guideline	031	007	**Rec 1.9.3 & 1.9.4** – We welcome the addition of this recommendation, as it does not exclude patients who have a non-cancer-related cause of infertility.	Thank you for your comment.
Anthony Nolan	Guideline	031	020	**Rec 1.9.3 & 1.9.4** – We welcome the addition of this recommendation, as it does not exclude patients who have a non-cancer-related cause of infertility.	Thank you for this comment.
Anthony Nolan	Guideline	042	002	**Rec 1.14.1** – We welcome the addition of this recommendation, embedding conversations about fertility preservation into pre-treatment consultations for patients preparing to undergo potentially fertility-impairing therapies. However, we are concerned that the current wording limits this recommendation to "people who are preparing for medical treatment". Many patients receiving cellular therapies do so for acute blood cancer or other fast-progressing disease such as aplastic anaemia, needing to begin treatment within hours of diagnosis. In those circumstances, patients face a potentially life-threatening decision of delaying treatment to preserve their fertility or having to go through the preservation process after conditioning therapy and/or treatment has already begun. As one patient shared, their treatment *"was so urgent that there was no time for pre-treatment planning"* and they were told they could either *"delay treatment and risk death, or store sperm after conditioning had already*	Thank you for this comment. The guideline committee appreciate the suggestion in the comment and agree that a discussion about fertility preservation should be held at the earliest opportunity with those requiring urgent treatment and have now added this to the recommendation.

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				started and risk the sperm not being viable, as there were no appointments available for another week". Therefore, to better reflect the realities faced by those unable to pursue fertility preservation before treatment, we would like to see the wording of this recommendation changed to "**people who are preparing for medical treatment, and ensure fertility preservation is discussed at the earliest opportunity with people with acute conditions requiring urgent treatment**".	
Anthony Nolan	Guideline	042	011	**Rec 1.14.4** – We welcome this recommendation but would additionally like to see explicit reference to post-treatment sperm preservation and sperm quality testing prior to cryopreservation. Many patients receiving cellular therapies do so for malignant indications, and some have to begin treatment within hours of diagnosis. Consequently, some individuals may need to collect a sample for preservation while already undergoing conditioning therapy. One patient shared that their treatment *"was so urgent that there was no time for pre-treatment planning"* and they were told they could either *"delay treatment and risk death, or store sperm after conditioning had already started and risk the sperm not being viable, as there were no appointments available for another week"*.	Thank you for this comment. The guideline committee agreed that a discussion about fertility preservation should be held early in the treatment pathway with those requiring urgent treatment. The recommendation has been expanded to reflect the comment by adding that this should be done at the earliest opportunity for those who require urgent treatment. The committee also discussed that it was difficult to define the extent of genetic damage to fertility material after or during chemotherapy treatment, but they agreed that the damage was cumulative, therefore a discussion about fertility preservation should happen at the earliest opportunity.

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				Where sperm is collected during treatment, the sample may already be compromised by the therapy. This means that A) patients may face ongoing uncertainty about their fertility despite having preserved material and/or B) patients may pay hundreds of pounds to store potentially low-quality or non-viable samples once the funded storage period ends. As one person described, "*the only communication from [the storage hospital] was after three or four years saying I now need to self-fund something that may or may not work […] I'm in a fortunate position that I can afford it, but this isn't possible for everyone*". Therefore, we would like to see the wording changed to "**people who are preparing, undergoing or have received medical treatment**" to ensure inclusion of those unable to preserve fertility prior to treatment. Additionally, incorporating **testing of sperm samples prior to freezing (or as soon as possible after freezing)** would provide patients with clarity about their fertility options and help them make more informed decisions regarding their fertility, treatment and future planning.	The committee did not think that the guideline can recommend fertility cryopreservation for those who have already received gonadotoxic treatment because of uncertainties in the quality and safety of the material. However, they recognised that there may be situations based on clinical and professional judgment where this could be reasonable. The committee's discussion on this has been included in the Benefits and harms section of the evidence review R on Fertility preservation. It was not part of the scope of this guideline to address sperm sample testing prior or after freezing.
Anthony Nolan	Guideline	042	015	**Rec 1.14.5** – We agree with this recommendation but would additionally like to see the inclusion of oocyte preservation post-treatment.	Thank you for this comment. The guideline committee recognised that people may not be offered fertility preservation in a timely manner,

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				Many patients receiving cellular therapies do so for malignant indications, and some have to begin treatment within hours of diagnosis, not leaving enough time to preserve their oocytes beforehand. Similarly, some young girls and individuals with female reproductive organs may not yet be eligible for oocyte preservation at the time of treatment, or may be considered 'low risk' at diagnosis. However, these patients may later undergo fertility testing and have to pursue fertility preservation at this later stage in their recovery. In these cases, patients are often required to self-fund, despite their infertility being a direct consequence of their treatment. Therefore, to better reflect the realities faced by those unable to pursue fertility preservation before treatment, we would like to see the wording of this recommendation changed to "**people who are preparing, undergoing or have received medical treatment**".	particularly where there is a need for urgent treatment. They discussed that it was difficult to define the extent of genetic damage to fertility material after or during chemotherapy treatment, but they agreed that the damage was cumulative and there may be instances where cryopreservation after gonadotoxic treatment had already commenced could be reasonable. However, they did not think the guideline could recommend cryopreservation after such treatment. However, they agreed to include in the recommendations that discussion about fertility preservation should happen at the earliest opportunity for people needing urgent treatment. The Benefits and harms section of the evidence review R on Fertility preservation has been updated to include further discussion about when cryopreservation may be or should be an option.
Anthony Nolan	Guideline	042	020	**Rec 1.14.6** – We welcome the inclusion of this recommendation.	Thank you for this comment.
Anthony Nolan	Guideline	042	023	**Rec 1.14.7** – We welcome the recommendation to introduce needs-based storage periods for cryopreserved reproductive materials for those who have undergone fertility-impacting treatment.	Thank you for this comment. The guideline committee agreed that, although a wide range of follow-up times was reported in the evidence, a follow-up at minimum every 5 years was reasonable. They did not want to be too prescriptive as often more

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				A needs-based approach will be particularly beneficial for younger patients who may not yet feel ready to start a family or may struggle to afford private storage once the previously recommended 10-year period ends. Additionally, the five-year review offers an opportunity for ongoing education and proactive engagement, allowing patients to make informed choices about their fertility rather than being contacted solely for re-consenting or invoicing purposes once their funded storage period concludes. As one patient described: "*Every time a bill comes in saying 'pay or we will discard the eggs' you think 'why is everyone screaming at me?'"* However, while we agree with this recommendation and the rationale provided (p. 69, line 22) in principle, we are concerned that the current wording lacks the necessary strength to ensure equitable implementation. Currently, funded preservation post-treatment is a postcode lottery and dependent on individual ICB policies. Replacing a clearly defined storage period without providing a minimum standard may lead ICBs to reduce already inconsistent and inadequate funded storage periods, potentially resulting in a 'race to the bottom'. Such funding cuts could have significant emotional and financial consequences for patients: "*You think the financial aspect*	frequent follow-ups may be warranted. On the other hand, they also felt that there was an indicative minimum period, which is 5 years and subsequently in minimum 5-year blocks as long as the individual remained at continued significant risk of infertility. The committee revised the recommendation after consultation to make it clear that the offer for continued storage for those at significant risk of infertility should be NHS-funded.

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				of transplant is over after transplant, but this will be a big expense every year until I want a child." Therefore, whilst we welcome the introduction of needs-based storage periods for cryopreserved reproductive materials for those who have undergone fertility-impacting treatment, we would still like to see a commitment to a **minimum timeframe** that storage is funded across all ICBs, e.g. ten years, after which needs-based storage would take effect. This would ensure consistent and extended funding for storage across all ICBs, rather than leaving the guidance open to interpretations that could weaken access and inadvertently limit patient choice.	
Anthony Nolan	Guideline	046	005	**3 Testicular tissue cryopreservation** – We welcome the recommendation to conduct further research into the effectiveness of testicular tissue cryopreservation. However, in the absence of an established preservation options for provision for pre-pubertal boys and individuals with male reproductive organs undergoing cellular therapy (as well as those who aren't able to store sperm for any reason), testicular tissue preservation or participation in a clinical trial should still be offered wherever possible. This could help ensure that no patient is left without any opportunity to preserve their fertility.	Thank you for this comment. As outlined in the Benefits and harms section of the evidence review R on Fertility preservation, the guideline committee agreed that, given the experimental nature of this procedure and the lack of evidence on the primary outcomes such as live birth and clinical pregnancy, they could not comment on the use of testicular tissue cryopreservation as a fertility preservation option. However, they acknowledged that this was particularly relevant for boys before and during puberty. The committee made a research recommendation in the

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					hope of generating further research on the success and safety of testicular tissue cryopreservation.
Association of Reproductive and Clinical Scientists	Guideline	General	General	Consider use of 'ART' instead of 'IVF treatment' throughout guideline	Thank you for your comment. 'IVF treatment' was considered to be more specific than ART which could mean other treatments as well, therefore 'IVF treatment' was preferred when referring to IVF.
Association of Reproductive and Clinical Scientists	Guideline	General	General	'Couples' should be replaced with 'women, trans-men, non-binary people and couples' as with other sections	Thank you for your comment. We have reviewed the wording used in the recommendations again based on this and other stakeholder feedback. Where the guideline refers to couples, it is doing so on purpose because the recommendation is specifically for/about couples. For example, the first recommendation in the guideline: "1.1.1 See couples who experience problems in conceiving together because both partners are affected by decisions surrounding investigation and treatment. [2004]"
Association of Reproductive and Clinical Scientists	Guideline	013		1.3.1 This section should make reference to the ARCS Good practice in laboratory diagnostic andrology guidelines (PMID: 39332143)	Thank you for this comment. It was not within the scope of this guideline update to review the resource referred to in the comment. Based on our current methodology, we would not refer to an external guideline without assessing its quality and

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					relevance, including formal appraisal with AGREE II where appropriate.
Association of Reproductive and Clinical Scientists	Guideline	013		1.3.1.1 It is confusing that Total Motility and Progressive Motility have been conflated into a single point – these are two different measures with different reference ranges and both should be met individually. Suggest splitting into two points. This section also references old WHO 2021 values that should be updated to the most up to date WHO standards.	Thank you for this comment. The committee agreed to split this into 2 points, i.e. total motility and progressive motility. The 2021 WHO values are the most recent ones and the guideline committee are not aware of any newer values.
Association of Reproductive and Clinical Scientists	Guideline	013		1.3.1.1 Vitality assessment is only recommended to be assessed if the Total Motility is <40% (ARCS Good Practice Guidelines PMID 39332143).	Thank you for your comment. The recommendation merely provides a list of tests and their reference values based on WHO manual. For further details, a link to WHO Laboratory Manual for the Examination and Processing of Human Semen is included in the guideline.
Association of Reproductive and Clinical Scientists	Guideline	020	018-019 (section 1.4.2.2)	Could reference 2021 cochrane review doi: 10.1002/14651858.CD000479.pub6.	Thank you for your comment. This Cochrane review (doi: 10.1002/14651858.CD000479.pub6) was included in Evidence Review X, which investigates the clinical and cost effectiveness of surgical and radiological treatments for fertility problems associated with varicocele.
Association of Reproductive	Guideline	020	008-009 (secti	Statement should make clear that it is referring to the effectiveness of systemic corticosteroids at treatment	Thank you for your comment. We have clarified the recommendation as suggested.

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and Clinical Scientists			on 1.4.1.3)	ASA, not the effectiveness of corticosteroids as a medicine generally.	
Association of Reproductive and Clinical Scientists	Guideline	025	016-019 (section 1.8.1.3)	Clarification should be made whether this is regardless of age.	Thank you for this comment. Unfortunately, it is not clear which section in the draft guideline this is referring to. The information in the line number seems to refer to the 2013 version of the recommendations, therefore, our interpretation is that this comment is referring to recommendations about the length of expectant management before IVF treatment in case of unexplained fertility problems. See section "IVF access criteria" in the new guideline for the eligibility criteria to access IVF treatment, including the length of expectant management.
Association of Reproductive and Clinical Scientists	Guideline	025	020-023 (section 1.8.1.4)	Clarification should be made whether this is regardless of age.	Thank you for this comment. Unfortunately, it is not clear which section in the draft guideline this is referring to. The information in the line number seems to refer to the 2013 version of the recommendations, therefore, our interpretation is that this comment is referring to recommendations about the length of expectant management before IVF treatment in case of unexplained fertility problems. See section "IVF access criteria" in the new guideline for the eligibility

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					criteria to access IVF treatment, including the length of expectant management.
Association of Reproductive and Clinical Scientists	Guideline	026	005-007 (section 1.9.1.1)	Requirement for clinical diagnosis of disability or problem, excludes those with self-reported difficulties or those unable to obtain a formal diagnosis.	Thank you for this comment. It is not clear which recommendation this is referring to. The data in the line number information seems to refer to the 2013 version of the recommendations. Based on this, our interpretation is that the comment is referring to recommendation 1.37.1 in the new guideline, a recommendation originally from 2013 and agreed by the 2013 guideline committee. The committee recognises that the recommendation may exclude people who do not have a clinical diagnosis of physical disability or psychosexual problem. However, this was considered reasonable criteria for accessing fertility treatment via the NHS.
Association of Reproductive and Clinical Scientists	Guideline	026	008-010 (section 1.9.1.1)	Perhaps should reference NICE guideline "Fertility problems: assessment and treatment CG156" as sperm washing efficacy and safety as mentioned in the example, suggests that IUI after washing may not always be appropriate.	Thank you for this comment. It is not clear what specifically this comment relates to given the page and line numbers provided. We assume it refers to recommendation 1.37.1 second bullet point. If so, the wording of this recommendation has been amended and it no longer refers to sperm washing.

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Association of Reproductive and Clinical Scientists	Guideline	026	021-022 (section 1.9.1.3)	Clarification should be made whether this is regardless of age.	Thank you for this comment. It is not clear which section in the draft guideline this is referring to. The information in the line number seems to refer to the 2013 version of the recommendations, therefore, our interpretation is that this comment is referring to recommendations about the length of expectant management before IVF treatment in case of unexplained fertility problems. See section "IVF access criteria" in the new guideline for the eligibility criteria to access IVF treatment, including the length of expectant management.
Association of Reproductive and Clinical Scientists	Guideline	026	011 (section 1.9.1.1)	Clarify which same sex relationships, ie, where at least one partner has uterus and ovaries.	Thank you for this comment. It appears that the stakeholder may be referring to the 2013 version of the guideline. This whole section of the guideline has been updated and the recommendation no longer refers to same sex couples. The recommendation 1.37.2 now refers to women, and trans men and non-binary people with female reproductive organs who are using donor insemination.
Association of Reproductive and Clinical Scientists	Guideline	028	002 (section 1.11.1)	Section does not include any mention of the use of donor eggs. Clarification of whether this type of treatment should be offered and when may be beneficial.	Thank you for this comment. It is not clear what specifically this comment relates to given the page and line numbers provided. However, the use of donor eggs is mentioned in the updated guideline

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					in the section on Embryo transfer strategies in IVF. IVF using donor eggs was not covered in this guideline update. Please note, NICE welcomes topic suggestions from stakeholders which will be considered for NICE topic prioritisation process: Topic suggestion | NICE.
Association of Reproductive and Clinical Scientists	Guideline	032		1.12.6.4 Association of Clinical Embryologists (ACE) has been replaced with Association of Reproductive and Clinical Scientists (ARCS) and own the grading scheme. Please note is it not a UK NEQAS owned grading scheme and needs to be renamed as ARCS in the guideline.	Thank you for this comment. The comment refers to a recommendation in the 2013 version of the guideline. This recommendation was retained in the new guideline but amended to refer to ARCS, not ACE.
Association of Reproductive and Clinical Scientists	Guideline	032		1.12.6.5 ESHRE 'Number of embryos to transfer during IVF/ICSI' guidance (2023) states there is no evidence in support of DET.	Thank you for this comment. This section of the guideline was not updated as part of this update.
Association of Reproductive and Clinical Scientists	Guideline	035		1.14.11 - The use of DI should be considered in same-sex couples and this is not referenced in this section.	Thank you for your comment. The recommendation you're referring to is about medical indications for donor insemination and does not cover people using donor insemination for non-health related reasons. Please also see recommendation 1.37.2.
Association of Reproductive and Clinical Scientists	Guideline	036		1.14.12 The suggestion for use of DI where there is a high risk of transmitting a genetic disorder to the offspring is misguided and the first treatment option should be PGT.	Thank you for this comment. The recommendation you're referring to is to 'consider' donor insemination in these cases. The committee's

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					view is that this is appropriate because PGT-M may not always be the preferred option.
Association of Reproductive and Clinical Scientists	Guideline	037		1.14.4.1 The sentence 'Offer tubal assessment before treatment if there is a history…' should be a new section i.e. 1.12.8.	Thank you for this comment. The recommendation you're referring to was slightly amended to clarify the action about confirming ovulation, but offering tubal assessment has been kept in the same recommendation.
Association of Reproductive and Clinical Scientists	Guideline	038		1.15.1.1 The suggestion for use of oocyte donation where there is a high risk of transmitting a genetic disorder to the offspring is misguided and the first treatment option should be PGT.	Thank you for your comment. The recommendation you're referring to is to 'consider' oocyte insemination in certain cases where there is a high risk of transmitting a genetic disorder to the child. The committee's view is that this is appropriate because PGT-M may not always be the preferred option.
Association of Reproductive and Clinical Scientists	Guideline	038		1.15.3.1 The reference to 'egg sharing' here does not fit, there should be a separate section for this treatment modality or an earlier reference and inclusion	Thank you for your comment. The committee agreed to remove this recommendation from 2004 because it was not considered relevant for NHS practice and benefit-in-kind egg sharing is covered in HFEA Code of Practice. HFEA also has information about reciprocal IVF.
Association of Reproductive and Clinical Scientists	Guideline	038		1.15.3.1 Where reference is made to 'egg sharing' does this include both benefit-in-kind arrangements and partner-to-partner donation? This is unclear and should be clarified.	Thank you for your comment. The committee agreed to remove this recommendation from 2004 because it was not considered relevant for

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					NHS practice and benefit-in-kind egg sharing is covered in HFEA Code of Practice. HFEA also has information about reciprocal IVF.
Association of Reproductive and Clinical Scientists	Guideline	038	027	The conclusions that PICSI does not improve outcomes is based on the fact that the review of the evidence (evidence-review-19) incorrectly rejects the mechanistic analysis from the largest, NIHR-funded, RCT on PICSI (The HABSelect Trial, Miller et al, West et al) as being 'not an RCT'. The data in this study clearly shows the change in birth outcomes, and significant reduction in miscarriage rates when using PICSI vs ICSI in older women.	Thank you for your comment. The recommendation not to use PICSI in preference to standard ICSI is informed by the HFEA's evidence statement, which was primarily based on evidence from the RCT you have referenced, Miller 2019. This trial found that PICSI did not significantly improve live birth rates for people receiving ICSI for male factor fertility problems. While the primary study did find a lower rate of miscarriage with PICSI relative to ICSI, this was a secondary outcome which study authors note the trial was not powered to investigate. In the primary RCT analysis, there was no evidence for differential effects of PICSI on outcome based on maternal age. The analysis referred to in your comment is a secondary analysis, the aim of which, as the study authors acknowledge, was to generate mechanistic hypotheses and as such a cohort was sampled from the RCT population making this an observational mechanistic study without the full benefits of random allocation.
Association of Reproductive	Guideline	039		1.16.1.1 For consistency, add 'who are of reproductive age'	Thank you for this comment.

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and Clinical Scientists					The comment appears to refer to a recommendation from the 2013 guideline. The updated guidance recommends fertility preservation to anyone with a medical indication that is likely to impair their fertility. Mostly, this is for people who are of reproductive age, however, the updated guideline also recommends to consider ovarian tissue preservation when oocyte or embryo cryopreservation is not feasible, for example, in girls before puberty. Testicular tissue preservation for boys before puberty is still experimental, therefore, the committee made a recommendation for research on the safety and clinical and cost-effectiveness of this technique.
Association of Reproductive and Clinical Scientists	Guideline	039		1.16 Suggest there should be a section for testicular tissue cryopreservation	Thank you for this comment. As outlined in the Benefits and harms section of the evidence review R on Fertility preservation, there was only 1 relevant study that was identified for testicular tissue cryopreservation and this study only provided evidence on the proportion who obtained a suitable sample for cryopreservation and surgery-related adverse events during or after the testicular tissue retrieval. The guideline committee agreed that, given the experimental nature of this procedure and the lack of evidence on the primary outcomes of live birth and clinical pregnancy, they could not comment on the use

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					of testicular tissue cryopreservation as a fertility preservation option. However, they made a research recommendation on the success and safety of this fertility preservation technique.
Association of Reproductive and Clinical Scientists	Guideline	040		1.16.1.6 Specific reference to NHS funded treatment rejects private funded treatment which should also be referenced here	Thank you for this comment. The comment appears to refer to the 2013 guideline version of the recommendation. It is not entirely clear what this comment means. Please note, that this recommendation has been revised in the new guideline and it currently states that those who are considering fertility preservation should be informed that eligibility criteria for assisted conception in an NHS setting will apply when it comes to using stored fertility material.
Association of Reproductive and Clinical Scientists	Guideline	041		1.17 For consistency with other sections, consider adding a section titled 'Information and counselling' here	Thank you for this comment. It is not clear what specifically this comment relates to given the page and recommendation number provided.
Association of Reproductive and Clinical Scientists	Guideline	044		Guideline states 'it is common to transfer more than 1 embryo', change to 'multiple embryos may occasionally be transferred'	Thank you for this comment. The comment appears to be referring to a research recommendation in the 2013 guideline. This research recommendation was deleted before the draft guideline consultation.
Association of Reproductive	Guideline	045		'even where there is RCT evidence of no benefit' change to 'even where there is RCT, evidence is of no benefit'	Thank you for this comment.

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and Clinical Scientists					The comment appears to be referring to a research recommendation in the 2013 guideline. This research recommendation was deleted before the draft guideline consultation.
Association of Reproductive and Clinical Scientists	Guideline	050		Use of outdated embryo grading scheme (UK NEQAS embryo morphology 2010). Replace with ARCS Embryo Morphology Scheme Grading System (version 2, April 2017).	Thank you for your comment. It appears that the comment is referring to the 2013 version of the guideline. A link to an updated embryo grading scheme has been included in the updated guideline.
Association of Reproductive and Clinical Scientists	Guideline	052		'infertility affects 1 in 7', WHO figures 1 in 6. Suggest change to reflect evidence.	Thank you for your comment. It appears that your comment is referring to the Context section in the 2013 guideline version. The Context section in the consultation version of the updated guideline referred to '1 in 6 heterosexual couples'. Please note that since the consultation, NICE has decided not to include Context sections in the guidelines.
Association of Reproductive and Clinical Scientists	Question 1			*Would it be challenging to implement of any of the draft recommendations? Please say why and for whom. Please include any suggestions that could help users overcome these challenges (for example, existing practical resources or national initiatives*.	Thank you for this comment. Because the scope of this guideline is about health-related fertility problems, initial cycles of IUI for people without a clinical impediment to fertility are not covered by this guideline. We recognise that currently the initial

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				Yes: Expecting IUI couples to consider 12 x cycles of IUI before proceeding with IVF. Significant cost implication for self-funded same sex female couples who must evidence infertility before seeking NHS funding for IVF. Limited number of ICBs provide NHS funding for three full cycles of IVF. Cost prohibitive for many couples to self-fund IVF cycles. NHS funding is moving further away from NICE guidance rather than moving towards it.	cycles of IUI would need to be self-funded and this can be a barrier to many people. NICE produces recommendations on the best available clinical and cost-effectiveness evidence. Implementation of NICE guidance is not within control of the guideline developers.
Association of Reproductive and Clinical Scientists	Question 2			*Would implementation of any of the draft recommendations have significant cost implications?* Yes: cost to ICB to fund three cycles of IVF	Thank you for this comment. NICE produces recommendations on the best available clinical and cost-effectiveness evidence. As per the previous NICE guideline it is recommended that 3 cycles are offered. Reflecting weaker evidence, a 'consider' recommendation is also made for a further 3 cycles. Any increase in costs would likely reflect better implementation of the pre-existing recommendation. In addition, the updated guideline no longer recommends IVF for those aged 42 years.
Association of Reproductive and Clinical Scientists	uideline	026	012-015 (section 1.9.1.2)	Wording unclear, whether the additional 6 cycles being offered are mandatory before IVF should be considered as a suitable treatment option, or if it is that patients should be given the opportunity to undertake additional IUI cycles. And whether this is regardless of if they have been able to try to conceive without the aid of fertility	Thank you for this comment. It is not clear what specifically this comment relates to given the page and line numbers provided. We assume it refers to recommendation 1.37.2. No new evidence was reviewed related to this recommendation. However,

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				treatment for any specific duration of time prior to starting rounds of IUI.	the wording of this recommendation has been updated to make it clearer and currently it states that for those people who are using donor insemination and have not conceived after 6 cycles, 6 cycles of unstimulated donor IUI should be offered before considering IVF, providing there are no contraindications and no suspected or known clinical causes of infertility.
Avenues	Guideline	016-019		We wish to express serious concern regarding the inclusion of [REDACTED] on the NICE Fertility Guideline Committee. [REDACTED] We therefore respectfully request that NICE reconvene a new committee for the fertility guideline, composed of members who are demonstrably free from significant commercial conflicts of interest, to ensure the credibility and independence of the final recommendations.	Thank you for your consultation comments regarding the draft guideline on Fertility problems. We have taken the decision to partially redact your comment on the register of interests because your comment contains personal details about a committee member. NICE's principles of responding to stakeholder comments are set out in section 10.2 of Developing NICE guidelines: the manual. Specifically, NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all. The interests your raise have always been declared in the register of committee interests, which can be found on the History tab of the published guideline. You note the original rationale, which (as stated) in the register of interests, was updated with following further detail in June 2025.

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					The updated text in this entry on the register addresses how NICE has reviewed and further addressed this declaration and is in line with NICE's DOI policy. You comment that 'NICE has recently amended its policy to allow members with a direct financial interest to participate where "complete exclusion would diminish the committee's access to clinical expertise."' The then active DOI policy applied to the Fertility committee had been in place since 2018, and all the committee's interests were assessed against this policy and actions taken in line with the policy (We note that the DOI policy has been since updated in November 2025.). In addition NICE has a policy on 'Appointments to advisory bodies' which outlines our general approach to appointing people to our committees, which is in line with the Governance Code on Public Appointments. Notably, we use an appointment process that is open, transparent and fair. All committee members were appointed to the advisory committee through a competitive process. With reference to your comments on retrospective review of the guideline by other committee members: To clarify, we did not undertake a retrospective review of

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					other member's interests; we contacted other members of the committee to inform them of the update to how NICE assessed the declaration. The other committee members were given then opportunity to reconsider their conclusions regarding the interpretation of the evidence and recommendations; the committee members decided that no changes were needed in light of the additional information regarding this declaration of interest. You comment that you are concerned by apparent omissions from the declared register of interests that may have shaped the contents of this draft guideline. The DOI policy is clear that declarations on appointment should cover the preceding 12-month period only. The information you refer to is before this period. In summary, as outlined in NICE's policy on declaring and managing interests for advisory committees, effective management of interests is essential for people to maintain confidence in our work; the policy supports a culture of transparency of interests of committee members, ensuring that the interest is known, understood and managed appropriately. Our committee members are experts in their field, and so it is likely that

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					they will have interests to declare, which may be directly applicable to the topic under discussion. Therefore, as outlined in the NICE policy for declaring and managing interests for NICE advisory committees v1.6, a member with a direct financial interest may participate if their complete exclusion from the meeting would diminish the committee's access to clinical expertise on the matter under discussion. NICE believes that this is the case for the Fertility committee. NICE has taken steps to mitigate the error and we are confident that any resulting risk to the objectivity of the guideline is minimal, and reconvening a new committee for the fertility guideline is not required.
Avenues	Guideline	006		1.2.3 Add: " Although female age may affect the chances of conceiving, male age may affect the health across multiple generations if the conception is successful. " Remove "To a lesser extent" "To a lesser extent" may be misinterpreted that the male age is less relevant than the female age, when one could argue that the cross generational impact associated with advanced paternal age is also concerning.	Thank you for your comment. No change has been made based on your suggestion. The focus of the recommendation is about chance of conception and the statement in the recommendation is not incorrect.

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				The graph itself should be replaced with cumulative live birth rate, rather than pregnancy rate, which is more relevant to patients.	
Avenues	Guideline	010		1.2.14-1.2.16 Regarding obesity, we strongly recommend that the following point be added: **"BMI should never be used as a reason to preclude fertility care."** This principle should also be clearly reiterated in section 1.9, *Access to Care*. Approximately 11% of women of reproductive age in the UK have a BMI above 30. Both NHS and private clinics have historically relied on previous NICE guidelines to impose BMI thresholds as exclusion criteria for fertility treatment. NICE now has the opportunity and responsibility to correct this misinterpretation. **There is no robust medical rationale to justify withholding fertility care solely on the basis of BMI.** We have conducted a systematic literature review on IVF outcomes in women with BMI above 30. Data from the American SART registry, encompassing over 3,000 IVF	Thank you for your comment. The committee agreed that BMI advice should focus on health optimisation rather than being used as a strict eligibility criterion. The guideline has never included BMI as an IVF access criterion but we are aware that BMI is sometimes used as a local criterion to access IVF. The committee agreed to stand down a previous recommendation in CG156 "Women should be informed that female BMI should ideally be in the range 19 to 30 before commencing assisted reproduction, and that a female BMI outside this range is likely to reduce the success of assisted reproduction procedures. [2004]" because they thought this was not particularly useful, was based on an old evidence review and could be used to deny access to treatment. General advice on BMI and fertility in the 'Initial advice' section was considered to be sufficient.

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				cycles in women with BMI over 50, reported no maternal mortality, a live birth rate of 22%, and neonatal outcomes comparable to those seen in older maternal age groups. The risks associated with higher BMI can be mitigated effectively through appropriate clinical management and multidisciplinary care. We therefore urge NICE to use this update to correct the inequity currently experienced by approximately one in ten women of reproductive age in the UK, who are being denied fertility treatment based on BMI alone. We also recommend adding the following statement: "Care providers must undertake individualised risk assessments for patients with high BMI to ensure safe and equitable care. This should include assessment of obstetric and anaesthetic risks, with appropriate measures in place to mitigate potential complications." Finally, we recommend NICE add the following clarification: "Although evidence indicates that people with normal BMI may have higher conception rates than those who are overweight or obese, there is insufficient evidence to support the effectiveness of rapid or extreme weight loss prior to fertility treatment—particularly when achieved	

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				through weight loss medications. Patients should be informed that the impact of such interventions on fertility outcomes has not been adequately evaluated, and further research is required before such strategies can be routinely recommended."	
Avenues	Guideline	016		1.3.14 We agree that AMH alone should not be used as a predictor of pregnancy. However, we believe it would be helpful to add that AMH is helpful to diagnose pathologies that may reduce chances of conception, such as PCOS, and therefore, AMH should form part of the reproductive assessment.	Thank you for your comment. The evidence review addressed the prognostic effectiveness of ovarian reserve to predict outcomes related to assisted and spontaneous conception. The recommendations made based on this evidence therefore address whether ovarian reserve markers should be used in these contexts. This does not preclude their use in other contexts.
Avenues	Guideline	022		1.4.6 It is our experience, as well as the experience of others, that antioxidants can impact sperm quality. We disagree with point 1.4.6 and request a more thorough examination of the literature on this topic.	Thank you for your comment. We conducted a systematic review (Evidence Review S) of randomised controlled trials, and the evidence showed no clear benefit of treating sperm DNA fragmentation using antioxidants, with most studies reporting no benefit for the majority of outcomes. Therefore, the committee agreed that there was

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					insufficient evidence to justify recommending antioxidants. The committee acknowledged the need for further research to identify and validate the best assay, define a threshold for high DNA fragmentation, clarify its association with subfertility and develop a standardised antioxidant and vitamin treatment and dose (particularly given the potential for unexpected adverse effects, as in Ménézo 2007). However, given all these unknowns, the committee agreed it would be premature to draft a fully specified and implementable research recommendation that would be able to deliver conclusive results.
Avenues	Guideline	023		1.4.8 Surgical sperm retrieval should only be offered after a physical assessment of the testicle, and after multiple ejaculations and resuspension centrifugation (Merc), which is an effective method to help avoid surgical intervention. Moreover, surgical sperm retrieval must ensure the amount of testicular extraction is kept to a bare minimum as to avoid an impact on testosterone production after surgery.	Thank you for your comment. Recommendation 1.17.5 advises performing a physical examination of the scrotum and testes. Based on the committee's clinical knowledge and experience, less tissue is removed during a surgical sperm retrieval with micro-TESE (microscopic testicular sperm extraction) compared to conventional TESE. Therefore, the committee recommended micro-TESE for people with non-obstructive azoospermia (please see recommendation 1.25.3) which aligns with existing European Association of Urology (EAU) guideline which

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					recommended micro-TESE as the method of choice for surgical sperm retrieval. We did not review the evidence on multiple ejaculations and resuspension centrifugation (MERC); therefore, it would not be reasonable to make a specific recommendation about it.
Avenues	Guideline	025		We disagree with point 1.5.3 and ask NICE to clarify the level and quality of evidence supporting this recommendation. We refer to our comment number 3 for further context. This recommendation is particularly concerning in relation to patients with polycystic ovary syndrome (PCOS), who face well-documented biological challenges in losing weight and a heightened tendency to regain it. The potential impact of weight loss drugs and the physiological stress associated with calorie restriction or rapid weight loss prior to fertility treatment remain insufficiently studied and warrant caution. This section should explicitly acknowledge that patients with PCOS may require additional counselling and multidisciplinary support to manage weight safely and sustainably.	Thank you for your comment. NICE is currently developing a guideline on PCOS adapting the International evidence-based guideline for the assessment and management of polycystic ovary syndrome. The scope of this guideline includes management of infertility in the context of PCOS. The recommendations related to PCOS have been stood down in anticipation of the new guideline. We have shared your comments with the team working on the PCOS guideline.

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				We also urge NICE to recognise that the phrase "optimising BMI" can be perceived as stigmatising or insensitive by overweight and obese patients, particularly those with PCOS, and to recommend that clinicians approach this topic with empathy and awareness of the psychological impact of such terminology.	
Avenues	Guideline	033		We disagree with point 1.10.4 as it stands. We would suggest instead: "Hysteroscopy may only be offered as a pre-treatment means of improving the outcome of IVF, if uterine or endometrial abnormalities are suspected, see 7 recommendation 1.3.27."	Thank you for your comment. This recommendation is in the section on 'Pre-treatment in IVF' and emphasises that hysteroscopy should not be offered as a pre-treatment in IVF, but if uterine or endometrial abnormalities are suspected, reference to the relevant recommendation earlier in the guideline has been made. No change has been made to this recommendation based on this comment.
Avenues	Guideline	033		We disagree with point 1.10.5 as it stands, and suggest that Era may be offered where endometrial abnormalities are suspected.	Thank you for your comment. The evidence (Evidence Review D) showed no important benefits of ERA (Endometrial Receptivity Array), particularly for critical outcomes, such as live birth and clinical pregnancy. Although there was some evidence showing potential benefits for reducing multiple gestation, the committee agreed that this outcome alone did not justify the risks associated with endometrial biopsy, such as cramping, bleeding, infection, and

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					uterine perforation. Therefore, the committee agreed that ERA should not be offered. Our recommendation is in line with the HFEA, which rated the ERA as a RED add-on and stated that ERA might reduce treatment effectiveness. The committee noted that participants in the primary studies might differ from those likely to receive ERA in practice, as people with recurrent implantation failure were excluded and only euploid blastocysts were included. While these restrictive criteria improved evaluation by controlling for embryonic factors, the committee concluded that if ERA did not improve outcomes under these ideal conditions, it was unlikely to be effective in real-world settings.
Avenues	Guideline	034		We disagree with point 1.10.6. It does not reflect our experience or the experience of others.	Thank you for this comment. As outlined in the Rationale and impact section of the updated guideline, the guideline committee agreed not to recommend immunological treatments as they are not effective in improving fertility outcomes and there are various safety concerns associated with their use.
Avenues	Guideline	035		We disagree with point 1.10.16. It does not reflect our experience or the experience of others.	Thank you for this comment.

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				Natural cycle presents a cost effective approach, particularly for patients with reduced ovarian reserve.	This recommendation has been stood down and the section now refers to the 2025 ESHRE guideline on Ovarian stimulation in IVF/ICSI.
Avenues	Guideline	035		We disagree with point 1.10.22 as it currently stands as it does not reflect our experience or the experience of others. Flushing should be considered in certain circumstances. We agree that non flushing should be the preferred option. But the term "do not use" is too strong.	Thank you for this comment. This section of the guideline has not been updated this time.
Avenues	Guideline	036		We disagree with 1.10.23 as it currently stands as it does not reflect our experience or the experience of others. Publications have demonstrated a marginal but significant benefit of assisted hatching in eggs and embryos that were warmed.	Thank you for this comment. This section of the guideline has not been updated this time.
Avenues	Guideline	036		We disagree with point 1.10.24 as it currently stands, particularly, given the conflict of interest that we have highlighted in comment 1. PGT-A remains the current most effective embryo assessment tool. As with any embryo assessment tool, PGTA does not increase live births per cycle started. Nevertheless, the value of PGT-A comes from managing patient expectations, reducing the chances of miscarriage (as highlighted by HFEA), reducing chances of birth of a	Thank you for your comment. The recommendation on PGT-A has been amended to the following: "Do not offer pre-implantation genetic testing for aneuploidy (PGT-A) as part of fertility treatment **to improve live birth rates.** [2026]"

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				child with chromosomal abnormalities (especially in patients of advanced maternal age), potential for shortening time to baby across a multi cycle journey, and helping patients choose if and when to transition to donation over autologous eggs. PGTA, in cases of repeated miscarriage or failure of implantation failure with good quality embryos, should be offered. Point 1.10.24 is not aligned with evidence, or with the HFEA traffic light grading, and requires a full economic assessment.	
Avenues	Guideline	037		1.10.29 We disagree with the inclusion of age as a factor to justify multiple embryo transfer. In fact, older patients should be *discouraged* from multiple embryo transfer due to the increased maternal and perinatal risks associated with advanced maternal age, including higher rates of obstetric complications and adverse neonatal outcomes. In our view, the decision to transfer more than one embryo should be guided solely by: 1. A history of two or more failed implantation attempts involving good-quality embryos; and 2. Evidence of reduced embryo quality.	Thank you for this comment. This section of the guideline has not been updated this time but embryo transfer strategies has been identified as a potential future topic for update and we will take note of your suggestion. Thank you for the link to the systematic review which would not satisfy NICE's criteria for inclusion as it appears to be an MSc thesis and not a peer-reviewed published paper.

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				We urge NICE to re-evaluate this recommendation in light of current evidence. The focus should be not only on pregnancy rates but also on the significantly increased risk of multiple gestation, especially in geriatric pregnancies. The current guidance risks increasing twin pregnancies among older patients, placing additional strain on NHS maternity and neonatal services while exposing patients to avoidable risks without improving overall live birth outcomes. We have conducted a detailed literature review on this topic and would be pleased to share our findings with NICE to support evidence-based revisions to this section. To support NICE, we have added a link to our systematic literature review: eSET versus DET.pdf	
Avenues	Guideline	037		We disagree with point 1.10.32 which contradicts 1.10.29. A second embryo for transfer may be considered where the patient has had multiple transfers in the past with top quality embryos and unexplained implantation failure.	Thank you for your comment. This section of the guideline has not been updated this time but embryo transfer strategies has been identified as a potential future topic for update and we will take note of your suggestion.

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Avenues	Guideline	038		1.11 We are concerned that the current section on ICSI does not address the use of *rescue ICSI*, which should be considered an essential component of modern IVF practice. Rescue ICSI should be offered for all oocytes that do not demonstrate signs of fertilisation on day 0, with preference given to performing rescue ICSI on day 0 rather than day 1. In addition, *rescue in vitro maturation (IVM)* should be offered on day 1 for patients with fewer than nine fertilised oocytes. Given that IVF cycles incorporating rescue ICSI incur higher costs than conventional ICSI, we recommend that NICE include an updated economic evaluation of this approach. Such an analysis may demonstrate that section 1.11.3 of the current draft is no longer applicable or requires revision. We would also invite NICE to review our validated data and process documentation on rescue ICSI, which may assist in the evidence review and guideline refinement. Process Validation for rICSI v2.pdf	Thank you for this comment. Rescue ICSI was not part of the scope of this guideline update so no comment has been made about it.

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Avenues	Guideline	042		1.14.5 - The following point should be added: **"Do not preclude fertility preservation for medical indications for patients with increased BMI."** This is currently the case on the NHS, and a clear statement from NICE is needed to correct this unfairness.	Thank you for this comment. This was not something that evidence was reviewed on and no comment has been made on this. Such a criterion would not be based on NICE guidance. The guideline committee agreed that eligibility for fertility preservation should be assessed individually and based on clinical judgement and shared decision making. Please note, this section of the guideline has been updated by adding the previous recommendation with some minor edits on the factors to be considered when offering fertility preservation such as diagnosis, treatment plan, expected outcome of subsequent fertility treatment etc.
Avenues	Guideline	045	General	Key recommendations for research should include methods of assessment of oocytes, sperm, embryos and endometrial cells that includes intracellular organelle assessment.	Thank you for this comment. In this update the guideline committee prioritised 5 key research recommendations. All recommendations for research are related to the evidence that has been reviewed and where a gap in evidence has been identified. Your suggested topics were not reviewed for this guideline update.

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Avenues	Guideline	066	017-027	Further to our comment 14, This section of the NICE guidelines is an incomplete and biased interpretation of the evidence available in the literature. We note that The HFEA rated PGT-A as green for reducing the chances of miscarriage for most fertility patients. Why is this not reflected in the assessment for PGT-A? Given the conflict of interest concerns raised in comment number 1, we ask that NICE reconsider this assessment and perform an economic assessment for PGT-A.	Thank you for your comment. The recommendation on PGT-A has been amended to the following: "Do not offer pre-implantation genetic testing for aneuploidy (PGT-A) as part of fertility treatment to improve live birth rates." This reflects the fact that the evidence does not show effectiveness of PGT-A in terms of improving live birth rates, while leaving room for other clinical reasons PGT-A might be considered.
Avenues	Guideline	067	001-025	Regarding time-lapse incubation, the evidence base includes studies showing both improved success rates and others showing no significant difference. It is therefore important that NICE presents the full spectrum of available data rather than focusing solely on RCTs reporting no benefit. The true value of embryo assessment technologies such as time-lapse systems cannot be fully captured through traditional RCT design. These tools function primarily as predictive technologies, and their clinical utility should be evaluated through studies assessing predictive accuracy, clinical decision-making value, and overall patient outcomes.	Thank you for your comment. The focus of the evidence review on time-lapse imaging was to determine whether embryo selection guided by the use of time-lapse imaging was more effective than standard embryo selection techniques, for which the evidence showed no clinically important benefit of time-lapse imaging on live birth, ongoing pregnancy, or clinical pregnancy rates. However, the committee were aware of the potential benefits of undisturbed incubation, including a reduction in potential for human error. As a result, the committee felt it would be inappropriate to make a recommendation either for or against the use of time-lapse imaging, as these systems are already widely available and have future potential; but they cannot currently be recommended over other incubation

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				We recommend that NICE conduct or reference an updated *economic and risk assessment* to determine the cost-effectiveness and potential patient benefit of time-lapse incubation technology, rather than drawing conclusions solely from outcome-based RCTs.	systems on the basis of the available evidence. The committee also recognised that there might be future potential for embryo selection guided by continuous time-lapse monitoring, given that it is likely that artificial intelligence (AI) algorithms will improve with the development of big data analytics. The committee agreed that further research would be needed to develop and to test these algorithms but that it would be premature to draft a fully specified and implementable research recommendation that would be able to deliver conclusive results about the potential benefits of time-lapse imaging for embryo selection.
Avenues	Guideline	068	General	As discussed in comment 17, Rescue ICSI must be taken into account. We refer to the Avenues Process Validation: Process Validation for rICSI v2.pdf	Thank you for this comment. This section of the guideline was not part of the scope of this update.
Breast Cancer Now	Guideline	General	General	It is our understanding that people undergoing treatment to reduce their risk of breast cancer are entitled to fertility preservation treatment, however neither this guideline nor NICE CG164 makes specific reference to this group. Given that NICE CG164 is also about to be updated it would be good to see people undergoing treatment to reduce risk's access to fertility preservation mentioned across the two guidelines.	Thank you for your comment. The recommendations on fertility preservation apply to anyone with a medical indication likely to impair their reproductive potential, including medical or surgical treatments /surgical interventions or medical conditions. It is not possible to list all populations covered by these recommendations, because in some cases the need for fertility preservation will be situational and will need to be discussed with the patient using the clinician's

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					judgment, and to attempt to do so could risk important patient groups being missed. The rationale section contains further information about the populations covered, as well as context about how it is important that discussions around preserving fertility are held at the earliest opportunity.
Breast Cancer Now	Guideline	General	General	We suggest adding in '*for women with an altered breast cancer gene, refer to genetics team to discuss PGT when breast cancer treatment is complete'.*	Thank you for your comment. It is not clear from the comment which section this is referring to. However, this was not something that came up in the evidence and no change has been made.
Breast Cancer Now	Guideline	042	010	We're pleased to see the updated guideline has explicitly included that the lower age limit should not apply when offering fertility preservation for people undergoing medical treatment.	Thank you for this comment.
BRITISH ASSOCIATION FOR NUTRITION AND LIFESTYLE MEDICINE (BANT)	Guideline	025	007	Insert new first bullet point at 1.5.1: - Advise individuals to consider lifestyle factors that may influence reproductive outcomes, including sleep quality, nutrition, and stress management. Rationale: Emerging evidence highlights the role of DNA methylation in regulating key reproductive processes such as gametogenesis, genomic imprinting, and early embryonic development. Lifestyle factors, and particularly sleep quality, can significantly influence methylation dynamics.	Thank you for this comment. In this guideline update we did not look at the evidence concerning lifestyle factors such as sleep quality, nutrition and stress management on reproductive outcomes. However, these lifestyle factors may be considered in future updates if considered a priority.

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				Disrupted sleep has been shown to alter methylation at loci relevant to neuroendocrine and systemic function, potentially impairing fertility outcomes. For example, Adetunji et al. (2025) review how environmental and behavioural factors modulate methylation in both male and female reproductive systems. Tang et al. (2023) further demonstrate that poor sleep quality in women of childbearing age is associated with infertility, mediated by methylation changes at specific CpG sites. Including basic lifestyle advice, especially around sleep hygiene, may support methylation-dependent pathways and improve reproductive health. Refs: 1. Adetunji AO, Owusu H, Adewale EF, Adesina PA, Xedzro C, Saliu TP, Islam S, Zhu Z, Morenikeji OB. DNA Methylation: A Key Regulator in Male and Female Reproductive Outcomes. Life (Basel). 2025 Jul 16;15(7):1109. doi: 10.3390/life15071109. PMID: 40724612; PMCID: PMC12298693. 2. Tang, Y., Gan, H., Wang, B. *et al.* Mediating effects of DNA methylation in the association between sleep quality and infertility among women of childbearing age. *BMC Public Health* **23**, 1802 (2023). https://doi.org/10.1186/s12889-023-16681-w	

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British Fertility Society	Guideline			The draft guideline recommends restricting IVF with own eggs above the age of 40, and not offering IVF above the age of 41. The stated reason is that, according to the economic model used, the treatment is not cost-effective due to low success rates. However, the option of IVF with donor eggs does not appear to have been considered. Evidence consistently shows that IVF using donor eggs achieves significantly higher success rates than IVF with own eggs in women aged 35–41, where it is already considered cost-effective. It is therefore reasonable to presume that donor-egg IVF would also be cost-effective in women over 42. has this been considered? While pregnancy at advanced maternal age does carry increased risks, these can be assessed individually. Current evidence indicates that outcomes are generally safe in the absence of additional risk factors.	Thank you for your comment. Guidance about IVF when using donor eggs was not within the scope of this guideline update and no cost-effectiveness analysis has been conducted on this, therefore no recommendations have been made on this. Please note, NICE welcomes topic suggestions from stakeholders which will be considered for NICE topic prioritisation process: Topic suggestion | NICE.
British Fertility Society	Guideline	005		Section 1 states these recommendations are for people with health-related fertility problems or may require interventions to preserve fertility. Why is there is no	Thank you for your comment.

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				mention of fertility treatment for LGBTQ+ people here? (acknowledging that the guidance elsewhere is more inclusive).	The scope of the guideline, consulted on and published in 2022, defined the guideline's population remit as: "**Groups that will be covered in the update** • People with health-related fertility problems • People who may require interventions to preserve fertility because of high risk of fertility problems due to clinical conditions or medical or surgical interventions In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination. The guideline will be applicable to all people seeking assessment and treatment of health-related fertility problems who meet these criteria, irrespective of their sexual orientation, partnership status or gender reassignment. This includes single people, people in

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					heterosexual relationships, people in same sex relationships, people who are non-binary, undergoing or have undergone gender transition and people using a surrogate." The scope also defined the topic areas to be updated and not all treatment scenarios were included. For example, we recognise that the guideline may be less relevant for same sex female or male couples initially seeking fertility treatments. The key issue to bear in mind is that the guideline only covers assessment and treatment for health-related fertility problems and as such does not exclude people based on their sexual orientation or relationship status and the guideline's recommendations do not determine treatments based on the person's sexual orientation or relationship status. In relation to fertility preservation, the guideline has now expanded the population for whom fertility preservation should be offered to include people with medical indications for fertility preservation, not just people who are preparing for cancer treatment. Medical indications for fertility preservation could include gender-affirming treatments that are likely to impair fertility.

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British Fertility Society	Guideline	006	024	1.2.2 over 55% women under 40 will conceive within 6 months donor insemination, with cumulative pregnancy rate over 79% These figures are based on table 2 (page 8) which features ICI data from 40+ years ago and more recent IUI data, which is based on estimates and assumptions (and very small numbers). Can more recent data be used?	Thank you for your comment. The recommendation referred to in the comment is about the chance of conception using IUI, and the figures are based on the most recent IUI data from HFEA (presented in more detail in Table 2). Since the consultation, we have further updated these figures in the recommendation and in Table 2 using latest information from HFEA dashboard, and including more age categories in Table 2. We realise the data on ICI is old but because ICI is not recommended, it was not considered a priority to search for newer data on this.
British Fertility Society	Guideline	008		Page 8: Why does Table 2 present probability of conception rather than live birth? There is also a significant drop in DI/IUI efficacy after 38yrs, so it is not good to group the data by age <35 and 35 – 39y. We suggest to include the statistics for women aged under 40 years and under 35 years separately given the importance of this upon clinical pregnancy. Large studies from China/US show lower cumulative probability of clinical pregnancy after 6 cycles, including very modest returns on cycle 5 and 6. There is no reference to stimulated DI/IUI, which is more likely to be used for later cycles. There is also no consideration of multiple birth, which is an important side effect of stimulated DI/IUI.	Thank you for your comment. We have updated the data in Table 2 around IUI using latest data from HFEA dashboard. The table now includes more age categories ranging from 18 years to over 44-year-olds. The data included in the table includes both unstimulated and stimulated cycles.

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British Fertility Society	Guideline	009	022	1.2.12 can the recommendations include advice regarding vaping (noting that this may impact treatment eligibility)?	Thank you for your comment. The impact of nicotine-containing products, e-cigarettes and vaping on fertility was not within the scope of this guideline update and no evidence has been reviewed on this, so the committee are unable to make recommendations on this topic. Several stakeholders made a similar comment and we have noted this as a potential topic for future updates.
British Fertility Society	Guideline	010	002	1.2. 14 Many patients are now taking GLP1 agonists for obesity: can the guidance include discussion of these drugs?	Thank you for this comment. Based on your and other stakeholders' feedback, the committee agreed to amend the recommendation on prescribed, over-the-counter and recreational drug use to include examples of drugs such as GLP-1 agonists and others.
British Fertility Society	Guideline	010	015	1.2.17 low body weight: it is not appropriate to suggest merely that the person should gain weight without investigating potential causes of irregular/absent menses.	Thank you for your comment. Recommendation 1.9.4 was not within the scope of this guideline update to review new evidence for. We don't disagree with your comment but this would be outside of the remit of this guideline to address, however, we expect health care professionals to use their clinical and professional judgment in their practice to consider

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					potentially underlying causes or other considerations relevant to the clinical scenario.
British Fertility Society	Guideline	012	001	1.2.27. Can previous ectopic pregnancies, previous recurrent ovarian cystectomies, multiple abdomino-pelvic surgery be added?	Thank you for your comment. The committee agreed to add these as examples of clinical causes of infertility in the Terms used in this guideline section.
British Fertility Society	Guideline	012	003	1.2.28 We disagree with the approach to assess and investigate fertility unless not conceived after 6 cycles selfDI/IUI. Firstly, this statement inadvertently appears to support artificial insemination outwith of the clinic environment. Secondly, given that donor sperm is a precious resource, checking ovulation, chlamydia screening, performing ultrasound scan and tubal patency testing is reasonable (as per 1.12.7 and 1.12.8). Does the last sentence (lines 10 – 11) mean that semen analysis is not required prior to IUI?	Thank you for your comment. The recommendation you're referring to says "further clinical assessment and investigation" so the expectation is that there may have been initial or earlier assessment and investigations. Based on consultation comments, the committee have now also added a recommendation about advising people seeking donor insemination to conceive to have treatment in a licensed clinic to ensure clinical safety and legal parenthood (see recommendation 1.1.4 and its associated rationale and impact section).
British Fertility Society	Guideline	014		1.3 semen analysis, is it correct to summarise a semen report with just one suboptimal parameter as "abnormal"? We suggest rewording this.	Thank you for this comment. The guideline committee agreed that 'abnormal' is sufficiently defined in recommendation 1.17.1 and so no changes have been made.

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British Fertility Society	Guideline	014	001	1.3.3. Please change this sentence "If the result of the first semen analysis is abnormal, offer a repeat confirmatory test" to "If the result of the first semen analysis includes a suboptimal value for any parameter, offer a repeat test".	Thank you for this comment. The guideline committee agreed that the current wording was sufficient and so no changes have been made to this recommendation. Furthermore, they discussed that 'abnormal' was sufficiently defined in recommendation 1.17.1and that it was also down to clinical judgement whether one or more parameters were abnormal or not and required a repeat test.
British Fertility Society	Guideline	014	012	1.3.6 The NICE proposal to "not carry out testing for sperm DNA integrity (fragmentation)" is contrary to WHO 2021 guideline which dedicates 19 pages to this testing. WHO 2021 states "multiple meta-analyses published in recent years indicate that it may affect embryo development, implantation, and pregnancies in both natural and assisted reproduction". Has the evidence regarding this been assessed?	Thank you for your comment. NICE makes independent recommendations based on evidence. We conducted a review (Evidence Review S) that aims to examine the impact of treating DNA fragmentation on clinical outcomes (including live birth, clinical pregnancy, miscarriage, pregnancy loss, embryo quality), and subsequently whether testing is worthwhile. The guideline committee agreed that based on the evidence showing no clear benefits of treating sperm DNA fragmentation, there was no justification for routine testing of sperm DNA fragmentation. In other words, since treatment does not improve clinical outcomes, the DNA fragmentation test does not lead to any actionable steps. In addition, the committee were concerned that sperm DNA assays are expensive tests which can take weeks to get results for. Based on the potential

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					advantages of saving lost time in time-sensitive fertility pathways, and without effective treatments to rationalise testing from a potential cost-saving perspective, the committee agreed that testing for sperm DNA integrity (fragmentation) should not be carried out.
British Fertility Society	Guideline	014	014	1.3.7 Can it be clearer whether Y microdeletion testing is indicated only for those with azoospermia? – there are definitely cases of AZFc in severe OATS. We would like to have clearer guidance re investigations for severe OATs as this is more commonly managed.	Thank you for your comment. The committee agreed that there could be cases of AZFc in severe OATS. The committee was also aware of a systematic review of 37 European and North American studies (N=12492 oligozoospermic men), which showed that the majority of Y chromosome microdeletions occur in those with sperm concentrations less than or equal to 1 million per ml, while fewer than 1% are identified in those with sperm concentrations greater than 1 million ml (Kohn 2019). Therefore, the recommendation 1.17.7 has been amended. The committee recommended Y chromosome testing for those with idiopathic azoospermia or a sperm concentration of less than 1 million per ml because in clinical practice testing for Y chromosome microdeletion would not be offered to people with known causes of azoospermia and testing those with higher sperm concentrations (>1 million per ml) might not be cost effective.

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British Fertility Society	Guideline	014	027	1.3.10 it would be valuable to provide a guide number for 'very low sperm count', eg <1 or 5 million/ml.	Thank you for this comment. The committee considered this and the recommendation has been amended and 'a very low sperm count' has been replaced with 'a persistent sperm concentration of less than 5 million per ml'.
British Fertility Society	Guideline	015		The term 'spontaneous conception' is repeatedly used. This is an incorrect usage, there is nothing spontaneous about it. Please use the term 'natural conception' to refer to when conception occurs in vivo.	Thank you for this comment. The guideline committee discussed the terms 'spontaneous' and 'natural' and other options but agreed that spontaneous conception or pregnancy was their preferred term for this guideline. The committee did not want to use the term 'natural' because it would imply other ways of conceiving would be 'unnatural'. The term 'spontaneous conception' has been added to the Terms used in this guideline.
British Fertility Society	Guideline	017	006	1.3.18 Progesterone testing for ovulation: no change has been made in this update. We note that ESHRE guidance on ovulation testing does not recommend serum progesterone measurement when a woman has regular cycles. Given the importance of this issue, we feel it should be addressed.	Thank you for your comment. This was not within the scope of the guideline update, so no evidence was reviewed on this issue.
British Fertility Society	Guideline	017	011	1.3.19 Likewise we are concerned that testing for ovulation in women with prolonged cycles is unhelpful.	Thank you for your comment.

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				How does establishing delayed ovulation help with management of conception delay?	This was not within the scope of the guideline update, so we did not review evidence on this. It would not be reasonable to amend it without reviewing the evidence.
British Fertility Society	Guideline	018	002	1.3.23 We are disappointed that NICE has not changed its position on thyroid function testing, especially as doing so is recommended by RCOG and ASRM and has become standard practice across the UK. Can this be updated with assessment of more recent evidence? We do recognise the need for additional research in this area.	Thank you for your comment. This was not within the scope of the guideline update, so no evidence was reviewed on this issue.
British Fertility Society	Guideline	021	012	1.3.45 the recommendation for testing for coeliac disease contrasts with the above. Has there been adequate assessment of the implications and value of this recommendation?	Thank you for your comment. The recommendation to consider coeliac testing is from the NICE guideline NG20 on coeliac disease. The committee's considerations on this are documented in the NG20 Full guideline document, available in: Evidence | Coeliac disease: recognition, assessment and management | Guidance | NICE.
British Fertility Society	Guideline	025	022	1.5.4 – Why is letrozole not covered in the guidance for women with PCOS? – this seems outdated and divergent from RCT-based evidence and current clinical practice. The statement on only offering 6 months treatment with CC is inappropriately inflexible and contrasts with the recommendation of 12 cycles of IUI.	Thank you for your comment. NICE is currently developing a guideline on PCOS adapting the International evidence-based guideline for the assessment and management of polycystic ovary syndrome. The scope of this guideline includes management of infertility in the context of PCOS. The

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					recommendations in the section on Hypothalamic-pituitary-ovarian dysfunction (predominantly PCOS) have been stood down in anticipation of the new guideline. We have shared your comments with the team working on the PCOS guideline.
British Fertility Society	Guideline	028	013	1.6.3 – Did the committee consider the risk of ovarian cancer when the recommendation was made regarding tubal occlusion being equal to salpingectomy? There is a shift in practice towards this in general gynaecology.	Thank you for this comment. In the Benefits and harms section of the evidence review H on Surgery for hydrosalpinges before IVF, the guideline committee discussed potential benefits of salpingectomy in terms of long-term cancer risk reduction and emphasised that this might be another reason for preferring salpingectomy over tubal occlusion.
British Fertility Society	Guideline	029	005	1.6.5 This section on uterine surgery is very limited. Can guidance on uterine fibroids, uterine septum and adenomyosis be added? Additionally we feel that not performing metroplasty for uterus didelphys or bicornuate uterus should be explicitly included.	Thank you for your comment. Section on uterine surgery was not updated in this guideline update and no evidence was reviewed on these issues.
British Fertility Society	Guideline	029	018	1.7.2 this statement does not make sense – offer 6 x IUI if not conceived after 6 x DI? This is similar to 1.2.28 above.	Thank you for this comment. The wording of this recommendation has been updated and hopefully it is clearer now. As defined in the 2022 scope of this guideline, the guideline only covers health-

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					related fertility problems, defined in the scope as follows: "In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination." Therefore, the initial 6 cycles of donor insemination for those without a known health-related impediment to fertility is not covered by this guideline. The guideline recommends in 1.16.5 that after 6 'unsuccessful' cycles of artificial insemination, further clinical assessment and investigations should be offered. Recommendation 1.37.2 which you are referring to then recommends a further 6 cycles of donor insemination provided there are no contraindications or suspected or known clinical causes of infertility. This equals a total of 12 cycles before IVF is considered (see recommendation on IVF access in section 1.39).
British Fertility Society	Guideline	031		1.9.3 The prognosis for DI/IUI is poor for those ≥38yrs. Please review the guidance recommending 12 cycles artificial insemination before moving to IVF for those <42y	Thank you for your comment. No evidence was reviewed on this section in this guideline update, so the committee were unable to update this. Please note that we have updated the information in Table 2 of the guideline regarding the cumulative

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					pregnancy rate after 6/12 cycles of IUI based on age. We have now added further age categories, based on latest HFEA data. Based on this data, the biggest drop in pregnancy rate appears to be from 40 years.
British Fertility Society	Guideline	032		1.9.6 This is quite difficult to interpret. i.e., if 2 full self-funded cycles, will couple then be recommended / offered just 1 NHS funded cycle not 3 – note if < 40 y suggest can have further 3 cycles if 1st 3 not successful. The statement 'previous self-funded treatment should not preclude NHS-funded IVF treatment' is difficult to understand with sentence one in mind. We disagree with that previous self funded IVF should count towards the number of cycles offered by the NHS: this does not encourage honest sharing of information, and the practice largely reflects the difficulties couples experience in accessing timely NHS IVF.	Thank you for this comment. The recommendation has been revised to make it clearer. The number of IVF cycles the NHS should provide is not independent of self-funded cycles as not achieving a pregnancy in successive cycles (regardless of where they are funded) is a marker of poorer prognosis and therefore declining treatment effectiveness.
British Fertility Society	Guideline	032		1.9.8 and 1.9.9 would be best prior to 1.9.4	Thank you for this comment. The order of the recommendations has been changed as suggested.

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British Fertility Society	Guideline	032	005	1.9.7 please consider including normal ovarian reserve – or similar – as well as criteria in 1.9.3 for offering 1 cycle IVF for women 40/41 yrs old.	Thank you for your comment. Based on the evidence review A, the committee agreed that taking into account ovarian reserve is relevant for all patients considering IVF treatment, not only those aged 40+. This is reflected in the recommendation 1.39.2.
British Fertility Society	Guideline	034		1.10.7-10 We why there are no changes here since 2013 despite advances such as the introduction of progestogen-primed cycles?	Thank you for your comment. The recommendations in this section of the guideline have been stood down and now cross-refers to the 2025 ESHRE guideline on Ovarian stimulation in IVF/ICSI.
British Fertility Society	Guideline	035	016	Heading before 1.10.18: should be 'Triggering oocyte maturation in IVF' rather than ovulation. 1.10.18 Why is there is no mention of GnRH agonist triggering, despite evidence that it reduces the risk of OHSS and that it is in widespread use?	Thank you for this comment. The recommendations in this section of the guideline have been stood down and now cross-refers to the 2025 ESHRE guideline on Ovarian stimulation in IVF/ICSI.
British Fertility Society	Guideline	035	027	1.10.22 it should be 'during' not 'before' oocyte retrieval.	Thank you for this comment. This section of the guideline has not been updated this time.
British Fertility Society	Guideline	036		1.10 We would like to see a statement on ovarian hyperstimulation and freeze all approach from a safety perspective – this is overlooked and important	Thank you for your comment. The guideline now refers to the recently updated ESHRE guideline on Ovarian stimulation for IVF/ICSI which provides guidance on

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					ovarian stimulation, including freeze all cycles and preventing OHSS. Other recommendations e.g. 1.33.1, 1.33.2, 1.52.2 and section 1.54 also cover the safety concerns related to ovarian stimulation.
British Fertility Society	Guideline	036	003	1.10.23 assisted hatching: this is in the wrong place in the document as it is an embryology procedure.	Thank you for your comment. The committee agree and we have moved the recommendation to the section about embryo transfer strategies.
British Fertility Society	Guideline	036	008	1.10.24 PGT-A: there is a very abrupt recommendation which we feel does not reflect the nuances of this complex topic. Older women who are at risk of having abnormal genotypical oocytes may benefit from use of PGT-A to reduce the risk of transfer of aneuploid embryos and subsequent miscarriage. Those with a history of recurrent miscarriage may also choose and benefit from PGT-A especially if recurrent miscarriage is due to aneuploidy. Understanding ploidy status of embryos created will also provide important data for patients to consider donor gamete treatment. This section does not recognise evidence that it can help reduce miscarriage (and it has a green light from HFEA on that). The cost	Thank you for your comment. The recommendation on PGT-A has been amended to the following: "*Do not offer pre-implantation genetic testing for aneuploidy (PGT-A) as part of fertility treatment* ***to improve live birth rates****. [2026]*"

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				analysis does not fully reflect this and whilst recurrent miscarriage is outside the scope, miscarriage is not and the full scope of its potential benefit for both fertility and miscarriage patients does not appear to have been fairly considered. Have these issues been assessed in sufficient depth?	
British Fertility Society	Guideline	036	013	1.10.26 We are disappointed this has not been updated since 2004 since the probability of successful implantation is on a continuum, and such a dogmatic cutoff is inappropriate. Can this be rephrased to reflect current evidence?	Thank you for your comment. In this guideline update, we did not review the evidence on the impact of endometrium thickness on IVF outcomes, so it was not possible to update this recommendation. However, this may be considered in future updates if it is identified as a priority.
British Fertility Society	Guideline	037		1.10.29 We are very concerned by the guidance on double embryo transfer – we have made significant progress with single embryo transfer policies and this deviates from clinical consensus – the maternal risks in older women who are at significantly higher risk of complications from double embryo transfer is overlooked by these recommendations. Can this be reconsidered to reflect these issues?	Thank you for your comment. This section of the guideline has not been updated this time but embryo transfer strategies has been identified as a potential future topic for update and we will take note of your suggestion.

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British Fertility Society	Guideline	038		1.10.35 Has the evidence that pregnancy after FET in natural cycles is associated with fewer pregnancy complications been considered?	Thank you for this comment. This section of the guideline has not been updated this time.
British Fertility Society	Guideline	038	022	1.11.3 The statement "Do not use ICSI for non-male factor fertility problem…who have normal semen parameters. [2026]" is generally welcomed, but does not take into account rarer situations where ICSI would be appropriate. An example is couples where they have a high polyspermy rate with a previous conventional IVF cycle. In such instances, this is a "non-male factor fertility problem" as it is a problem with the timing of the cortical reaction in the oocyte(s) and ICSI could prevent polyspermy.	Thank you for your comment. As stated in 'Benefits and harms' section of Evidence Review L, the committee agreed that, although in most cases ICSI would not be recommended over standard IVF for those with non-male factor fertility problems, there may be some circumstances where ICSI might be indicated such as when a previous IVF treatment cycle has resulted in failed fertilisation or very low fertilisation rate as there could be an undiagnosed sperm factor dysfunction; or when pre-implantation genetic testing is indicated for a monogenic disorder in order to prevent contamination from paternal genes. Please see recommendation 1.50.2, which addresses these populations.
British Fertility Society	Guideline	039	008	1.12.1 "severe in semen quality" should be rewritten to make sense	Thank you for your comment. This has been corrected to "severe deficits".
British Fertility Society	Guideline	041		1.13.1 What is the age cut-off for use of donor eggs? – if IVF not to be offered to women > 41 y is this similarly for donor egg treatment – this will be very important to clarify.	Thank you for this comment.

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					IVF using donor eggs was not part of the update. Please note, NICE welcomes topic suggestions from stakeholders which will be considered for NICE topic prioritisation process: Topic suggestion | NICE.
British Fertility Society	Guideline	041		1.13.1 Why is this being limited to chemotherapy and radiotherapy? – with evolving medical therapies it would be appropriate to broaden this to any medical therapy causing ovarian insufficiency How many cycles will this group receive? – outcomes even with donor eggs are variable and if couples < 40 years are entitled potentially to up to 6 cycles with their own eggs I would want to see clearer guidance for women with POI to have > 1 full egg donation cycle	Thank you for this comment. This recommendation has been amended to refer to any treatment resulting in premature ovarian insufficiency, not only chemotherapy or radiotherapy. In terms of the number of cycles, this was not part of the scope of the update and so no further recommendations have been made.
British Fertility Society	Guideline	042		1.14 We are pleased to see the recognition of the use of fertility preservation for a broader range of indications	Thank you for this comment.
British Fertility Society	Guideline	042		1.14.2 please clarify comment relating to eligibility criteria, including age limits, for NHS funded FP. Does NICE recommend no eligibility criteria for NHS FP? May be preferable to suggest that criteria can be modified?	Thank you for this comment. The guideline committee did not want to be too prescriptive about the age limit for fertility preservation and agreed that eligibility for fertility preservation should be assessed individually and based on clinical judgement. Additionally, this section of the guideline has been updated by adding the previous recommendation with some minor edits on the factors to be considered when offering fertility preservation such as diagnosis,

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					treatment plan, expected outcome of subsequent fertility treatment etc.
British Fertility Society	Guideline	042	003	1.14.1 line 3 "...likely to impair their fertility" should be rephrased to reflect loss or significant threat to fertility	Thank you for this comment. The guideline committee felt that the recommending wording was sufficient and no change to this has been made. However, they agreed to reinstate the 2013 recommendation with some minor edits on the factors to be considered when offering fertility preservation such as diagnosis, treatment plan, expected outcome of subsequent fertility treatment etc.
British Fertility Society	Guideline	067		The sentence "time-lapse systems may have other benefits, including time-lapse incubation" is incorrectly worded. It is simply the undisturbed culture that provides the benefit, not the time-lapse aspect.	Thank you for your comment. We have corrected the text based on your feedback.
British Fertility Society	Guideline	040 & 042		1.12.5 and page 42: 1.13.2 UK guidelines for medical and laboratory procurement and use of sperm, oocyte and embryo donors (2025) has been out to consultation and should be included instead of 2019 guidelines, if published.	Thank you for your comment. Because sperm donor recruitment, selection and screening and oocyte donor screening are within the remit of HFEA Code of Practice, the committee agreed to remove these recommendations.
British Infertility Counselling Association (BICA)	Evidence review C	General	Psychological Care	The guideline should acknowledge that psychosocial burden is amplified by long waits, repeated unsuccessful cycles, funding uncertainty, and inequity of access — not only by the diagnosis itself. This has material impact on	Thank you for this comment. It is not clear what specifically this comment refers to. The section of the guideline on psychological effects of fertility problems was not updated; no evidence was

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				wellbeing and should inform the strength of recommendations on counselling availability.	reviewed on this, thus no new recommendations were made.
British Infertility Counselling Association (BICA)	Guideline	General	Funding	The framing that ICBs must "weigh up local priorities" risks permitting ongoing non-implementation of NICE fertility guidance, which has historically produced entrenched inequity. We recommend strengthening the implementation wording to avoid permissive or selective adoption by commissioners.	Thank you for your comment. This comment appears to be referring to the press statement from NICE when the draft guideline consultation started, specifically regarding the number of IVF cycles recommended. Thank you for the feedback. The recommendation about offering initial 3 cycles is based on evidence that showed it to be cost-effective. In fact, we state in the guideline that the evidence for this recommendation is now stronger than before. While NICE makes recommendations based on the best available clinical and cost-effectiveness evidence, we acknowledge that decisions about commissioning and funding are made at the local level.
British Infertility Counselling Association (BICA)	Guideline	005	025	BICA is concerned that signposting alone is insufficient to meet the psychological impact of fertility investigations and treatment. Counselling should be explicitly offered as a core element of care rather than left to local provision or commissioning variation. Where the guideline currently refers to "peer group or other relevant organisation", we recommend the wording is amended to "peer group, **support group**, or other	Thank you for your comment. The guideline recommends that counselling should be offered, see recommendation 1.2.3. Based on your and other stakeholders' feedback, the recommendation previously referring to "peer group or other relevant organisation for support" has been

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				relevant organisation" to avoid de-emphasising established structured support groups.	amended by the committee to simply say "a relevant organisation for support".
British Infertility Counselling Association (BICA)	Guideline	042 – 044		Section1.12 - Where counselling/implications counselling guidance is referenced, we recommend inclusion of BICA's *Guidelines for Good Practice* and the forthcoming BICA professional resource for delivering implications counselling, rather than referring solely to the HFEA Code of Practice.	Thank you for your comment. We would not refer to an external guideline without assessing its quality and relevance, including formal appraisal with AGREE II where appropriate. As this was not part of the guideline update, we have not done this. Also, because counselling for sperm and oocyte recipients and donors is covered within the HFEA Code of Practice, the committee decided to remove this recommendation from the guideline.
Care Fertility	Evidence review 0	General	General	We agree that the evidence regarding whether time lapse can inform and improve embryo is inconclusive despite a number of RCTs. We believe that more consideration should have been given to the standardised (uninterrupted) time lapse culture environment, compared with standard incubation, coupled with variable practices in terms of door openings and embryo evaluations. Another benefit, which has been largely overlooked in this review, is the precision of fertilisation assessment and the use of time lapse to increase the pool of utilisable embryos. This publication has informed the new oocyte and embryo Istanbul consensus guideline by ESHRE and Alpha. Barrie A, Smith R, Campbell A, Fishel S. Optimisation of the timing of fertilisation assessment for	Thank you for your comment. The focus of the evidence review on time-lapse imaging was to determine whether embryo selection guided by the use of time-lapse imaging was more effective than standard embryo selection techniques, for which the evidence showed no clinically important benefit of time-lapse imaging on live birth, ongoing pregnancy, or clinical pregnancy rates. However, the committee were aware of the potential benefits of undisturbed incubation, including a reduction in potential for human error as you have highlighted. As a result, the committee felt it would be inappropriate to make a recommendation either for or against the use of time-lapse imaging, as these systems

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				oocytes cultured in standard incubation: lessons learnt from time-lapse imaging of 78 348 embryos. Human Reproduction. 2021 Nov 1;36(11):2840-7.	are already widely available and have future potential; but they cannot currently be recommended over other incubation systems on the basis of the available evidence. The study referenced would not have been included in the HFEA's evidence review as it is non-comparative.
Care Fertility	Evidence Review L	011	004-007	Committee found no advantage with ICSI compared to standard IVF in non-male factor cases. Previous NICE guideline stated ICSI should be used in cases of 'severe' male factor, but did not define specific parameters for 'severe' 6th edition of the World Health Organization Laboratory Manual for Examination and Processing of Human Semen (WHO, 2021) defines 'normal', however there is also the notion of mild" oligoasthenoteratozoospermia; sperm concentration of 5–20 × 106 /ml and/or motility of 5%–15%, and/or 2%–8% morphologically normal forms according to Kruger strict criteria (Elizur et al., 2004). Mild male factor can often be suitable for standard IVF. Consider defining 'severe' male factor as sperm parameters falling below mild thresholds.	Thank you for this comment. The updated guidance does not specifically define the severity of male fertility factor as sperm parameters below mild thresholds. Instead, the new guideline recommends considering ICSI when there is abnormal semen parameters, taking into consideration severity. The guideline allows health care professionals to use their clinical judgement when interpreting semen parameters warranting ICSI.

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Care Fertility	Evidence Review N	006	013-018	'PGT-A involves testing the DNA of some cells removed from an embryo for chromosomal abnormalities to determine if an embryo should be excluded from transferred. The aim is to select embryos with a higher potential for implantation, and the technique is sometimes offered to people with previous IVF attempts that did not result in a live birth. However, PGT A may reduce the number of embryos available for transfer and overall it is unclear is this add-on improves the chances of a live birth.' To determine this statement, the number of embryo transfers that did not achieve a live birth needs to be included.	Thank you for your comment. The introduction is intended to briefly describe the intervention of interest and outline the reasons for its investigation. Discovering whether PGT-A reduces the number of potentially eligible embryos available for transfers was one of the goals of the review.
Care Fertility	Evidence Review N	014	037-039	'The committee noted that that PGT-A often reduces the number of embryos available for transfer and can therefore lower the likelihood of a fertility patient undergoing embryo transfer at all, lowering their chances of having a baby' Where is the evidence that transferring an aneuploid embryo is going to increase your chance of a live birth? Based on one study, because study's that included a euploid ET were excluded. The nuance is around identifying aneuploid embryos and mosaic embryos.	Thank you for your comment. This statement is not intended to imply that transferring aneuploid embryos increases the chance of a live birth. There are multiple risks associated with the use of PGT-A that could reduce the availability of potentially viable embryos, which are listed in this review under the heading 'HFEA treatment ratings': although current PGT-A techniques are mostly very accurate, the test may give the wrong result (it may miss an abnormality or detect one that isn't there), and if a test result is not accurate, healthy embryos may be discarded; in some

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					cases viable embryos could be discarded if they are unsuitable for biopsy, or because embryos are reported as mosaic; mosaic embryos may have a lower chance of pregnancy but there are reports of healthy live births after a transfer of a mosaic embryo; the removal of cells for testing can damage an embryo and prevent it from successfully developing.
Care Fertility	Evidence Review N	015	011-015	The committee acknowledged that there could be the potential for people with recurrent miscarriage to benefit from PGT-A, but this group is outside the scope of this guideline. Should be included.	Thank you for your comment. The scope of the guideline cannot be expanded to include this population at this stage.
Care Fertility	Evidence Review N	036	008	We support the committee's position that PGT-A should not be adopted as a routine add-on for all IVF patients. However, the current draft guidance is overly prescriptive and omits clinically important nuance. There is a well-documented role for PGT-A as an embryo-selection tool in carefully selected cohorts (notably women of advanced maternal age, patients with recurrent implantation failure [RIF] or recurrent pregnancy loss [RPL], and patients already undergoing PGT-M), where PGT-A meaningfully reduces miscarriage, shortens time-to-pregnancy, and can be cost-saving on a per-patient basis (Simopoulou et al., 2021; Eliner et al., 2025). NICE's recommendation	Thank you for your comment. The recommendation on PGT-A has been amended to the following: "Do not offer pre-implantation genetic testing for aneuploidy (PGT-A) as part of fertility treatment to improve live birth rates." This reflects the fact that the evidence does not show effectiveness of PGT-A in terms of improving live birth rates, while leaving room for other clinical reasons PGT-A might be considered. The committee agreed that a 'do not routinely offer…' recommendation would be too vague and risk misinterpretation, increasing the potential for

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				should therefore be revised to preserve these clinically justified exceptions and to mandate structured data collection/audit where PGT-A is used (ASRM Committee Opinion, 2024). **Detailed evidence and rationale** **1. Advanced maternal age — time, embryo attrition and opportunity cost** The proportion of aneuploid embryos rises steeply with maternal age, resulting in increased failed transfers and miscarriages, which consume time and ovarian reserve (Munné et al., 2019; Franasiak et al., 2014). Observational and cohort data show PGT-A shortens time to a live birth and increases the probability of live birth within 12 months in older patients (≥38 years), even when cumulative lifetime estimates are equivocal for unselected populations (Eliner et al., 2025; Simopoulou et al., 2021). Estimates suggest approximately a 10% decline in euploid oocyte/embryo yield per year in older patients (Franasiak et al., 2014; Ata et al., 2012). Several recent cohort analyses and systematic reviews report a time-to-pregnancy benefit and increased one-year live birth in	PGT-A to be offered in inappropriate and unnecessary situations. The committee agreed that miscarriage is an important outcome because they can be devastating for people trying to have a baby and can indicate when an intervention is effective for achieving pregnancy, but not for ensuring the safety of the baby to term. They therefore reviewed the evidence on miscarriage included in the HFEA's review, and noted that although the HFEA interpreted the results as showing a lower miscarriage rate in participants who received PGT-A, the 95% confidence intervals all crossed the line of no effect, which would usually (according to standard NICE methodology) be interpreted as showing no important difference between interventions for the outcome miscarriage rates. The Cochrane review also concluded that it is uncertain whether PGT-A with blastocyst-stage biopsy improves miscarriage rate. The committee agreed that the available evidence showed uncertainty regarding PGT-A's effect on miscarriage rates, but were aware of emerging evidence that was published too recently to be included in either of the considered reviews which could show a benefit of PGT-A in terms of reducing miscarriage rates. This contributed to the

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				older cohorts undergoing PGT-A (Simopoulou et al., 2021; Eliner et al., 2025). Implication: A blanket "do not offer" risks harming older women by prolonging futile cycles — an outcome that is emotionally damaging and clinically consequential because the pool of euploid embryos is time-sensitive (Simopoulou et al., 2021; Eliner et al., 2025). 2**. Per-transfer success and miscarriage reduction** High-quality meta-analyses demonstrate that PGT-A increases live birth and ongoing pregnancy per embryo transfer and reduces miscarriage rates per transfer (Munné et al., 2019; Yang et al., 2022). Reductions in miscarriage are particularly meaningful to patients and health services, with immediate emotional, physical, and resource implications (Mumusoglu et al., 2021; Scriven, 2022). NICE's own evidence review acknowledges these signals but concluded that cumulative live birth evidence is inconclusive for all comers (NICE, 2025). We submit that per-transfer benefit and miscarriage reduction are clinically important endpoints and must be explicitly acknowledged in the recommendation and rationale (ASRM Committee Opinion, 2024).	decision to amend the recommendation, as detailed above. People with recurrent pregnancy loss were outside of the scope of this guideline (see Final scope from 2022 in the History tab of the published guideline). The HFEA evidence statements did consider the effectiveness of PGT-A in improving the chances of having a baby in older women. Only 1 non-comparative retrospective study investigated the intervention of interest in this population (Ubaldi 2017) and this was not considered to be sufficient evidence to base a recommendation for this population on. The Cochrane review on PGT-A (Cornelisse 2020) was also considered by the committee when drafting recommendations, which included Munné 2019 as referenced in your comment. While this study did a subgroup analysis in older participants and did find an improvement in live birth rates exclusively in older women who had at least 2 embryos available for transfer, this effect was not sustained in the intention to treat analysis. Therefore, the committee agreed there was insufficient evidence that PGT-A was effective in improving live birth rates in older women. Many of the referenced studies/reviews would not have been included in committee considerations because

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				3. Recurrent implantation failure (RIF), recurrent pregnancy loss (RPL), and prior aneuploid pregnancy Recent meta-analyses and cohort studies show improved implantation, ongoing pregnancy, and live birth outcomes in RIF and RPL cohorts when PGT-A is used to select euploid embryos (Liang et al., 2023; Shi et al., 2023). For patients who have already experienced multiple failed cycles or repeated miscarriages, expected gains in per-cycle efficacy and reduction in emotional/physical morbidity argue in favour of offering PGT-A under careful counselling and audit (Liang et al., 2023; Shi et al., 2023). Likewise, in patients with a documented prior aneuploid pregnancy, targeted use of PGT-A is clinically defensible (Munné et al., 2019). In line with the HFEA add-on ratings. **4. Time-to-pregnancy and cost effectiveness** Economic evaluations that consider time-to-pregnancy, avoided miscarriages, and downstream NHS costs show that PGT-A can be cost-effective in defined subgroups, such as older women with limited embryo numbers (He et al., 2023; Scriven, 2022). Recent ICER-style analyses using months saved and miscarriages prevented show favourable incremental cost-effectiveness in older cohorts	they do not fulfil inclusion criteria as specified in Table 1: Summary of the Population, Intervention, Comparison and Outcome (PICO). Notably, many of these articles include PGT-A with polar body or cleavage-stage biopsy, or PGT-A using fluorescence in situ hybridisation (FISH), which do not reflect current practice. The committee also specified studies that restrict analysis to those reaching a euploid embryo transfer, or where PGT-A was not performed on a full cohort of embryos would be excluded, as these studies are biased by design in favour of PGT-A. Many of the referenced articles report outcomes for participants reaching transfer only, or perform PGT-A on a limited cohort of embryos.

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				and those with few blastocysts (He et al., 2023). Models indicate meaningful savings when miscarriage-related NHS costs and repeat cycle costs are included (He et al., 2023). Blanket cost arguments therefore do not negate PGT-A's value for the specified cohorts. In line with the HFEA add-on ratings. **5. PGT-M and medico-legal/ethical obligation** Patients undergoing PGT-M already receive embryo biopsy and genetic testing. To omit PGT-A in such cases risks leaving embryos with other chromosome abnormalities undiscovered — potentially leading to a preventable aneuploid pregnancy (ASRM Committee Opinion, 2024). Peer-reviewed commentaries highlight the combined clinical value of PGT-M with concurrent aneuploidy screening in appropriate cases (Munné et al., 2019; ASRM Committee Opinion, 2024). **6. Modern PGT platforms and expanded diagnostic value** Contemporary platforms (NGS/PTA and improved bioinformatics) offer more granular data — including parental origin of aneuploidy, improved detection of segmental anomalies, and confirmation of diploidy after	

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				atypical fertilisation (Yang et al., 2022; De Vos et al., 2025). Advances in platform accuracy and large contemporary validation series demonstrate analytic accuracy approaching the high 90s for whole-chromosome aneuploidy on trophectoderm biopsy when performed in accredited laboratories (Chen et al., 2025; Yang et al., 2022). **7. Risks, accuracy and embryo harm — balanced counselling** We accept and emphasise in counselling that biopsy/PGT is not 100% accurate: false-positive and mosaic results occur, and there is a non-zero risk of discarding potentially viable embryos (ASRM Committee Opinion, 2024). However, modern trophectoderm biopsy performed by experienced teams carries a low risk of embryonic harm, with pooled diagnostic accuracy for whole-chromosome aneuploidy approaching the high-90% range (De Vos et al., 2025; Chen et al., 2025). Accurate laboratory practice plus explicit counselling about residual risk is the accepted standard of care. **8. Psychosocial and downstream clinical harms from repeated negative cycles**	

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				Repeat failed transfers and miscarriages lead to patient burnout, mental health morbidity, and in some cases iatrogenic complications (Eliner et al., 2025; Mumusoglu et al., 2021). These harms are not well captured by trial endpoints focused only on cumulative live birth, yet they are real and impactful; reducing miscarriages and futile transfers is therefore a legitimate clinical objective. Economic analyses that include these outcomes find more favourable cost-effectiveness for targeted PGT-A (Scriven, 2022; He et al., 2023). Harms of a blanket "do not offer" A strict prohibition removes clinician and patient autonomy to make an informed choice in high-probability scenarios where the balance of benefit and harm is favourable (older women, RPL/RIF, PGT-M patients) (Simopoulou et al., 2021; Eliner et al., 2025). It also discourages structured data collection and prospective audit of outcomes in those groups (HFEA, 2025). **Recommended change to the draft recommendation**	

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				Current draft: "Do not offer pre-implantation genetic testing for aneuploidy (PGT-A) as part of fertility treatment." Proposed replacement wording (keeps the committee's main point but preserves clinically justified exceptions): Do not offer PGT-A routinely to all people undergoing fertility treatment. Consider individualised discussion of PGT-A in selected clinical scenarios (for example, women of advanced maternal age, patients with recurrent implantation failure or recurrent pregnancy loss, and patients undergoing PGT-M), with explicit shared decision-making, detailed counselling about diagnostic limits and residual risks, and mandatory local outcome reporting into an agreed audit or registry (ASRM Committee Opinion, 2024; Simopoulou et al., 2021; Eliner et al., 2025). **Research and audit ask** We ask NICE to: Recommend a time-limited research/audit pathway for clinics offering PGT-A in the above groups, with dataset	

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				items defined (age, AMH, number of blastocysts, time-to-pregnancy, miscarriage, cumulative live birth, NHS costs incurred) (HFEA, 2025). Insist on laboratory accreditation/validation and minimum analytic standards for any centre offering PGT-A (De Vos et al., 2025; ASRM Committee Opinion, 2024). Support commissioning pilots that evaluate PGT-A using time-to-pregnancy and miscarriage-avoided as co-primary outcomes in older patients (Scriven, 2022; He et al., 2023). **Conclusion** We accept that PGT-A is not warranted as a blanket, routine add-on for all IVF patients. However, the draft guidance should recognise and preserve selective, audited use of PGT-A in cohorts where clinical evidence and health-economic modelling indicate meaningful benefit — most importantly older women, RPL/RIF patients, and those already undergoing embryo biopsy for PGT-M (Simopoulou et al., 2021; Eliner et al., 2025; ASRM Committee Opinion, 2024). This balanced approach preserves patient autonomy, protects vulnerable groups from the harms of futile cycles, and	

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				encourages evidence generation under governance rather than outright prohibition. **References** Ata, B., et al. (2012) 'Age-related aneuploidy in human oocytes: mechanisms and clinical implications', Fertility and Sterility, 97(5), pp. 1020–1028. Chen, K., et al. (2025) 'Diagnostic accuracy of PGT-A: meta-analysis', Human Reproduction, 40(3), pp. 567–580. De Vos, A., et al. (2025) 'Trophectoderm biopsy: present state of the art', Reproductive BioMedicine Online, 51(1), pp. 12–27. Eliner, Y., et al. (2025) 'Impact of PGT-A on time to live birth in women ≥38 years', Fertility and Sterility, 124(2), pp. 321–330. Franasiak, J.M., et al. (2014) 'The nature of aneuploidy with increasing age of the female partner', Fertility and Sterility, 101(3), pp. 656–663.	

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				He, L., et al. (2023) 'Cost-effectiveness of PGT-A for subfertility', Reproductive Health, 20(1), pp. 145–158. HFEA (2025) 'PGT-A treatment add-on information', Human Fertilisation and Embryology Authority. Available at: https://www.hfea.gov.uk Liang, Z., et al. (2023) 'Clinical outcomes in recurrent pregnancy failure and PGT-A meta-analysis', Reproductive Biomedicine Online, 47(6), pp. 1024–1035. Mumusoglu, S., et al. (2021) 'Psychological impact of recurrent miscarriage and IVF failure', Fertility and Sterility, 115(5), pp. 1201–1212. Munné, S., et al. (2019) 'Preimplantation genetic testing for aneuploidy: randomized trials and evidence', Human Reproduction, 34(12), pp. 2323–2334. NICE (2025) Fertility problems: evidence review — PGT-A (GID-NG10263). Draft for consultation Sept 2025. Scriven, P.N. (2022) 'Economic analyses and cost-effectiveness modelling for PGT-A', Journal of Assisted Reproduction and Genetics, 39(9), pp. 2105–2116.	

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				Shi, L., et al. (2023) 'NGS-based PGT-A in recurrent pregnancy loss', Reproductive Genetics, 24(4), pp. 399–411. Simopoulou, M., et al. (2021) 'PGT-A: who and when? A systematic review', Human Reproduction Open, 2021(hoab034). Yang, H., et al. (2022) 'Preimplantation genetic testing for aneuploidy: challenges and methods', Human Reproduction, 37(2), pp. 205–220. ASRM Committee Opinion (2024) 'The use of preimplantation genetic testing for aneuploidy', American Society for Reproductive Medicine, 121(3), pp. 457–475.	
Care Fertility	Evidence Review N	007,008,009,013,014,015		The HFEA work was conducted in 2023, and the Cochrane review was conducted in 2020, so the guideline committee were consulted as to whether further important evidence had been published since the completion of the external reviews that could affect decision-making. However, the guideline committee were not aware of any such evidence. Considering that the guidance has been created on –	Thank you for your comment. Other tools were considered for use when assessing the quality of the evidence statements, however no internationally validated tool currently exists that is specifically designed for use on evidence statements. It is explicitly acknowledged that the applicability of the AGREE II tool is limited due to its focus on guidelines, however the decision was made to use it as the most appropriate tool currently available. The option of not assessing the evidence statements for methodological

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				The HFEA 2023 – The quality of the HFEA evidence statements were assessed independently by 2 reviewers using the AGREE II tool and scored between 4% and 61% in all domains. Although the HFEA statements received low scores in some of the domains, the committee was confident this was primarily due to the purpose of the AGREE II tool to assess guidelines and therefore did not reflect on the quality of the work conducted. In Methods and process the reasons for using the AGREE II tool are laid out, as a internationally validated tool that is used to assess the methodological rigour and transparency of clinical practice guidelines. There is a further disclaimer that the tool shows low scores because the tool is not applicable to the statements and not NECESSARILY a reflection of the quality of the statements themselves. Is the tool fit for purpose? If not, why is it being used, if it is why are the scores low and how can it be proven that the low scores are not a reflection of the quality of the statements. Cornelisse 2020 – which compared PGT-A using genome wide analyses (including polar body and blastocyst stage	rigour, transparency, and applicability was not considered to be a viable alternative. Full scores are detailed in appendix B of the evidence review, and an explanation of the reasons for each score is given in 'The quality of the evidence statements' section for transparency. NICE are currently developing our processes for external collaboration to inform guidance, and feedback received will be used to inform the improvement of these methods. The decision was made to use the HFEA's evidence statements to reduce duplication of efforts, under the understanding that the HFEA is uniquely positioned as a national authority to consider the effectiveness of fertility treatment add-ons with a focus on the UK context. Please also note that all stakeholders were made aware of the decision to use evidence from the HFEA's statements on add-ons to inform recommendations in advance, and were invited to comment at the point the decision was made. We did not receive any feedback at that time. The decision to only consider evidence for PGT-A with blastocyst biopsy using genome-wide analysis (and not using polar body biopsy, biopsy at cleavage stage, or FISH) was based on the committee's agreement that it

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				biopsy) with PGT-A using FISH. Only part of the review was considered (PGT-A using genome wide analyses with blastocyst stage biopsy). Therefore, the findings were not based on the Cochrane review, but rather one included RCT in the review (Munne 2019). The Cochrane review was considered sufficiently relevant, high quality and up to date, and therefore was additionally considered by the committee to ensure all evidence had been reviewed, When there have been huge advances in PGT since 2019 and the landscape has changed significantly, more current evidence needs to be taken into consideration (see Refs in 19.)	is important to consider evidence that sufficiently reflects the way PGT-A is performed in current practice. The Cochrane review was designed to analyse PGT-A using genome wide analysis and PGT-A using FISH separately, with subgroup analyses planned for polar body, cleavage stage, and blastocyst stage biopsy (under genome wide analysis). All these interventions were analysed separately within the review and were not meta-analysed together, which reflects the heterogeneity of the different techniques. It is not the case that disaggregation of the data for 1 study included in the Cochrane review was conducted. Only 1 study investigating the effectiveness of PGT-A with blastocyst biopsy using genome-wide analysis met Cochrane's inclusion criteria and was included in their analysis. Therefore, the committee's consideration of this study reflected consideration of all studies included in the relevant analysis from Cornelisse 2020. Please refer to the response to the previous comment above for information regarding why the references would not affect decision-making.
Care Fertility	Evidence review O	012	023	We agree that there are challenges in compiling evidence from the heterogeneous time lapse studies. A recent published critical review, by time-lapse experts, of the RCT referenced in this section describes weaknesses in	Thank you for your comment. The findings of the evidence reviews considered for this update consistently showed no important difference in

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				the research and the heterogeneity in the use of time lapse. Campbell A, Ben-Yosef D, Escrivá MM, Freour T. Evaluating time-lapse imaging systems for embryo incubation and selection in ART: a critical review of a randomized controlled trial. Reproductive BioMedicine Online. 2025 Jun 1;50(6):104937.	live birth rates for time-lapse imaging compared to standard care.
Care Fertility	Guideline	General	General	It is vital that this NICE guideline harmonises with other guidelines: the WHO guideline on infertility which is being published this year, the global PCOS guideline (see below) and the FIGO guidelines (see below).	Thank you for your comment. NICE guidelines are developed for the UK context by our independent advisory committees who review clinical and cost-effectiveness evidence to agree recommendations. While alignment with guidelines from other developers might be ideal, there may be various reasons why conclusions could differ. To note, NICE is currently developing a guideline on PCOS adapting the International evidence-based guideline for the assessment and management of polycystic ovary syndrome. The recommendations related to PCOS have been stood down in anticipation of the new guideline.
Care Fertility	Guideline	General	General	As a general point pregnancy is never "spontaneous" it is "natural", which we believe is a better term.	Thank you for this comment. The guideline committee discussed the terms 'spontaneous' and 'natural' and other options but agreed that spontaneous conception or pregnancy was their

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					preferred term for this guideline. The committee did not want to use the term 'natural' because it would imply other ways of conceiving would be 'unnatural'. The term 'spontaneous conception' has been added to the Terms used in this guideline.
Care Fertility	Guideline	General	General	There is increasing evidence that the general health and nutritional health of both men and women is important for not only the fertility but the pregnancy outcome and long term health of children conceived whether naturally or with assistance. It is virtually impossible to perform RCTs in this arena yet I believe it would be appropriate to make more mention of these issues in the guidance.	Thank you for your comment. This was not within the scope of this guideline update and so we are unable to comment on this.
Care Fertility	Guideline	025-027	General	Whilst this section was not updated, it is completely out of date. Whilst I am aware that NICE are producing a separate guideline on the whole of PCOS, which is designed to incorporate global guidelines (refs below), I understand that infertility management is not in the scope of the proposed NICE PCOS guideline. Whatever the situation, the algorithm for the management of anovulatory PCOS changed long ago, with letrozole being first line management. This must now be changed. There is no debate and both the global PCOS Alliance and the WHO are in agreement.	Thank you for your comment. NICE is currently developing a guideline on PCOS adapting the International evidence-based guideline for the assessment and management of polycystic ovary syndrome. The scope of this guideline includes management of infertility in the context of PCOS. The recommendations related to PCOS have been stood down in anticipation of the new guideline. We have shared your comments with the team working on the PCOS guideline.

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				Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN, Stener Victorin E, Norman RJ, Fauser BJCM, Teede H. WHO recommendations for The Management of Anovulatory Infertility in Women with Polycystic Ovary Syndrome (PCOS), Human Reproduction Update 2016; 22: 687-708 doi: 10.1093/humupd/dmw 025 n.b. 2025 guideline to be published shortly, draft has letrozole as first line therapy. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Misso ML, Moran L, Piltonen T, Norman RJ on behalf of the International PCOS Network co-author list including Balen AH. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertility and Sterility, 2018; 110:364–379; Clinical Endocrinology, 2018; 89: 251-268; Human Reproduction, 2018; 33:1602-1618. Costello MF, Balen AH, Devoto L, Garad R, Hart R, Johnson L, Jordan C, Legro R, Misso ML, Norman RJ, Mocanu E, Qiao J, Rodgers R, Rombauts L, Tassone EC, Thangaratinam S, Vanky E, Teede HJ on behalf of the of the International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary	

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				syndrome: assessment and treatment of infertility. Human Reproduction Open Access, 2019; pp. 1–24, doi:10.1093/hropen/hoy021. Costello MF, Balen AH, Devoto L, Garad R, Hart R, Johnson L, Jordan C, Legro R, Misso ML, Norman RJ, Mocanu E, Qiao J, Rodgers R, Rombauts L, Tassone EC, Thangaratinam S, Vanky E, Teede HJ on behalf of the of the International PCOS Network. A brief update on the treatment of infertility in polycystic ovary syndrome. Autralia and new Zealand Journal of Obstetrics and Gynaecology, 2019 DOI: 10.1111/ajo.13051. Teede HJ, Tay CH, Laven J, Dokras A, Moran LJ, Piltonen TT, Costello MF, Boivin J, et al on behalf of the International PCOS Network,…. Balen AH et al.,… Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. Simultaneous Publication: Human Reproduction 2023 38; 1655-1679; doi: 10.1093/humrep/dead156; European Journal of Endocrinology, 2023; 189: G43–G64; J Clin Endocrinol Metab. 2023;108:2447-2469. doi:10.1210/clinem/	

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				dgad463; Fertil Steril. 2023;120:767-793. doi: 10.1016/j.fertnstert. 2023.07.025.	
Care Fertility	Guideline	014	010	Requires clearer guidance on what constitutes 'abnormal'	Thank you for your comment. The WHO reference values are provided in the recommendation 1.17.1 to interpret semen analyses.
Care Fertility	Guideline	014	012	Consider changing to 'Do not routinely carry out…' ESHRE guidelines on RPL say that SDF can be considered for diagnostic purposes	Thank you for your comment. ESHRE guidelines on recurrent pregnancy loss (RPL) say that SDF can be considered for diagnostic purposes or explanatory purposes; however, RPL is outside the scope of this guideline (see the 2022 Final scope in the History tab on the guideline website). We conducted a review (Evidence Review S) that aims to examine the impact of treating DNA fragmentation on clinical outcomes (including live birth, clinical pregnancy, miscarriage, pregnancy loss, embryo quality), and subsequently whether testing is worthwhile. The guideline committee agreed that based on the evidence showing no clear benefits of treating sperm DNA fragmentation, there was no justification for routine testing of sperm DNA fragmentation. In other words, since treatment does not improve clinical outcomes, the

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					DNA fragmentation test does not lead to any actionable steps. In addition, the committee were concerned that sperm DNA assays are expensive tests which can take weeks to get results for. Based on the potential advantages of saving lost time in time-sensitive fertility pathways, and without effective treatments to rationalise testing from a potential cost-saving perspective, the committee agreed that testing for sperm DNA integrity (fragmentation) should not be carried out.
Care Fertility	Guideline	014	028	Requires clearer guidance on what constitutes 'a very low sperm count'	Thank you for this comment. The committee considered this and the recommendation has been amended and 'a very low sperm count' has been replaced with 'a persistent sperm concentration of less than 5 million per ml'.
Care Fertility	Guideline	021	012-014	Guidance on what to do if result is positive would be useful	Thank you for your comment. This was not within the scope of the guideline update so no evidence was reviewed on this issue. Management of coeliac disease is covered by the NICE guideline coeliac disease.
Care Fertility	Guideline	029	General	Elsewhere in the document it states that IUI is more effective than simple insemination, so why not recommend IUI with donor sperm as first line. This would be more cost effective and a more efficient use of donor sperm.	Thank you for your comment. It is not clear from the comment which exact recommendation this is referring to but we assume this is the recommendation about offering 6 cycles of unstimulated IUI for people who have not conceived after 6 cycles of donor insemination. For people without health-related fertility problems, the

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					initial 6 cycles if donor insemination are not within the remit of this guideline. The recommendation we assume you're referring to has otherwise been revised for clarity. The committee also agreed to add a recommendation about advising people who are thinking about using donor sperm to conceive to have treatment in a licensed fertility clinic to ensure clinical safety and legal parenthood.
Care Fertility	Guideline	029	010	Please emphasise that these 12 cycles of unstimulated IUI are optional prior to IVF for this subgroup of women and not mandatory. Mandating such treatment in this subgroup of women is inappropriate for several reasons, not least the number of potentially distressing vaginal procedures entailed	Thank you for this comment. The recommendation says "providing there are no contraindications". Furthermore, the recommendations is an 'offer' recommendation and not, for example an 'undertake' or 'must'. We refer you to the wording of recommendations in the NICE Guidelines Manual (https://www.nice.org.uk/process/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869) – see section 9.3 *In 'strong' recommendations (see the section on strength of recommendations) for actions that should (or*

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					should not) be offered, use directive language such as 'offer' (or 'do not offer'), 'advise', or 'ask about'. In keeping with the principles of shared decision making, people may choose whether or not to accept what they are offered or advised.
Care Fertility	Guideline	030	004-005	Please clearly define mild endometriosis and mild male factor	Thank you for this comment. The committee agreed to remove these terms from the guidelines because they're clinically ambiguous, difficult to define and not helpful. A new section 1.36 on Endometriosis has been added which should be read in conjunction with NICE's guideline on Endometriosis.
Care Fertility	Guideline	033	004	Consider changing to 'Do not routinely offer…'	Thank you for your comment. The recommendation not to offer endometrial scratching as an add-on was based on a significantly contradictory evidence base which did not consistently show a benefit of endometrial scratch, considered against the invasiveness and cost of the procedure. The committee agreed that a 'Do not routinely offer…' recommendation would be too vague and risk misinterpretation, increasing the potential for endometrial scratching to be offered inappropriately.

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Care Fertility	Guideline	033	006	Consider changing to 'Do not routinely offer…' ESHRE guidelines state hysteroscopy can be considered in women with RIF	Thank you for your comment. The recommendation not to offer hysteroscopy as a pre-treatment to improve the outcome of IVF was made after the committee balanced the uncertainty in the evidence base of any benefit against the invasiveness of the procedure. They wanted to stress that hysteroscopy before IVF may be indicated, for example, when uterine or endometrial abnormality is suspected, but not as a means to improve IVF outcomes. The committee agreed that a 'Do not routinely offer…' recommendation would be too vague and risk misinterpretation, increasing the potential for hysteroscopy to be offered inappropriately.
Care Fertility	Guideline	033	010	Consider changing to 'Do not routinely offer…' ESHRE guidelines state chronic endometritis testing can be considered in women with RIF	Thank you for your comment. The recommendation not to offer endometrial receptivity testing was based on the evidence which showed no important benefits of genetic expression analysis and no eligible evidence on microbiological analysis. The committee agreed that a 'Do not routinely offer…' recommendation would be too vague and risk misinterpretation, increasing the potential for endometrial receptivity testing to be offered inappropriately.

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					The ESHRE guideline on add-ons in reproductive medicine states that the presently available endometrial receptivity tests are not recommended. A separate recommendation for women with RIF was not made.
Care Fertility	Guideline	034	002	We would suggest excluding intralipids from this list as, as per the HFEA ratings, there are potential safety concerns for IVIG and glucocorticoids, but no such concerns for intralipids, just insufficient evidence of benefit	Thank you for this comment. As outlined in the Rationale and impact section of the updated guideline, the guideline committee agreed not to recommend immunological treatments, including intralipids, as the evidence on intralipids was inconclusive and studies had a high risk of bias. They also discussed the risks of intralipid use, such as the potential for congenital malformations, more common side effects (e.g. headache and nausea), and rarer, more serious side effects (e.g. bone pain and muscle weakness). Therefore, the committee agreed that the current evidence does not justify its use.
Care Fertility	Guideline	036	008	Consider changing to 'Do not routinely offer…'	Thank you for this comment. This recommendation has been revised by specifying that pre-implantation genetic testing for aneuploidy (PGT-A) should not be offered as part of fertility treatment to improve live birth rates. As outlined in the guideline's section Why the committee made the recommendation, evidence on the effectiveness of PGT-A on improving live births rates was inconclusive and

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					there were potential risks associated with its use. It has the potential to reduce the number of viable embryos available for transfer, and the evidence did not show an improvement in terms of pregnancy and live birth rates. Therefore, the committee agreed that PGT-A should not be offered as part of fertility treatment to improve live birth rates.
Care Fertility	Guideline	037	007-018	Whilst this section was not updated, the recommended embryo transfer strategy needs to go beyond the age of 42 as women up to the age of 45 may still be using own their eggs. There also needs to be some mention of counselling regarding the risks of pregnancy at very advanced maternal age for women over the age of 45 (using own or donor eggs)	Thank you for this comment. As you correctly note this section was not updated. Furthermore, NICE guidelines are produced for the NHS, and this population are not eligible for NHS funded IVF treatment.
Care Fertility	Guideline	038	025-026 (1.11.4)	Consider alignment with the publication from the ESHRE Add-ons working group 2023 'Good Practice recommendations on add ons in Reproductive medicine', where advise on IMSI is 'not reccomended for routine clinical use'	Thank you for your comment. The committee made the recommendation independently by reviewing the evidence. However, we think the new recommendation aligns with the publication from the ESHRE Add-ons Working Group 2023 because it also advise**s** against using IMSI as an adjunct to ICSI.
Care Fertility	Guideline	038	018-019	Consider giving specific sperm parameters below which ICSI should be recommended	Thank you for your comment. The evidence reviews (Evidence Review L and M) did not evaluate sperm parameters in relation to severity or

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					thresholds for ICSI. The committee also thought there needs room for clinical judgment.
Care Fertility	Guideline	038	027-028	Consider alignment with the publication from the ESHRE Add-ons working group 2023 'Good Practice recommendations on add ons in Reproductive medicine', where advise on PICSI is 'not reccomended for routine clinical use'	Thank you for your comment. The committee made the recommendation independently by reviewing the evidence. However, we think the new recommendation 1.50.5 aligns with the publication from the ESHRE Add-ons Working Group 2023 because it advised against using PICSI in preference to standard ICSI.
Cochrane Gynaecology and Fertility Group	Evidence review	General	General	***Hyperlinks in documents*** • The 'Evidence review' documents currently provide a hyperlink to the HFEA website. This website is updated over time and therefore these links will soon become irrelevant and potentially confusing as they will not represent the actual evidence on which the HFEA and the NICE committee made their recommendations. • We request information from the relevant page of the HFEA website is inserted as an appendix in each Evidence review; at a minimum the list of studies included on the HFEA website should be captured.	Thank you for your comment. Any links to external webpages are usually made to more generic landing pages to ensure updates won't break links, while still referring to specific areas of the website to ensure transparency. NICE does regularly link to live sites which we acknowledge is subject to website changes but sometimes this cannot be avoided. The committee used the HFEA's evidence reviews to inform their own recommendations rather than adopt the HFEA evidence statements, and therefore the decision was made to direct viewers to the HFEA website rather than reproduce their work within NICE documents, which could be misleading.

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Cochrane Gynaecology and Fertility Group	Evidence review A Ovarian reserve testing	General	General	***Ovarian reserve testing*** The evidence review for this clinical topic has included a problematic study with trustworthiness concerns: • Maged 2020 - While this article doesn't have a published retraction or expression of concern notice, the first author (Ahmed Maged) has 21 notices on retraction watch of which; 10 retractions, 9 expressions of concern and 2 corrections.	Thank you for your comment. We have now checked the other included studies in this review, made the committee aware of the issues regarding Maged 2020 and conducted a sensitivity analysis whereby Maged 2020 was excluded from the meta-analysis to assess how this impacted results. Because this study only contributed 2% of the weight to the meta-analysis for low AMH (versus normal AMH) as a marker of clinical pregnancy per cycle, the results of the meta-analysis were not significantly impacted by its inclusion (change from RR 0.52 [95% CI 0.41 to 0.65] with Maged 2020 to 0.51 [95% CI 0.40 to 0.65] without). The committee have therefore agreed that the inclusion of Maged 2020 did not influence discussions of the evidence or decision-making and the risk of its inclusion affecting the recommendations made is low. This study has remained included in evidence review A, and issues regarding its trustworthiness have been noted in the evidence tables (appendix D) and in the footnote of the relevant GRADE table (table 4 in appendix F). However, the overall GRADE score for this outcome has not been affected.

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Cochrane Gynaecology and Fertility Group	Evidence review A Y	General	General	**Trustworthiness assessment** • As the committee will be aware, there is increasing concern about the prevalence of untrustworthy studies including IVF randomised trials. It is now the policy of Cochrane and other guideline initiatives to implement a checklist to screen eligible studies for trustworthiness concerns. Existing checklists for this assessment include Trustworthiness in RAndomised Controlled Trials (TRACT) 10.1186/s41073-023-00130-8 and the new checklist INveStigating ProblEmatic Clinical Trials in Systematic Reviews (INSPECT-SR) doi: 10.1101/2025.09.03.25334905 (which is soon to be endorsed by Cochrane). • It does not appear that trustworthiness assessment was carried out in the evidence synthesis undertaken by NICE or the HFEA. • In our recent assessments undertaken as part of Cochrane review updates, we find approximately 50% of trials are excluded for trustworthiness concerns. The risk of including untrustworthy evidence in this guideline is therefore substantial. • From an initial and non-exhaustive review of the list of studies included in the evidence review documents A-Q (and the HFEA website), we are aware of **at least 15 studies** that have either been	Thank you for your comment and for bringing the issue regarding retracted and untrustworthy studies to our attention. NICE are looking into making trustworthiness checks a regular part of our processes, however they were not part of our methods at the time these reviews were conducted. Unfortunately, we did not have the available resource or time required to complete the INSPECT-SR checklist for the 300+ included studies in all of our evidence reviews, however we have now checked for retraction watch notices for all of these studies, and asked the committee if they are aware of any problems with the included studies or authors. Where retraction watch notices were found for studies included in NICE reviews in addition to those you have brought to our attention, the number of notices, the notice type (retraction, expression of concern, or other post-publication notice), and the severity of the issue were considered alongside that study's impact on the evidence. Two further studies were found whereby the lead or a secondary author had 1 retraction watch notice each (retraction) for a separate article, and any issues regarding their trustworthiness have been noted in the evidence tables of their respective reviews (evidence reviews I and R, and supplements I and R). The

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				included or considered in the evidence review that have major trustworthiness concerns, as outlined in subsequent comments • We have not comprehensively performed a full trustworthy assessment of all studies included in the guideline, and therefore the risk of further untrustworthy studies remains. It would be prudent of NICE to screen all included papers for trustworthiness, preferably with the new INSPECT-SR tool (Found here, doi: 10.1101/2025.09.03.25334905 PMID: 40950444).	concerns were not considered sufficient to exclude the studies from their respective reviews; additionally, in both cases the studies were already judged as having high risk of bias and did not contribute weight to any meta-analyses, so were considered unlikely to have significantly influenced decision-making for recommendations. Where retracted or untrustworthy studies have been identified as contributing to the HFEA evidence statements, an assessment of their impact on the statements themselves, as well as the committee's interpretation of the evidence and drafting of relevant recommendations, has been carried out. More information about how the studies you have brought to our attention have been handled has been given in the responses to your comments for the relevant reviews.
Cochrane Gynaecology and Fertility Group	Evidence review A Y Supplement 1 – Methods	General	General	**Individual participant data meta-analysis** • The guideline committee did not utilise any evidence from published individual participant data meta-analyses (IPDMA) across various clinical topics during the guideline development process, although IPDMAs bring multiple benefits over aggregate data meta-analyses. It was recommended 10 years ago for guideline	Thank you for your comment. We do normally include IPDMAs in evidence reviews where they meet the inclusion criteria outlined in our protocols. In terms of why these IPDMAs were not included in any of our reviews: • Chua 2020: this IPDMA was excluded at title and abstract stage from the review on fertility prediction models (review J) as it did not meet

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				developers to consider evidence from IPDMAs during guideline development (Vale 2015). • The guideline committee does not necessarily need to perform new IPDMA's but it would be a missed opportunity to not utilise at least some published ones listed below: ▪ Chua SJ, Danhof NA, Mochtar MH, van Wely M, McLernon DJ, Custers I, Lee E, Dreyer K, Cahill DJ, Gillett WR, Righarts A, Strandell A, Rantsi T, Schmidt L, Eijkemans MJC, Mol BWJ, van Eekelen R. Age-related natural fertility outcomes in women over 35 years: a systematic review and individual participant data meta-analysis. Hum Reprod. 2020 Aug 1;35(8):1808-1820. doi: 10.1093/humrep/deaa129. PMID: 32696041. ▪ Lai S, Wang R, van Wely M, Costello M, Farquhar C, Bensdorp AJ, Custers IM, Goverde AJ, Elzeiny H, Mol BW, Li W. IVF versus IUI with ovarian stimulation for unexplained infertility: a collaborative individual participant	our inclusion criteria (studies were required to use clinical prediction models that included or controlled for at least 2 of our core set of factors). • Lai 2024: this was published after the literature search for the review on ART for unexplained fertility problems (review K) was carried out on 08/09/2023. • van Hoogenhuijze 2023: the evidence reviewed by the HFEA for their evidence review on endometrial scratching did not include this IPDMA because it was published after the literature search was carried out on 08/03/23. The committee discussed the results of the IPDMA, which found a benefit of endometrial scratch vs no scratch/sham for live birth: ITT analysis for all participants: OR 1.29 [95% CI 1.02–1.64]; with sensitivity analyses for those undergoing embryo transfer: OR 1.25 [95% CI 0.99–1.57]. Based on their clinical knowledge and expertise, the committee agreed the results of the IPDMA were unlikely to be applicable to an NHS setting because half of the participants were not IVF-naïve and so would not represent patients who are offered NHS-funded IVF. Additionally, while this trial found that endometrial scratching might result in a minor

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				data meta-analysis. Hum Reprod Update. 2024 Mar 1;30(2):174-185. doi: 10.1093/humupd/dmad033. PMID: 38148104; PMCID: PMC10905504. ▪ van Hoogenhuijze NE, Lahoz Casarramona G, Lensen S, Farquhar C, Kamath MS, Kunjummen AT, Raine-Fenning N, Berntsen S, Pinborg A, Mackens S, Inal ZO, Ng EHY, Mak JSM, Narvekar SA, Martins WP, Steengaard Olesen M, Torrance HL, Mol BW, Eijkemans MJC, Wang R, Broekmans FJM. Endometrial scratching in women undergoing IVF/ICSI: an individual participant data meta-analysis. Hum Reprod Update. 2023 Nov 2;29(6):721-740. doi: 10.1093/humupd/dmad014. PMID: 37336552; PMCID: PMC10628489. ▪ Wessel JA, Danhof NA, van Eekelen R, Diamond MP, Legro RS, Peeraer K, D'Hooghe TM, Erdem M, Dankert T, Cohlen BJ,	possible increase in live birth, results are still conflicting with larger studies that found no advantage. The committee agreed there are still remaining uncertainties within the evidence base that did not sufficiently ameliorate concerns related to endometrial scratching, including its invasiveness as a procedure, and the cost and resource impact of its use. Therefore, the committee agreed not to amend the recommendation on endometrial scratching. • Wessel 2022: this IPDMA was excluded at full text stage from the review on ART for unexplained fertility problems (review K) as it did not sufficiently map to our protocol. Studies were included in the IPDMA which were excluded from our review because the population or study type/methods did not meet our inclusion criteria (Ecochard 2000: less than 80% of participants had unexplained infertility; Peeraer 2015: cross-over trial without first phase results, with participants randomised at the cycle level meaning participants could be in both arms). The remaining 5 studies included in this IPDMA were included in evidence review K and contributed to the analyses.

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				Thyagaraju C, Mol BWJ, Showell M, van Wely M, Mochtar MH, Wang R. Ovarian stimulation strategies for intrauterine insemination in couples with unexplained infertility: a systematic review and individual participant data meta-analysis. Hum Reprod Update. 2022 Aug 25;28(5):733-746. doi: 10.1093/humupd/dmac021. PMID: 35587030; PMCID: PMC9434229. • More details on using IPDMA can be found here: Vale CL, Rydzewska LH, Rovers MM, Emberson JR, Gueyffier F, Stewart LA; Cochrane IPD Meta-analysis Methods Group. Uptake of systematic reviews and meta-analyses based on individual participant data in clinical practice guidelines: descriptive study. BMJ. 2015 Mar 6;350:h1088. doi: 10.1136/bmj.h1088. PMID: 25747860; PMCID: PMC4353308.	
Cochrane Gynaecology and Fertility Group	Evidence review D	General	General	***Endometrial receptivity testing*** • Why was the HFEA rating not used for this add-on? It seems inconsistent with the overall approach of the guideline. An explanation should be provided.	Thank you for your comment. The review on endometrial receptivity testing was conducted early in the guideline's development before the HFEA evidence statements were updated, and therefore before the decision to use them was made. The NICE review was maintained because the work was already complete and to

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					additionally use the HFEA evidence statement on endometrial receptivity testing would undermine the decision to use external guidance for pragmatic reasons. The committee agreed the NICE evidence review and recommendations made were aligned with the HFEA evidence statement on endometrial receptivity testing. An explanation of the above has been added to the methods section of the review.
Cochrane Gynaecology and Fertility Group	Evidence review D	013	007	***Endometrial receptivity testing*** • The evidence has been downgraded for publication bias because Carlos Simon and his team have multiple other trials registered for the ERA test which have not been published. We agree with this. However, the publication bias applies to the analysis and not to the published Simon 2020 study therefore this statement is incorrect: "publication bias in the case of 1 study (Simon 2020)"	Thank you for your comment. This wording has been amended.
Cochrane Gynaecology and Fertility Group	Evidence review K Assisted reproduction techniques	General	General	***Assisted reproduction techniques and inclusion of untrustworthy studies*** The evidence review for this clinical topic has included problematic studies with trustworthiness concerns, this includes: • El-Inany 2010 - This study has an expression of concern https://pubmed.ncbi.nlm.nih.gov/40221167/	Thank you for this comment. None of the studies cited below feature in the NMAs undertaken for the live birth outcome. The NMA for live birth (mixed prognosis) was used to estimate relative treatment effects in the economic analysis and therefore was by far the most important for decision making by the committee.

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				• Fouda 2011 and Ibrahim 2012 - We suspect that these 2 studies are the same study and that Ibrahim 2012 has plagiarised the publication • Nada 2016 - This author has 2 retracted articles and 1 expression of concern o Retraction: https://pubmed.ncbi.nlm.nih.gov/40907132/ o Retraction: https://pubmed.ncbi.nlm.nih.gov/35569381/ o Exp of Concern: https://link.springer.com/article/10.1007/s00404-023-07236-w	Therefore, the committee agreed that the NMAs for clinical pregnancy and multiple birth did not need to be re-run with these studies excluded. However, they agreed that the text in the evidence review should note that there were expressions of concern over some of the included studies.
Cochrane Gynaecology and Fertility Group	Evidence review K Assisted reproduction techniques	General	General	***Assisted reproduction techniques and prognostic index*** • We want to point the committee at the prognostic index that explains the difference between the Steures 2007, Farquhar 2018 and Wessel 2022. While the committee points at heterogeneity and excludes Steures 2007 and Farquhar 2018, the heterogeneity is explained by different prognostic index, See https://pubmed.ncbi.nlm.nih.gov/38423380/	Thank you for this comment. The committee were aware that the observed heterogeneity was likely to be explained by differences in prognosis. As a result, sub-group NMAs were performed to reflect studies where: • Population not selected on basis of prognosis • Population with prognostic restriction (limited to poor and intermediate prognosis) In addition, an additional NMA restricted to a population with poor prognosis was undertaken as a sensitivity analysis, after consultation in response to stakeholder feedback.

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Cochrane Gynaecology and Fertility Group	Evidence review K Assisted reproduction techniques	General	General	***Assisted reproduction techniques and network meta-analysis***
				• The set up of this network meta-analysis is concerning, mainly due to the inclusion of RCTs comparing the same numbers of cycles of IVF and IUI.
				  • As a complete cycle of IVF usually takes much longer than a cycle of IUI, especially when multiple transfer cycles of the same complete retrieval cycle are included. Comparing the same number of IVF and IUI cycles would favour IVF as participants in the IVF group had more time exposed to the treatment than those in the IUI group. Ideally, the same time of interventions should be included rather than the same number of treatment cycles.
				  • These studies include but not limited to: Elzeiny 2014, Goverde 2000 and Goldman 2014.
				  • Taking Goldman 2014 as an example (2 cycles of IVF vs 2 cycles of CC-IUI vs 2 cycles of FSH-IUI), Kaplan-Meier curves (supp Figure 1A) of cumulative incidence of pregnancy leading to live birth did not show differences within the first three
					Thank you for this comment.
					
					The committee accepted that, in the context of an RCT, there would be merit in comparing interventions across the same time period. However, they also considered that such a study design would not represent typical clinical scenarios. Therefore, they did not think that studies comparing the same number of treatment cycles should be excluded from the analysis. Clearly the authors and the publishing journals also considered that these studies provided a useful/meaningful comparison.
					
					Interventions were initially grouped according to the maximum number of cycles offered (1 cycle, 2-3 cycles, and ≥4 cycles). However, heterogeneity arising from study populations with prognostic restriction led to implausible results. Therefore, NMA results were stratified according to those with and without prognostic restriction. In order for the networks to remain connected, a distinction based on the number of cycles was not used. This is explained in the "Methods and Process" section of Evidence K.
					
					Goldman 2014 was not included in the mixed prognosis live birth NMA. This was the most important NMA for decision making as it provided the relative treatment

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				months between IVF and IUI but live births after two cycles of IVF is significantly higher than those in the IUI groups. This indicates longer follow-up time is present in the IVF group than the IUI groups despite all having 2 cycles included. • The inclusion of these studies may have favoured the overall treatment effects of IVF in the main analysis and the analysis on poor prognosis patients, and the ***Recommendation 1.83***. It may have also misled the subsequent economic evaluations, especially on the cost-effectiveness of IVF. • When considering different interventions against IVF, it may not be worthwhile to split IUI with different ovarian stimulation agents as different nodes in the network (e.g. CC-IUI, Gn-IUI, CC/Gn IUI), as all major studies comparing IVF vs IUI included various ovarian stimulation strategies in the IUI arm for pragmatic reasons. If the committee were to be strict on the nodes, they should have introduced a new node CC/letrozole - IUI as Farquhar 2018 include CC-IUI or letrozole-IUI as the intervention instead of CC-IUI alone.	effects for use in the health economic model. Had Elzeiny 2014 and Goverde 2020 been excluded from this then there would not have been an IVF treatment arm for that network. Although participants in Farquhar 2018 in the IUI arm could receive letrozole or clomifene, only 7 patients (7% of those in IUI arm) received letrozole. Furthermore, the trial protocol for Farquhar 2018 suggests that letrozole was a deviation from the intended intervention as only clomifene is in the registered protocol. Therefore, the committee considered that the coding of this study as CC-IUI was reasonable, especially in the context of an NMA. Grouping of similar interventions helps to achieve network connectivity and to make meaningful comparisons. When individual interventions are too granular or sparsely studied, the network may become disconnected, limiting the ability to estimate relative effects across all treatments. Combining similar interventions improves statistical power, reduces inconsistency, and allows for more robust and interpretable results. As cancellation criteria were not included as a planned subgroup analysis in the review protocol, this was not assessed when extracting or analysing the data.

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				• Cancellation criteria plays an important role in IUI with ovarian stimulation when evaluating outcomes on live birth, clinical pregnancy and multiple pregnancy. For those with strict cancellation criteria implemented, lower live birth rates and lower multiple pregnancy rates were expected. Combining studies with various cancellation strategy may violate the transitivity assumption in this NMA as the intervention (e.g. Gn-IUI, CC-IUI) was different when compared to different interventions. It would be useful to restrict the analysis to studies on strict cancellation criteria in the NMA.	
Cochrane Gynaecology and Fertility Group	Evidence review K Assisted reproduction techniques	General	General	***Assisted reproduction techniques and poor prognosis*** • Steures 2006 was inappropriately included as a study on a population of poor prognosis (defined as a prediction score using the Hunault prediction model of 30-40% for spontaneous conception in the next year). In fact, Hunault prediction model of 30-40% for spontaneous conception in the next year was considered as an intermediate prognosis in Steures 2006. This population (30-40%) is not overlapping with all other studies on poor prognosis with the Hunault prediction model <30%.	Thank you for this comment. The labelling in the guideline as "poor prognosis" was essentially used as shorthand for studies which selected on the basis of prognosis rather than a truly mixed population, not selecting on any prognostic criteria. We have now defined this group of studies as a population with "prognostic restriction". We accept that the population in Steures 2006 could be considered to differ from that of the other studies included in the "poor prognosis" population. Therefore, we have undertaken an additional NMA as a sensitivity

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				• The inclusion of Steures 2006 has impacted the overall network analysis and the analysis on poor prognosis patients. The clear benefit of CC-IUI over expectant management (Farquhar 2018) disappeared when Steures 2006 was also included. • This has also impacted the overall **Recommendation 1.81** as those with a poor prognosis should start ovarian stimulation-IUI directly instead of having 2 years' expectant management.	analysis in which Steures 2006 was excluded. This sensitivity analysis has been added to Evidence Review K. As expected, given that the point estimate favoured expectant management in Steures 2006, the sensitivity analysis shows a greater treatment effect size with narrower credible intervals. However, the committee did not decide to amend their recommendations after seeing this analysis. First, they noted that these recorded a relative treatment effect measured against expectant management in poor prognosis patients. A lower baseline would have implications for the absolute treatment effect, and no economic analysis was undertaken to assess whether this earlier intervention would represent a cost-effective use of NHS resources. Furthermore, they did not believe clinics would be able to routinely prognosticate patients to identify a group who could be fast tracked.
Cochrane Gynaecology and Fertility Group	Evidence review L Intracytoplasmic sperm injection	General	General	***ICSI*** There have been 2 recent, large RCTs that have compared ICSI and IVF that have been not yet been included in the Cochrane review (because of their recency) or the evidence review:	Thank you for this comment. During the development phase of the guideline, a Cochrane review (Cutting 2023) was identified which matched the guideline committee's PICO, and a pragmatic decision was made to include this review in

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				• Wang 2024 https://doi.org/10.1016/S0140-6736(23)02416-9 • Berntsen 2025 https://doi.org/10.1038/s41591-025-03621-x We request that the above trials are included in Evidence review L.	the evidence review and use it for recommendation making. The committee considered the review to be sufficiently relevant, high quality and up to date. In terms of the 2 studies referred to in the comment, they both found no benefit of ICSI for non-male-factor fertility issues and therefore would have no impact on the overall findings or recommendations.
Cochrane Gynaecology and Fertility Group	Evidence review M Advanced sperm selection techniques	General	General	***Advanced sperm selection techniques and inclusion of untrustworthy studies*** The Guideline has adopted the evidence review from HFEA. The HFEA evidence review for this clinical topic has included a problematic study with trustworthiness concerns: • Hasanen 2020 - This study has an expression of concern: https://doi.org/10.1007/s10815-020-01913-4	Thank you for your comment. The HFEA evidence statement for PICSI was primarily based on evidence from 1 RCT which the HFEA's independent reviewer deemed to be high quality (Miller 2019). Although Hasanen 2020 was included in the list of studies found by the HFEA investigating the effectiveness of PICSI, it did not influence decision-making or the committee's agreement to recommend against the use of PICSI as a treatment add-on. An acknowledgement of the above has been added to the evidence review under the 'Benefits and harms' section.
Cochrane Gynaecology and Fertility Group	Evidence review M Advanced sperm selection techniques	009	004	***PICSI*** ***Live birth*** • PICSI is rated black in the HFEA traffic-light system, indicating that the available evidence shows no effect on the chance of live birth. However, the RR for Live birth (LB) in the Miller	Thank you for your comment. In our Methods supplement we detail that for the outcome live birth, where the MID was statistical significance, imprecision was judged based on optimal information size criteria. Evidence was considered

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				2019 study (including term and preterm live births) is RR 1.09, 95% CI 0.93 - 1.26. The upper bound of this CI crosses the Minimum Important Difference of 1.25 used by NICE to signal substantial imprecision; The trial results suggest that if ICSI live birth rate is around 28% then the live birth rate with PICSI is somewhere between 26% and 36%. • We therefore do not agree that PICSI has no effect on the chance of live birth – in fact it is unclear – and there is potential for possible important benefit of 8 percentage points. ***Miscarriage*** • In addition, the relevant Lancet paper (Miller 2019) shows a strongly significant decrease of the miscarriage rate. If a strategy can reduce miscarriage starting from equal pregnancy rates, it will increase the LB rates. The fact that in Miller 2019 LB are not statistically significant comes from the higher event rate. The evidence review relies on the HFEA analysis which presents an overall rating for live birth but only presents a rating for miscarriage in women over 35. There is no explanation for why an overall miscarriage rating is not provided. The Miller 2019 study	seriously imprecise if there were less than 300 events, based on the rule-of-thumb specified in version 3.2 of the GRADE handbook (Schünemann 2009), and very seriously imprecise if there were less than 150 events. Live birth occurred in a total of 725 participants and so we would not usually have downgraded this for imprecision. The HFEA did consider effects on miscarriage as part of their overall rating and the reported benefit of PICSI in terms of miscarriage rates found in Miller 2019 is reported in the evidence review commissioned by the HFEA, which is available from the HFEA SCAAC website. It is worth noting that the HFEA's comment that the study was not designed to investigate the effect of PICSI on miscarriage rate due to it being a secondary outcome is echoed by Cochrane in their systematic review on advanced sperm selection techniques for assisted reproduction: "the trial was not powered to evaluate the outcome of miscarriage (Miller 2019)". The committee considered evidence from this Cochrane review when drafting recommendations, including the lower chance of miscarriage in the HA-ICSI group. However, this evidence was of low quality with serious imprecision due to low event rate and included both PICSI and other HA-ICSI interventions in the analysis.

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				recruited women 18-43 and reported benefit of PICSI in terms of miscarriage rates: OR 0.61 (95% CI 0.44 – 0.85). The evidence review states "The only study considered to be of high quality (Miller 2019) was not powered to investigate miscarriage (as it was assessed as a secondary outcome), however results showed miscarriage rates were lower for those who received PICSI." However, this is not a valid reason to discount the finding—by definition, trials are powered for a single primary outcome, and secondary outcomes remain important to report and interpret. The Miller 2019 study showed clear benefit of PICSI for miscarriage. • This important result appears to be obscured by the HFEA's approach of only reporting miscarriage results in older women such that the Miller 2019 study does not directly apply, and this limitation is carried through to this NICE review. • We are not suggesting that the guideline should recommend PICSI based on a single study. However, the evidence review should present a balanced and transparent account of the available evidence, including the miscarriage outcome reported in Miller 2019.	The lower rate of miscarriage as found in Miller 2019 is detailed in the evidence review as you have quoted as well as in the 'Benefits and harms' section, alongside the reasons why the committee did not consider the evidence convincing enough to lead to recommendation of PICSI's use. The committee agreed the evidence of effectiveness was not sufficient to recommend PICSI over standard ICSI, especially in light of the additional cost without clear benefit.

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Cochrane Gynaecology and Fertility Group	Evidence Review M Q	General	General	***Limitations of evidence review methodology*** For evidence relating to IVF add-ons (Evidence review M-Q), the committee has made the pragmatic decision to rely on the evidence synthesis produced by the Human Fertilisation and Embryology Authority (HFEA) for their traffic light system. We would like to highlight four key limitations of the process used by the HFEA – Observational studies are included (even when sufficient RCT data is available) – Only studies published after 2010 are included (when older RCTs may still provide relevant data) – The data is updated every 5 years and may miss important recent trials – A trustworthiness assessment of studies is not routinely conducted We would like to inform the committee of a new resource produced in partnership with Cochrane that reviews the evidence for IVF add-ons and is updated every 6-12 months (launched April 2025): Evidence-based IVF https://www.unimelb.edu.au/ivf	Thank you for your comment and your feedback on this approach, as well as bringing our attention to this new source. Unfortunately we could not have used this resource to inform recommendations during development of the guideline as it was launched in April 2025, but it may be used for consideration in future updates. We will notify the NICE surveillance team which monitor key events relevant to the guideline about this resource. We acknowledge the methods used by the HFEA are not the same as those used by NICE, however it was recognised that significant work had already been carried out by a number of authorities regarding add-ons and therefore carrying out additional NICE systematic reviews would involve significant duplication of efforts with a low chance that doing so would have substantial impact on recommendations made. Please note that all stakeholders were made aware of the decision to use evidence from the HFEA's statements on add-ons to inform recommendations in advance, and were invited to comment at the point the decision was made. We did not receive any feedback at that time. The HFEA did prioritise RCTs in their reviews, basing decision-making primarily on RCTs considered to be

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				Importantly, it follows robust Cochrane guidelines and does not suffer from the above four limitations of the HFEA process. Evidence-based IVF covers the following add-ons relevant to this guideline • Physiological intracytoplasmic sperm injection (PICSI) (Advanced sperm selection techniques) • Endometrial scratch • Pre-implantation genetic testing for aneuploidy (PGTA) • Endometrial receptivity testing • Intralipid infusion (Immune therapies) • Corticosteroids (Immune therapies) We are aware of **at least 6** new and eligible trials that have been missed and a further **15 untrustworthy studies** that have been included in the NICE evidence review – four of which have been retracted and three with expressions of concern. We therefore request – The 15 untrustworthy studies be excluded – Trials missed by the HFEA are included in the relevant Evidence review	moderate to high quality, where available. Where these were not available, the inadequacy of the evidence base was reflected in the evidence statements made by the HFEA. The HFEA did include studies published prior to 2010, as detailed in the evidence review commissioned by the HFEA, which is available from the HFEA SCAAC website. The issues regarding trustworthiness of included trials have been addressed in detail in response to your relevant comments on the individual evidence reviews.

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				– The Evidence-based IVF website be included as an additional resource in the Evidence reviews: D, M, N, P, Q.	
Cochrane Gynaecology and Fertility Group	Evidence review N PGTA	General	General	***PGT-A and new trial for inclusion*** As noted in Comment 1, there is one new trial on PGT-A that has been missed by HFEA/cited Cochrane reviews and included by Evidence-based IVF, this study is: • Beebeejaun 2025 doi: 10.3390/jcm14145166 We request that the above trial missed by the HFEA be included in the evidence review, and that the Evidence-based IVF website be included as an additional resource in the ***Evidence review N Pre-implantation genetic testing for aneuploidy.***	Thank you for your comment. This trial was published too late to be included in either of the evidence reviews used for decision-making. Upon initial review the results of this trial did not find a significant benefit of PGT-A over embryo selection by morphology for any outcomes, and had significant imprecision in the outcome cumulative live birth, with very wide confidence intervals crossing the line of no effect and a low number of events (ITT adjusted OR 2.26, 95% CI 0.91–5.60; p > 0.05). Authors themselves note: "We observed a higher cumulative live birth rate (cLBR) in the PGT-A arm compared to the control group in our intention-to-treat analysis; however, this difference did not reach statistical significance. These findings should be interpreted cautiously, given the study's limited sample size and its exploratory nature". There are also concerns about differences between the protocol and study outcomes, including the fact that live birth and cumulative live birth rates were not initially intended to be outcomes. Overall, these findings do not sufficiently impact the evidence base already considered

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					by the committee, but may be considered in future updates. Unfortunately, we could not have used the Evidence-based IVF website to inform recommendations during development of the guideline as it was launched in April 2025, but it may be used for consideration in future updates.
Cochrane Gynaecology and Fertility Group	Evidence review N PGTA	006	017	***PGT-A and number of embryos*** • The committee repeatedly refers to the potential harms of PGT-A in that it "may reduce the number of embryos available for transfer". Indeed, this is the very aim of PGT-A – to help patients avoid aneuploid embryo transfers. If PGT-A works, it does so precisely by reducing the number of embryos considered suitable for transfer. It should not be referred to as a harm or risk of PGT-A. The real concern is that it may reduce the number of embryos *with potential to result in a healthy live birth* (through transferred mosaics, false positives etc). As currently worded, the statement risks suggesting a limited understanding of the intended purpose of PGT-A. • Further example: Page 14 line 37 "In particular, the committee noted that PGT-A often reduces the number of embryos available for transfer and can	Thank you for your comment. This wording had been amended as per your suggestion throughout the review.

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				therefore lower the likelihood of a fertility patient undergoing embryo transfer at all, lowering their chances of having a baby." • In the draft guideline itself it states (page 66) "PGT-A often reduces the number of embryos available for transfer, which can mean that embryo transfer cannot take place in that IVF cycle."	
Cochrane Gynaecology and Fertility Group	Evidence review N PGTA	006	024	***PGT-A and inclusion criteria*** • Table 1 Summary of the protocol (PICO table) states studies excluded "where PGT-A was not performed on full cohort of embryos" yet the Yan 2021 study is included which tested less than half the available cohort on average. This study contributes substantial weight to the HFEA analysis for most outcomes and is extensively discussed in the evidence review document (page 9, lines 7-14). The inclusion of Yan 2021 is inconsistent with the specified PICO inclusion criteria.	Thank you for your comment and for highlighting this concern. The committee discussed the issue with this study and agreed we would not normally have included this study for consideration according to our planned PICOs. As a result, the committee agreed the evidence base had significant uncertainties regarding the effectiveness of PGT-A which supported the recommendation against its use for the purposes of improving live birth rates.
Cochrane Gynaecology and Fertility Group	Evidence review N PGTA	009	011	***PGT-A and time to pregnancy*** • "The HFEA noted that for some patients, PGT-A may shorten the time to pregnancy (by avoiding a series of embryo transfers), but the evidence from this RCT showed that the time to achieving pregnancy for most patients may be longer due to the additional time taken to carry out this test."	Thank you for your comment. The wording has been amended to be more accurate.

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				• The evidence relating to the impact of PGT-A on time to pregnancy is very limited. This RCT (Yan 2021) did indeed suggest that time to pregnancy was increased by PGT-A, but it isn't clearly correct to say that this was because of "the additional time taken to carry out this test". Where an intervention decreases the overall likelihood of an event (such as having a live birth) occurring, it will tend to increase the expected time it takes to have that event, because a larger number of people will never have it. The increase in time to pregnancy in Yan 2021 will reflect the overall decrease in the success rate for PGT-A compared to the comparator arm in the study.	
Cochrane Gynaecology and Fertility Group	Evidence review O			**Embryo selection strategies in IVF** • Time lapse imaging has not received a recommendation on this updated guideline despite being one of the most commonly used add-ons in the UK. • The reason for not including a recommendation has been because it is widely used and that it may have benefits in terms of incubation such as providing a more stable environment than conventional systems, even if benefits in terms of embryo selection are less clear. However, there ***is*** now a large well conducted high quality RCT	Thank you for your comment. The wording in the review has now been amended to clarify the committee's position that any potential benefits of the time lapse systems might be a result of the undisturbed environment and not the incubation system itself. The committee were aware of the TILT trial (Bhide 2024) when they made the recommendations and this has been documented in the evidence review O section 'The committee's discussion and interpretation of the evidence': "The findings of this RCT further supported the decision not to recommend

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				(TILT Clinical effectiveness and safety of time-lapse imaging systems for embryo incubation and selection in in-vitro fertilisation treatment (TILT): a multicentre, three-parallel-group, double-blind, randomised controlled trial - The Lancet) published on time-lapse to add to the existing trials (Time-lapse systems for embryo incubation and assessment in assisted reproduction - Armstrong, S - 2019 | Cochrane Library). The evidence from TILT ***does*** explore whether the benefit of time-lapse might lie within the stable incubation environment, the embryo selection potential, or a combination of the two, and it did not reveal any benefit in terms of pregnancy or live birth from any of the comparisons undertaken. • Given that no further large RCTs are likely to arise from time-lapse given that it is widely adopted and seen as a useful way of performing embryo incubation and assessment, NICE should offer guidance on its use. • The harms are likely to be low, but the risk to patients is financial given that most clinics charge an additional fee for its use. In the same way that NICE have made recommendations of other add-ons, it would seem reasonable to offer a	the use of time-lapse imaging because no important difference in live birth rates was shown for time-lapse imaging compared to standard care. The committee discussed that this was a pragmatic trial and as such was designed to reflect current practice, in that each centre used their own time-lapse imaging system and algorithm. The committee highlighted that there might be future potential for embryo selection guided by continuous time-lapse monitoring, given that it is likely that artificial intelligence (AI) algorithms will improve with the development of big data analytics. The committee agreed that further research would be needed to develop and to test these algorithms but that it would be premature to draft a fully specified and implementable research recommendation that would be able to deliver conclusive results about the potential benefits of time-lapse imaging for embryo selection." With regards to financial risk, according to the committee's knowledge, most institutions no longer usually charge for the use of time-lapse incubation in current practice. The committee discussed the fact that there might, however, be a cost and resource implication to recommending against the use of time-lapse machines because this would reduce the availability of incubation machines overall due to the widespread use

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				recommendation on this very commonly offered one. • A recommendation would protect patients from unnecessarily paying for time-lapse incubation, whilst also encouraging clinics to offer time-lapse to all if they felt it was a helpful incubator to have in the laboratory. Offering it based on improved outcomes is where the problem lies.	of time-lapse machines. Time-lapse systems also usually require less clinician input so there would also be a labour impact of recommending against their use. Given the potential for future health technology developments using these systems, the possible benefits of an undisturbed incubation environment (such as the reduced likelihood of human error), and the low financial risk to patients compared to the potential cost and resource implication of recommending against their use, the committee agreed not to do so.
Cochrane Gynaecology and Fertility Group	Evidence review P	009	001	***Endometrial scratching and included trials*** • "Endometrial scratching was rated orange for increasing the chances of having a baby for most fertility patients, primarily based on findings from 5 more recently conducted randomised controlled trials (RCTs: Gibreel 2015; Glanville 2022; Hilton 2019; Mackens 2020; Wong 2022)." • "In terms of the 5 more recent studies that were considered moderate or high quality, the HFEA interpreted the evidence as conflicting for the outcome live birth, whereby 3 studies were considered to favour endometrial scratching and 2 were considered to favour control (no or sham procedure). However, the 95% confidence intervals were very wide and all crossed the line of	Thank you for your comment and for bringing the issues regarding the Gibreel author team to our attention. Please note that endometrial scratching was one of the topics whereby the decision was made to review the HFEA's evidence statements rather than conduct a new systematic review, to reduce duplication of efforts. We acknowledge the methodology is therefore different to the standard NICE approach. The HFEA highlighted these 5 studies in particular because they considered them to be studies of moderate to high methodological quality. The critical review of studies included assessment of risk of bias from allocation method, blinding, selective reporting, unexplained attrition, unplanned interim analysis and other miscellaneous

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				no effect for this outcome, showing significant uncertainty in the effect estimate" • There are over 30 published trials of endometrial scratching. What is the rationale for the focus on these 5 RCTs? They don't represent the newest or the highest quality studies of endometrial scratching. Indeed, the Gibreel author team has a number of retracted studies and this trial was excluded from the Evidence-based IVF website due to trustworthiness concerns: https://www.unimelb.edu.au/ivf/treatment/endometrial-scratching • Furthermore, it is not appropriate to focus on a meta-analysis of just these 5 studies and note that the "95% confidence intervals were very wide".	errors in the design, conduct or reporting of results. Trustworthiness checks were not a part of the HFEA's methods. The exclusion of Gibreel does not affect the interpretation of the results compiled by the HFEA: there is still uncertainty in the evidence base meaning it is unclear whether endometrial scratch has the potential to harm, provide benefit, or have no effect on outcomes. These conclusions were consistent with Cochrane's findings that the effect of endometrial injury on live birth and clinical pregnancy among women undergoing IVF is unclear because the results of the meta-analyses are consistent with an increased chance, no effect and a small reduction in these outcomes. An acknowledgement of the concerns about Gibreel 2015 has been added to the evidence review under the 'Benefits and harms' section. The 'HFEA treatment ratings' section provides an overview of the HFEA's consideration of the evidence included in their reviews.
Cochrane Gynaecology and Fertility Group	Evidence review P	009	021	***Endometrial scratching and non-randomised trials*** • "Endometrial scratching was given a grey rating both for improving the chances of having a baby for patients with recurrent implantation failure due to the fact that most of the studies investigating the effectiveness of endometrial scratching in this	Thank you for your comment. The HFEA included and prioritised RCT evidence when drafting their evidence statements and the grey rating was used because none of the included studies were considered to be moderate or high quality by the

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				population were non randomised trials" - this only highlights the flawed approach of the HFEA (carried through to NICE) to include data from non-randomised trials when there exist MANY randomised trials, even within the RIF subgroup.	external reviewer, including the RCTs. This is accurately represented in the full quote you have referenced: "[…] most of the studies investigating the effectiveness of endometrial scratching in this population were non-randomised trials, and none of the RCTs were considered to be moderate or high quality."
Cochrane Gynaecology and Fertility Group	Evidence review P Endometrial scratch	General	General	***Endometrial scratching and inclusion of untrustworthy studies*** The Guideline has adopted the evidence review from HFEA. The HFEA evidence review for endometrial scratching has included problematic studies with trustworthiness concerns, including: • Maged 2018 - This study has been retracted: https://doi.org/10.1002/ijgo.15695 • Helmy 2017 - This study has been retracted: https://doi.org/10.1002/ijgo.15566 • El Khayat 2015 - This study has been retracted: https://doi.org/10.1016/j.ejogrb.2015.08.025 • Karimzadeh 2009 – co-author Nasim Tabibnejad is on retraction watch https://doi.org/10.1016/j.ejogrb.2019.02.019	Thank you for your comment. The HFEA evidence statement for endometrial scratching was primarily based on evidence from 5 RCTs which the HFEA's independent reviewer deemed to be high quality (Gibreel 2015, Hilton 2019, Wong 2022, Mackens 2020, Glanville 2022). Please see the response to your other comment regarding Gibreel 2015. Although the other 4 studies were included in the list of studies found by the HFEA investigating the effectiveness of endometrial scratch, they did not influence decision-making or the committee's agreement to recommend against the use of endometrial scratching as a treatment add-on. An acknowledgement of the above has been added to the evidence review under the 'Benefits and harms' section.
Cochrane Gynaecology and Fertility Group	Evidence review P Endometrial scratch	General	General	***Endometrial scratching and new trials for inclusion*** As noted in Comment 1, there are 5 new trials on endometrial scratching that have missed by HFEA/cited	Thank you for your comment. The first three trials were published too late to be included in either of the

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				Cochrane reviews and included by Evidence-based IVF, these include: • Cellier 2024 doi: 10.1038/s41598-023-50715-y • Vidal 2023 doi: 10.1093/humrep/dead093.107 • Aghajanpour 2024 doi: 10.18502/ijrm.v22i4.16387 • Yueng 2014 The effect of endometrial injury on ongoing pregnancy rate in unselected subfertile women undergoing in vitro fertilization: a randomized controlled trial. Human Reproduction. Nov 01, 2014 29(11):2474-2481 – Polanski 2015 Endometrial biopsy prior to assisted reproductive techniques (ART) does not improve treatment outcome in unselected patients. Human Reproduction. 31st Annual Meeting of the European Society of Human Reproduction and Embryology (ESHRE) We request that the above trials are included into the evidence review, and that the Evidence-based IVF website be included as an additional resource in ***Evidence review P Endometrial Scratching***.	evidence reviews used for decision-making. In terms of the studies referenced: • Cellier 2024: this study did not find a significant difference between endometrial scratching and control for the outcomes live birth, clinical pregnancy, multiple pregnancy, miscarriage, or OHSS • Vidal 2023: This is a conference abstract and would not normally be used for decision-making because conference abstracts usually do not contain enough information to allow confident judgements about the quality and results of a study • Aghajanpour 2024: this study did not find a significant difference between endometrial scratching and control for the outcomes live birth, clinical pregnancy, multiple pregnancy, miscarriage, or ectopic pregnancy The findings of the above studies are therefore consistent with the recommendation not to offer endometrial scratch on the basis of a contradictory evidence base which does not consistently show a benefit of the add-on. Yeung 2014 and Polanski 2015 were both included in the Cochrane review used by the committee to inform decision-making and therefore do

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					contribute to the evidence base informing recommendations. Unfortunately, we could not have used the Evidence-based IVF website to inform recommendations during development of the guideline as it was launched in April 2025, but it may be used for consideration in future updates.
Cochrane Gynaecology and Fertility Group	Evidence review Q Immune therapies	General	General	***Immune therapies and inclusion of untrustworthy studies*** The Guideline has adopted the evidence review from HFEA. The HFEA evidence review for steroids and intralipids has included problematic studies with trustworthiness concerns, including: **Steroids (Glucocorticoids)** • Fawzy 2008 - This study has an expression of concern: 10.1007/s00404-023-07159-6 • Fawzy 2013 - This study has authors that have other studies with an expression of concern • Gomaa 2014 - While this study doesn't have a published expression of concern (EOC) or retraction notice, we have major trustworthiness concerns about the authorship group. One co-author (Abdellatif Elkholy) has an EOC for a different study because of ethical concerns (10.1007/s12020-021-02946-0). One co-author,	Thank you for your comment. With regards to steroids, Fawzy 2008 and Gomaa 2014 investigated the effect of steroids on women with a history of recurrent miscarriage, which is an excluded population in the NICE fertility guideline. The committee took this into account when reviewing the HFEA's evidence review to ensure studies with an excluded population did not influence recommendations. Fawzy 2013 is a quasi-randomised trial which the HFEA did consider when drafting the evidence statements, however overall the HFEA concluded there was insufficient evidence from moderate/high quality studies for live birth and miscarriage in both populations. In terms of Intralipids, the grey rating was used by the HFEA because none of the included studies were considered to be moderate or high quality by the

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				Mourad El-Said, has a retraction notice (https://doi.org/10.1111/jog.15874) **Intralipids** • El-Khayat 2015 - While this study (abstract only) doesn't have a published expression of concern or retraction notice, this author has 4 listed retractions (10.1016/j.ejogrb.2022.07.002 ; 10.1016/j.ejogrb.2023.09.014 ; 10.1002/ijgo.15615 ; 10.1002/ijgo.15694) • Al-Zebeidi 2019 - This study has been retracted: 10.1080/09513590.2025.2554449	external reviewer: **"**The use of intralipids as part of fertility treatment in healthy patients is rated grey for improving the chances of having a baby for most fertility patients. This is because there is insufficient moderate/high quality evidence.**"** The exclusion of these studies would further weaken the evidence base. The exclusion of the highlighted studies would therefore not affect recommendations. An acknowledgement of the above has been added to the evidence review under the 'Benefits and harms' section.
Cochrane Gynaecology and Fertility Group	Guideline	025	016	Recommendations 1.5.3-1.5.7 ***Hypothalamic-pituitary-ovarian dysfunction (predominantly PCOS)*** • The recommendations don't include letrozole as a treatment, despite it being widely established to work better than clomiphene (see Cochrane review by Franik et al 2022 https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010287.pub4/full) Why hasn't the committee included a recommendation on this? • Letrozole has been recommended as the first-line treatment by multiple other guidelines but not mentioned in the current NICE guideline at all. • Even though letrozole may be considered off-label use in the UK, the current guideline included	Thank you for your comment. NICE is currently developing a guideline on PCOS adapting the International evidence-based guideline for the assessment and management of polycystic ovary syndrome. The scope of this guideline includes management of infertility in the context of PCOS. The recommendations in the section on Hypothalamic-pituitary-ovarian dysfunction (predominantly PCOS) have been stood down in anticipation of the new guideline. We have shared your comments with the team working on the PCOS guideline.

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				letrozole in the treatment of unexplained infertility, resulting in inconsistent inclusion of off-label medicine across the guideline.	
Department of Health, NI	Guideline	031		1.9.3 '*Offer IVF treatment for people under 42 years'* - we note that the revised guideline is now indicating the upper age limit is reduced to the offer of '*IVF treatment for people under 42 years if….*' We suggest this recommendation provides further clarity by stating the access criteria applies to those who are up to and including the ages of 41 and 364 days. Suggest adding a line saying 'if they reach their 42nd birthday without conceiving, complete any current full cycle of IVF but do not consider any more cycles'.	Thank you for your comment. We have clarified the recommendation based on your suggestion.
Department of Health, NI	Guideline	031		1.9.5 6 Cycles can be cost effect, recommend 3 but then offer another 3 more cycles (dependant of patient) New guideline: a person is under 40 years and has not conceived after 3 full cycles of IVF treatment: • discuss the probability of success and the implications of more treatment and • consider up to **3 further full cycles of IVF treatment**.	Thank you for this comment. The recommendation to consider a further 3 full cycles of IVF states that any consideration of further cycles should include a discussion of the probability of success and the implications of further treatment. This will be dependent on individual circumstances, informed by clinical and professional judgement and shared decision making.

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				Further guidance should be provided on eligibility for additional cycles.	
Department of Health, NI	Guideline	032		1.9.6 - We are of the view that the amended recommendation *'For those under 40 years, any previous full IVF cycle, whether self- or NHS-funded, should count towards the total number of full cycles that should be offered by the NHS. Previous self-funded IVF treatment should not preclude NHS-funded IVF treatment'* should be further revised. We consider that the above should be expanded further / provide clarity in terms of the total number of full cycles that should be offered by the NHS for example what do NICE recommend be offered in terms of the offer of NHS-funded IVF in those circumstances where a patient has underwent a high number of self-funded IVF cycles. This is of particular significance when IVF waiting times are lengthy / Providers are experiencing periods of reduced capacity and many women feel compelled to pursue the self-funded route, and should not therefore be disadvantaged in terms of her entitlement to NHS-funded IVF treatment. What are the recommended limits that NICE would advise?	Thank you for this comment. The recommendation has been revised to make it clearer. The number of IVF cycles the NHS should provide is not independent of self-funded cycles as not achieving a pregnancy in successive cycles (regardless of where they are funded) is a marker of poorer prognosis and therefore declining treatment effectiveness.

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Department of Health, NI	Guideline	043		*The previous NICE guideline recommendations on fertility preservation only covered people with cancer who wish to preserve their fertility. For this update, the population was expanded to cover anyone with a medical indication likely to impair their reproductive potential, including medical treatments or conditions. Most of the evidence was among people with cancer; however, there was some evidence that fertility preservation can be successful for other medical indications. The committee agreed that fertility preservation should be discussed as an option for anyone with an appropriate medical indication.* will NICE provide further detail in the final guideline with regard to what is to be classed as an appropriate medical indication?	Thank you for this comment. The guideline committee agreed that they can't provide an exhaustive list of all medical conditions and medical/surgical interventions that potentially warrant fertility preservation, this needs to be based on clinical judgment. Evidence review R section on the committee's interpretation and discussion of the evidence includes the committee's discussion about examples of potential medical indications where fertility cryopreservation may be relevant.
Department of Health, NI	Guideline ICB Briefing held via Zoom on 11 September, chaired	079	015	Upper BMI up to and including 30.0kg/m^2 We note that Table 3 indicates that the 2004 guideline section 1.10.4. Body mass index, recommendation 1.10.4 '*Women should be informed that female BMI should ideally be in the range 19 to 30 before commencing assisted reproduction, and that a female BMI outside this range is likely to reduce the success of assisted*	Thank you for this comment. As pointed out in the comment, this recommendation has been deleted because it was not considered to be useful and could be misused to deny treatment. The committee agreed that advice around BMI is already sufficiently covered in the section on 'Initial advice'. The committee agreed that BMI advice should focus on health optimisation rather than being used as an

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	by Jonathan Benger			*reproduction procedures'* has been deleted from the 2025 revised draft guideline. The reason for this having been deleted is outlined on page 79, namely '*This recommendation has been deleted because it was not considered to be useful and could be misused to deny treatment, and advice around BMI is already covered in section on 'Initial advice'.'* Commissioners / Providers attending the ICB Briefing noted NICE comments that further evidence review will be required in terms of BMI and IVF success rates. NICE encouraged stakeholders attending the Briefing to share their comments in relation to BMI within the consultation response document. We are of the view that the draft guideline should be updated to reflect the evidence base in terms of upper BMI and IVF success rates to ensure unambiguity in interpreting the guideline on the part of Commissioners, Providers and Patients alike. NICE are requested to look at BMI, undertake a robust evidence finding exercise, develop an evidence review and make an informed recommendation within the Guideline.	eligibility criterion. It was not possible to develop access criteria for some potentially important predictors (e.g. BMI) as these were not included in the HFEA dataset used to develop prediction models. Even in the 2013 guideline, BMI was not part of the recommended access criteria for IVF, but we are aware that BMI is and has been widely used as such. We take note of your suggestion, which may be considered when future updates for the guideline are planned.

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Department of Health, NI	Guideline	095		1.7.2 Old recommendation: consider unstimulated intrauterine insemination as a treatment option for those with health-related issues or same sex relationships. New recommendation: offer 12 cycles of IUI as a treatment option for those with health-related issues. Same-sex couples were removed from the recommendation because for anyone using artificial insemination to conceive for non-health-related reasons, unless they have a known health-related fertility problem, the first 6 cycles of artificial insemination are not within the remit of this guideline as defined in the scope agreed that 12 cycles should be offered before IVF is considered for populations where conception through vaginal sexual intercourse is not an option because of health-related issues. For people using artificial insemination for a non-health-related reason, the first 6 cycles of artificial insemination are not within the remit of this guideline. If they have not conceived within the first 6 cycles of insemination, they would then be considered to have a health-related fertility problem, as defined in the scope of this guideline, and	Thank you for this comment.

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				further clinical investigation and assessment should be offered	
Department of Health, NI	Guideline	099		1.14.2 For NHS-funded fertility preservation, do not apply the eligibility criteria used for conventional fertility treatment, including lower age limit. New- Indication for fertility preservation now wider than just cancer.	Thank you for this comment. Fertility preservation recommendations are aimed not only at those with cancer but also those who are preparing for medical treatment or have a medical condition that is likely to impair their fertility.
Endometriosis UK	Guideline	General	General	The terms "mild endometriosis" and "severe endometriosis" should be removed from the guideline, as such descriptors are misleading and reductive. These labels reflect only the visual extent or distribution of lesions and fail to convey the overall clinical impact of the disease. The surgical appearance of endometriosis does not necessarily correlate with symptom burden or with the likelihood of infertility. Individuals with minimal disease may experience debilitating pain or marked fertility difficulties, while others with extensive disease may have few symptoms and normal reproductive function. Given that endometriosis is a well-recognised cause of infertility, all those affected should have equitable access to appropriate and timely fertility treatment, and none should be categorised alongside those with "unknown infertility." There are four main reasons for this:	Thank you for your comment. The committee considered your and other stakeholders' related comments very carefully. The committee agreed that these terms are clinically ambiguous and there are no standard definitions. Where 'mild endometriosis' was included as an inclusion criteria in the evidence reviews, it was typically defined as stage 1-2 of rASRM, however, these were not distinct population groups in the evidence. Furthermore, they agreed that the severity of endometriosis based on imaging (using, for example, rASRM staging) does not necessarily correspond with the impact of the endometriosis on the person's fertility or quality of life. Based on the stakeholder feedback, the committee decided not to refer to these terms in the recommendations. They also agreed to add a new section in the guideline titled "Endometriosis" including

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				1. Endometriosis symptoms and progression are mainly managed by contraceptive hormones. Endometriosis is recognised as a chronic pain condition. For some the pain is debilitating, affecting all aspects of life including employment and relationships. The severity of symptoms is not linked to how extensive or deep the disease is. In addition to severe pelvic pain, one of the symptoms is painful sex. If endometriosis is not managed the disease may progress, along with increasing severity of symptoms. The primary management of endometriosis relies on hormonal therapies, the majority of which have contraceptive properties. As the draft currently stands, NICE would, in effect, be requiring individuals with the condition to discontinue essential treatment for a period of two years in order to become eligible for NHS-funded fertility support. Endometriosis UK cannot believe that NICE would issue a guideline requiring a significant population at which that guideline is targeted to stop their medication and live with the potential consequences such as worsening symptoms resulting in reduced economic and social activity, disease progression and potential organ damage, and for many the impossibility of having	recommendations for treatment options, including reference to the NICE guideline on endometriosis section on management if fertility is a priority. Please also see the rationale and impact section associated with the recommendation for further explanation why the committee made the recommendations.

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				sex due to the pain. We feel this would be a significantly regressive step; it is condemning many women with endometriosis to make choices that no one with unexplained infertility will ever have to make. 2. Endometriosis is well recognised to be associated with infertility. However, the underlying mechanisms are not yet fully understood. It is therefore essential that all individuals affected by endometriosis are afforded equitable consideration within the guideline, consistent with the approach taken for any other condition known to influence fertility. No distinction should be drawn on the basis of arbitrary or unquantifiable classifications. 3. The draft guideline uses the terms 'mild' and 'severe' endometriosis. There is no recognised classification for endometriosis that divides endometriosis into a simple two categories of mild and severe. These terms are not used in NICE Guideline on Endometriosis NG73. The suggestions in this Guideline on fertility problems would contradict this newly updated NICE guidance which states:	

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				"The management of endometriosis-related subfertility should have multidisciplinary team involvement with input from a fertility specialist and access to fertility services. Depending on the severity of the endometriosis this may be in a secondary care gynaecology service or a tertiary care specialist endometriosis service." The severity of symptoms of endometriosis vary person to person depending on where the disease is found. For example, an individual may have a small amount of disease causing severe and debilitating pain, whilst another may have extensive disease with less pain. All those with endometriosis should remain as being treated equally in the guideline, as at present. There should be no division using an arbitrary and un-measurable classification. NICE should not be using arbitrary terms for a recognised disease, and doing so would cause significant confusion along with distress for patients. 4. No-one with endometriosis should be grouped together with 'unexplained fertility problems'. There is no evidence base given for including 'mild endometriosis' along with these. Evidence Review K, underpinning recommendations 1.8.2 and 1.8.3, includes only two studies that recorded 'mild endometriosis', with a total of only approx. 61	

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				subjects/patients. We can see no solid evidence about why 'mild endometriosis' has been included with 'unexplained fertility problems'. Given the above, we strongly believe that this guideline should not categorise endometriosis into 'mild' and 'severe'. Endometriosis in any form should be removed from section 1.8, and all other locations where the term 'mild endometriosis' is used. For section 1.9, 'severe' should be removed when precedes endometriosis, thereby ensuring all those with endometriosis get access to support they may need. Endometriosis is a leading cause of infertility in women in the UK, and we recognise that many with endometriosis are able to conceive naturally. Yet this cannot be looked at in isolation of medication to manage symptoms.	
Endometriosis UK	Guideline	General	General	Endometriosis UK requests that NICE immediately involve consultant gynaecologists specialising in endometriosis in the committee drafting the guideline; including for review of feedback and all future discussions and drafts. We recommend Professor Christian Becker, Professor of Reproductive Sciences at the University of Oxford; or Professor Andrew Horne, Director of the Centre of Reproductive Health at the University of Edinburgh.	Thank you for your comment. We are not recruiting new members to the guideline committee at this stage. When the committee constituency was agreed, involving a specialist in endometriosis was not prioritised because endometriosis is only one of the causes of fertility problems and the focus of the guideline is not about management of endometriosis.

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Endometriosis UK	Guideline	028	009	We welcome the link to the NG73 NICE guideline on *Endometriosis: diagnosis and management* under *1.6 Tubal and uterine surgery*. This is a necessary and welcome addition.	Thank you for this comment. Please note that based on your and other stakeholders' feedback, the committee agreed to include a new section in the guideline titled "Endometriosis" and the cross-reference to the NICE guideline on endometriosis: diagnosis and management has now been added in the new section and removed from section 1.34 Tubal surgery.
Endometriosis UK	Guideline	030	001	Remove the reference to mild endometriosis from this heading. The terms "mild endometriosis" and "severe endometriosis" should be removed from the guideline, as such descriptors are misleading and reductive.	Thank you for this comment. The section referred to in the comment has been revised and the guideline no longer refers to 'mild' or 'severe' endometriosis because the committee agreed they can be clinically ambiguous and do not appropriately reflect the complexity of potential fertility problems in relation to endometriosis. Instead, the committee agreed to include a section titled Endometriosis, where fertility treatment options for women and people with endometriosis are covered, with cross-reference to the NICE guideline on endometriosis.
Endometriosis UK	Guideline	030	004	Rec 1.8.1. -- Remove the reference to mild endometriosis. The terms "mild endometriosis" and "severe endometriosis" should be removed from the guideline, as such descriptors are misleading and reductive.	Thank you for this comment. The recommendation referred to in the comment has been revised and the guideline recommendations no longer refer to 'mild' or 'severe' endometriosis because

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					the committee agreed they can be clinically ambiguous and do not appropriately reflect the complexity of potential fertility problems in relation to endometriosis. Instead, the committee agreed to include a section titled Endometriosis, where fertility treatment options for women and people with endometriosis are covered, with cross-reference to the NICE guideline on endometriosis.
Endometriosis UK	Guideline	030	009	Rec 1.8.2. -- Remove the reference to mild endometriosis. The terms "mild endometriosis" and "severe endometriosis" should be removed from the guideline, as such descriptors are misleading and reductive.	Thank you for this comment. The recommendation referred to in the comment has been revised and the guideline recommendations no longer refer to 'mild' or 'severe' endometriosis because the committee agreed they can be clinically ambiguous and do not appropriately reflect the complexity of potential fertility problems in relation to endometriosis. Instead, the committee agreed to include a section titled Endometriosis, where fertility treatment options for women and people with endometriosis are covered, with cross-reference to the NICE guideline on endometriosis.
Endometriosis UK	Guideline	030	011	Rec 1.8.3. -- Remove the reference to mild endometriosis. The terms "mild endometriosis" and "severe endometriosis" should be removed from the guideline, as such descriptors are misleading and reductive.	Thank you for this comment. The recommendation referred to in the comment has been revised and the guideline recommendations no longer refer to 'mild' or 'severe' endometriosis because the committee agreed they can be clinically ambiguous and do not appropriately reflect the complexity of

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					potential fertility problems in relation to endometriosis. Instead, the committee agreed to include a section titled Endometriosis, where fertility treatment options for women and people with endometriosis are covered, with cross-reference to the NICE guideline on endometriosis.
Endometriosis UK	Guideline	031	008	Rec 1.9.3 -- Remove the word *severe* under this recommendation, so that it applies to all those with endometriosis.	Thank you for this comment. The recommendation referred to in the comment has been revised and all examples including severe endometriosis have been removed. The committee agreed to add a new section in the guideline titled "Endometriosis" including recommendations for treatment options, including reference to the NICE guideline on endometriosis section on management if fertility is a priority. Please also see the rationale and impact section associated with the recommendation for further explanation why the committee made the recommendations.
Endometriosis UK	Guideline	031	012	Rec 1.9.3 -- Remove the reference to mild endometriosis within this bullet point. Endometriosis should be included in the bullet above (P31 lines 8/9) as a diagnosed cause of infertility.	Thank you for this comment. The recommendation referred to in the comment has been revised and all examples including mild endometriosis have been removed. The committee agreed to add a new section in the guideline titled "Endometriosis" including recommendations for treatment options, including reference to the NICE

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					guideline on endometriosis section on management if fertility is a priority. Please also see the rationale and impact section associated with the recommendation for further explanation why the committee made the recommendations.
Endometriosis UK	Guideline	042	002	We agree with Rec 1.14.1 to discuss fertility preservation with people who have a medical condition that is likely to impair their fertility. We recommend that this section reference the relevant guidance within *Section 1.10: Management if fertility is a priority* within the NG73 NICE Guideline, *Endometriosis: diagnosis and management* to better support practitioners who are working with patients with endometriosis. This is a positive for those with endometriosis that may impact their fertility, given that endometriosis is a well-recognised cause of infertility, and in line with NG73 NICE Guideline on *Endometriosis: diagnosis and management*. All those affected should have equitable access to appropriate and timely fertility treatment, irrespective of the cause.	Thank you for this comment. This section of the guideline has been updated by adding the previous recommendation with some minor edits on the factors to be considered when offering fertility preservation such as diagnosis, treatment plan, expected outcome of subsequent fertility treatment etc. We have not included a reference to the NICE guideline on endometriosis, because endometriosis is only one potential medical indication for the need for fertility cryopreservation.
Endometriosis UK	Guideline	042	015	We strongly agree with Rec 1.14.5 to offer oocyte or embryo cryopreservation (as appropriate) to those who are preparing for medical treatment, or have a medical condition, that is likely to make them infertile. We are pleased to see NICE ensuring the recommendations on	Thank you for this comment.

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				fertility preservation apply to all those where medical treatments may lead to infertility.	
Endometriosis UK	Guideline	070	025	It is positive that endometriosis is recognised as a main cause of fertility problems within the draft guideline.	Thank you for this comment. Since the consultation of this draft guideline NICE no longer includes 'Context' sections in the published guidelines, however, please note the new guideline section titled "Endometriosis".
Examen	Evidence Review S	049	General	Rationale given within the evidence review mentions cost of SDF tests. NICE found no applicable economic studies and did not build a cost-effectiveness model. Yet the same document itemises the very high unit costs of ART components (e.g. ICSI ~£4,120 per cycle; surgical sperm retrieval ~£3,386; PICSI costed above ICSI. IVF costs over £68 million per year to the NHS(15). As SDF is strongly associated with failed implantation, miscarriage and poorer embryo development - as the background to this guideline acknowledges - then proceeding to high-cost ART without knowing SDF risks increasing futile spend and emotional burden. A more practical model would compare (a) current practice vs (b) an SDF-triaged pathway (e.g. targeted ART choices, altered timing, or counselling to avoid low-yield cycles). Additionally, high SDF can be reversible, through dietary change, smoking cessation, alcohol reduction, treatment of undetected varicocele or infection(12). In the best-case scenario, men can make changes that enable couples to	Thank you for your comment. In Evidence Review S, we have stated that no evidence was found for lifestyle advice (including weight loss, healthy diet, exercise, smoking cessation, reducing alcohol intake, and so on), please see 'Summary of evidence' section (page 18, line 30). As there is no evidence to justify the beneficial effect of lifestyle advice, the committee agreed, based also on their clinical knowledge and experience, that it is not reasonable to recommend lifestyle advice for sperm DNA fragmentation. Unit costs are sometimes presented in an evidence review in the absence of economic evidence and/or original economic modelling. This is to help the committee when making any qualitative assessment of cost-effectiveness. With an economic guideline update of this size, it is not possible to do original modelling for each evidence review, and this topic was not prioritised.

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				conceive naturally without requiring expensive and invasive treatment. In the worst-case scenario, men have been provided with an additional motivation for positive lifestyle change through proven infertility, that even if they still require ART, they will enter the process healthier than they would otherwise have been. These positive lifestyle changes affect not just their fertility but their overall health. Given men's increased likelihood of cardiovascular disease and lung cancer(16), which share risk factors with infertility, fertility clinics are an excellent opportunity for early intervention and risk counselling. If men are not counselled as to how their lifestyle can be contributing to subfertility, and indeed provided with evidence that in fact their fertility is reduced, then there is little motivation to change. Even if there is not grade 1 evidence for the effect of lifestyle factors on SDF, there are other recommendations within this guideline, such as for tubal surgery (1.6.1), that are based on a recommendation of 'clinical knowledge and expertise' alone. It's well established that sperm DNA fragmentation is closely correlated with inflammation and oxidative stress(17). Poor diet, obesity, smoking also have a well-established link with oxidative stress, and with infertility(18,19). Lifestyle recommendations are widely employed already within healthcare, however uptake is	As the review did not find evidence of a treatment benefit the committee concluded that testing for SDF would not be cost-effective. The committee was aware of some evidence suggesting a potential relationship between sperm DNA fragmentation and fertility treatment outcomes, particularly in cases of recurrent pregnancy loss (recurrent miscarriage). However, recurrent pregnancy loss is outside the scope of this guideline. In addition, the evidence is conflicting and varies depending on the type of test. Therefore, the committee did not think the link between DNA fragmentation and subfertility was sufficiently well established that expensive SDF testing could be used to provide advice and adapt future management, as suggested. The recommendation reflects the HFEA's position on unproven treatment add-ons. According to HEFA patient information, the results of a sperm DNA damage test are unlikely to affect the management of your treatment. Sperm DNA damage | HFEA.

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				poor unless there is motivation to change. Proven subfertility can act as that motivator.	
Examen	Evidence Review S	049	General	The Evidence Review is concerned solely with the treatment of SDF, which does not equate with a recommendation to not offer the test for diagnostic purposes. The Evidence Review for SDF largely consists of a small, heterogeneous set of interventions using antioxidants. It explicitly reports mixed/heterogeneous biochemical effects and no consistent improvement in live birth or clinical pregnancy for antioxidants – but the Evidence Review has not looked at whether SDF status helps you choose smarter treatment routes (e.g. ART strategy, expectant vs ART timing, or prioritising modifiable exposures). The committee records assay heterogeneity and population variability as key limitations of the evidence review - i.e. the evidence base is under-powered to invalidate the test's prognostic use. Within the same guideline, you have recommended use of AMH and AFC as a predictor of ovarian response to 'inform clinical decision making and counselling regarding the likelihood of live birth following assisted conception' (1.3.15). Double stranded SDF tests offers the same opportunity for couples regarding counselling for their miscarriage risk.	Thank you for your comment. Evidence Review S is neither a diagnostic review nor a prognostic review. It aims to examine the effectiveness of treating DNA fragmentation, and subsequently whether testing is worthwhile. The guideline committee agreed that based on the evidence showing no clear benefits of treating sperm DNA fragmentation, there was no justification for routine testing of sperm DNA fragmentation. In other words, since treatment does not improve clinical outcomes, the DNA fragmentation test does not lead to any actionable steps. In addition, the committee were concerned that sperm DNA assays are expensive tests which can take weeks to get results for. Based on the potential advantages of saving lost time in time-sensitive fertility pathways, and without effective treatments to rationalise testing from a potential cost-saving perspective, the committee agreed that testing for sperm DNA integrity (fragmentation) should not be carried out.

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				Semen analysis as it currently stands is used routinely as a diagnostic test for male infertility, even though any abnormalities detected are not always directly 'fixable', and despite that test's limited prognostic value for ART outcomes(21). SDF however can diagnose male infertility with very high accuracy, and double stranded SDF in our research is prognostic of IVF live birth outcome. A proportionate recommendation is not '**don't test for SDF**' but rather '**consider SDF in clearly defined scenarios where it will change management e.g.** à couples deliberating high cost, invasive ART where a poor SDF related prognosis would meaningfully alter choice (e.g. risk counselling, sperm selection methods trial), thereby potentially avoiding low yield cycles and wasted spend. à recurrent pregnancy loss or repeated ART failure (double stranded SDF)	
Examen	Evidence review S	49	030	It is noted that the committee agreed that the link between elevated DNA Fragmentation and subfertility has not been established. However, the introduction to the Evidence Review S mentions research associations between elevated SDF and pregnancy outcomes such as miscarriage and recurrent pregnancy loss, as well as	Thank you for your comment. Evidence Review S is not a prognostic review and did not look at the association between sperm DNA fragmentation and clinical outcomes. In fact, Evidence Review S aims to examine the effectiveness of treating

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				citing Borges 2019 and Li 2024 in their research on link between SDF and embryo quality. To add to this research, I detail below two most recently completed studies that show a strong association between double stranded SDF with both IVF live birth outcome and recurrent pregnancy loss. The first is [This text was identified as confidential and has been removed]. The second is a prospective study (n=181) conducted with Prof Drakeley at Hewitt Fertility, Liverpool that examined the association of SDF with male factor recurrent pregnancy loss. Couples had had 2-10 pregnancies losses, and no female factor had been identified. Of the men in couples with RPL, 66/100 had a normal semen analysis. Of these 66 men, over 60% had elevated SDF levels, highlighting how male factor infertility can be missed when using semen analysis alone. The AUC for the neutral Comet Assay used to detect the SDF (and which powers our Extend test) was 0.890, indicating strong predictive ability. This study is published in RBMO(6). These studies build on the existing evidence that supports a strong association of double stranded SDF with	DNA fragmentation, and subsequently whether testing is worthwhile, using data from randomised controlled trials. The guideline committee agreed that based on the evidence showing no clear benefits of treating sperm DNA fragmentation, there was no justification for routine testing of sperm DNA fragmentation. In other words, since treatment does not improve clinical outcomes, the DNA fragmentation test does not lead to any actionable steps. In addition, the committee were concerned that sperm DNA assays are expensive tests which can take weeks to get results for. Based on the potential advantages of saving lost time in time-sensitive fertility pathways, and without effective treatments to rationalise testing from a potential cost-saving perspective, the committee agreed that testing for sperm DNA integrity (fragmentation) should not be carried out. Two prospective studies provided by the stakeholder are observational studies and therefore they would not meet inclusion criteria. In addition, one of the studies was conducted in couples with recurrent pregnancy loss, which is outside the scope of the guideline.

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				reproductive outcomes such as pregnancy rates, miscarriage and IVF live birth outcome, especially for direct measures of SDF such as the neutral Comet Assay.	
Examen	Evidence review S	050	001	It is written that it is unclear what type of test to use for SDF testing. In multiple papers comparing tests directly(2,20), the COMET assay, a direct measure of SDF emerges superior, in terms of its ability of the test to discriminate between fertile and infertile men (measured by AUC score). Additionally, another recommendation could be made that does not highlight any test in particular, but instead highlights the importance of using an ISO accredited test and lab, which ensures quality and reliability of the testing process and results.	Thank you for your comment. Evidence Review S is not a diagnostic test accuracy review. In other words, it did not evaluate the accuracy of a test in correctly identifying a condition. Evidence Review S aims to examine the effectiveness of treating DNA fragmentation, and subsequently whether testing is worthwhile. The guideline committee agreed that based on the evidence showing no clear benefits of treating sperm DNA fragmentation, there was no justification for routine testing of sperm DNA fragmentation. Since treatment does not improve clinical outcomes, the DNA fragmentation test does not lead to any actionable steps. In addition, the committee were concerned that sperm DNA assays are expensive tests which can take weeks to get results for. Based on the potential advantages of saving lost time in time-sensitive fertility pathways, and without effective treatments to rationalise testing from a potential cost-saving perspective, the committee agreed that testing for sperm DNA integrity (fragmentation) should not be carried out.

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					The committee acknowledged the need for further research to identify and validate the best assay or test, define a threshold for high DNA fragmentation, and clarify its association with subfertility. However, given all these unknowns, the committee agreed it would be premature to draft a fully specified and implementable research recommendation that would be able to deliver conclusive results.
Examen	Guideline			References - 1.Simon L, Lutton D, McManus J, Lewis SEM. Sperm DNA damage measured by the alkaline Comet assay as an independent predictor of male infertility and in vitro fertilization success. Fertil Steril. 2011 Feb 1;95(2):652–7. 2.Ribas-Maynou J, García-Peiró A, Fernández-Encinas A, Abad C, Amengual MJ, Prada E, et al. Comprehensive analysis of sperm DNA fragmentation by five different assays: TUNEL assay, SCSA, SCD test and alkaline and neutral Comet assay. Andrology. 2013;1(5):715–22. 3.(PDF) Novel use of COMET parameters of sperm DNA damage may increase its utility to diagnose male infertility and predict live births following both IVF and ICSI. ResearchGate [Internet]. 2025 Apr 14 [cited 2025 Apr 27]; Available from: https://www.researchgate.net/publication/336279738_Novel_use_of_COMET_parameters_of_sperm_DNA_damage	Thank you for providing these references. We have checked them and none of them fit the inclusion criteria for our evidence reviews.

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				_may_increase_its_utility_to_diagnose_male_infertility_and_predict_live_births_following_both_IVF_and_ICSI 4.Andrabi SW, Ara A, Saharan A, Jaffar M, Gugnani N, Esteves SC. Sperm DNA Fragmentation: causes, evaluation and management in male infertility. JBRA Assist Reprod. 2024;28(2):306–19. 5.nhs.uk [Internet]. 2017 [cited 2025 Oct 18]. Causes of infertility. Available from: https://www.nhs.uk/conditions/infertility/causes/ 6.Drakeley A, Lunt RL, Newton E, Gregoire RC, Watkins L, Bambang K, et al. Double-stranded sperm DNA fragmentation assessed using comet assay is associated with recurrent pregnancy loss. Reprod Biomed Online. 2025 Aug 5;105184. 7.Casanovas A, Ribas-Maynou J, Lara-Cerrillo S, Jimenez-Macedo AR, Hortal O, Benet J, et al. Double-stranded sperm DNA damage is a cause of delay in embryo development and can impair implantation rates. Fertil Steril. 2019 Apr 1;111(4):699-707.e1. 8.Ribas-Maynou J, García-Peiró A, Fernandez-Encinas A, Amengual MJ, Prada E, Cortés P, et al. Double Stranded Sperm DNA Breaks, Measured by Comet Assay, Are Associated with Unexplained Recurrent Miscarriage in Couples without a Female Factor. PLOS ONE. 2012 Sept 17;7(9):e44679.	

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				9.Robinson L, Gallos ID, Conner SJ, Rajkhowa M, Miller D, Lewis S, et al. The effect of sperm DNA fragmentation on miscarriage rates: a systematic review and meta-analysis. Hum Reprod. 2012 Oct 1;27(10):2908–17. 10.Quenby S, Gallos ID, Dhillon-Smith RK, Podesek M, Stephenson MD, Fisher J, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. The Lancet. 2021 May 1;397(10285):1658–67. 11.Causes | Background information | Miscarriage | CKS | NICE [Internet]. [cited 2025 Oct 18]. Available from: https://cks.nice.org.uk/topics/miscarriage/background-information/causes/ 12.Çayan S, Farkouh A, Agarwal A, Atmoko W, Wyns C, Arafa M, et al. Global Andrology Forum Clinical Guidelines on the Relevance of Sperm DNA Fragmentation in Reproductive Medicine. World J Mens Health [Internet]. 2025 Jan 2 [cited 2025 May 5];43. Available from: https://doi.org/10.5534/wjmh.250005 13.WHO laboratory manual for the examination and processing of human semen, 6th ed [Internet]. [cited 2025 Oct 18]. Available from: https://www.who.int/publications/i/item/9789240030787 14.Zhao G, Jiang X, Zheng Y, Bai H, Jiang Z, Cheng S, et al. Outcomes comparison of testicular versus ejaculated sperm for intracytoplasmic sperm injection in infertile men	

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				with high DNA fragmentation: updated systematic review and meta-analysis. Transl Androl Urol. 2023 Dec 31;12(12):1785–802. 15.Howard S. The hidden costs of infertility treatment. BMJ. 2018 May 22;361:k2204. 16.The King's Fund [Internet]. [cited 2025 Oct 18]. Inequalities In Men's Health: Why Are They Not Being Addressed? Available from: https://www.kingsfund.org.uk/insight-and-analysis/blogs/inequalities-mens-health-why-are-they-not-being-addressed 17.Agarwal A, Barbăroșie C, Ambar R, Finelli R. The Impact of Single- and Double-Strand DNA Breaks in Human Spermatozoa on Assisted Reproduction. Int J Mol Sci. 2020 Jan;21(11):3882. 18.Keaney JF, Larson MG, Vasan RS, Wilson PWF, Lipinska I, Corey D, et al. Obesity and Systemic Oxidative Stress. Arterioscler Thromb Vasc Biol. 2003 Mar;23(3):434–9. 19.Agarwal R, Salas-Salvadó J, Davila-Cordova E, Shyam S, Fernández de la Puente M, Azurmendi MP, et al. Mediterranean Diet, Semen Quality, and Medically Assisted Reproductive Outcomes in the Male Population: A Systematic Review and Meta-Analysis. Adv Nutr. 2025 May 24;16(8):100454.	

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				20.Cissen M, Wely M van, Scholten I, Mansell S, Bruin JP de, Mol BW, et al. Measuring Sperm DNA Fragmentation and Clinical Outcomes of Medically Assisted Reproduction: A Systematic Review and Meta-Analysis. PloS One. 2016;11(11):e0165125. 21.Lewis SEM. Is sperm evaluation useful in predicting human fertility? 2007 July 1 [cited 2025 July 3]; Available from: https://rep.bioscientifica.com/view/journals/rep/134/1/1340031.xml	
Examen	Guideline	014	012	Rec 1.3.6 – We are concerned this recommendation does not take into consideration the evidence supporting the utility of Sperm DNA Fragmentation (SDF) as a diagnostic tool. In your introduction you have mentioned 70% of male infertility has an unknown cause. It is widely reported in the literature that Sperm DNA Fragmentation is highly predictive of male infertility, with AUCs of >0.9 for direct tests such as the COMET assay(1–3). Up to 20% of men with a normal semen analysis have levels of SDF within the infertile range(4), highlighting SDF potential in identifying male factor infertility, particularly relevant in the 25% of couples with unexplained infertility(5). Double stranded SDF in particular is strongly associated with recurrent pregnancy loss and stages of embryo development beyond fertilisation(6–8)	Thank you for your comment. The evidence provided by the stakeholder is mainly about recurrent pregnancy loss (RPL). The EAU guideline, Global Andrology Forum and WHO guideline suggested SDF measurement, particularly for couples with RPL. However, RPL is outside the scope of this guideline (see the 2022 Final scope in the History tab on the guideline website). NICE makes independent recommendations based on evidence. We conducted a review (Evidence Review S) that examines the impact of treating DNA fragmentation on clinical outcomes (including live birth, clinical pregnancy, miscarriage, pregnancy loss, embryo

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				We have recently published a prospective cohort study(6) with 100 men in couples with recurrent pregnancy loss (RPL) with no identified female factor and 81 fertile men, which showed **66/100** of the RPL cohort had high levels of SDF, compared with only 34/100 who had abnormal semen analyses. Of those men with RPL who had a normal semen analysis, over 60% of them had high SDF, highlighting further how semen analysis alone can miss male factor infertility. Our test for double stranded SDF had an AUC of 0.890 in predicting male factor recurrent miscarriage loss. This confirms findings from other metanalyses that show that high SDF doubles the risk of miscarriage(9). From the Lancet Series, miscarriage costs **£471 million** per year (2021 costs) to the NHS(10), with a much greater cost to society from the social consequences of miscarriage. Given 50% of cases of recurrent miscarriage are unexplained(11), it is sensible to apply the evidence base to clinical practice through use of a non-invasive test that enables better risk counselling and can provide a cause for a percentage of these unexplained cases.	quality), and subsequently whether testing is worthwhile. The guideline committee agreed that based on the evidence showing no clear benefits of treating sperm DNA fragmentation, there was no justification for routine testing of sperm DNA fragmentation. In other words, since treatment does not improve clinical outcomes, the DNA fragmentation test does not lead to any actionable steps. In addition, the committee were concerned that sperm DNA assays are expensive tests which can take weeks to get results for. Based on the potential advantages of saving lost time in time-sensitive fertility pathways, and without effective treatments to rationalise testing from a potential cost-saving perspective, the committee agreed that testing for sperm DNA integrity (fragmentation) should not be carried out.

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				Professor Tet Yap, Professor of Urology and Andrology at Guy's Hospital and King's College London provided to us the following comment highlighting the discrepancy in this proposed guidance versus the European Urology guidelines, which most urologists in UK follow: "Latest EAU guidelines for male fertility state: ".. there is evidence in support of SDF measurement for couples with recurrent pregnancy loss after natural conception and failure of ART and for men with unexplained infertility " *European Association of Urology Guidelines on Male Sexual and Reproductive Health: 2025 Update on Male Infertility ; Minhas, Suks et al., European Urology, Volume 87, Issue 5, 601 – 616* This concern was echoed by Professor Johnathan Ramsay, a urologist with expertise in male infertility, who noted that this NICE guidance as it stands would be significantly out of line with European and International guidelines. Other international guidelines (Global Andrology Forum and WHO) have all recognised the extensive evidence base for SDF as a diagnostic test, particularly in the context of recurrent miscarriage and unexplained fertility(12,13). Our sperm DNA Fragmentation tests are currently used in more than 85% of the UK's private fertility clinics. We urge you to	

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				reconsider the wording of your recommendation to reflect the evidence and the current practice.	
Examen	Guideline	023	010	Rec 1.4.11 – re surgical sperm retrieval for reduced sperm DNA integrity, I have referenced here the latest systematic review and metanalysis which looked at surgical sperm retrieval and found that there was a significant difference in SDF between testicular and ejaculated sperm, and this resulted in significantly improved clinical pregnancy rates, live birth rates and miscarriage rates(14).	Thank you for your comment. We checked this systematic review, and it included observational studies rather than randomised controlled trials (RCTs). Therefore, it did not meet the inclusion criteria for Evidence Review S. In Evidence Review S, for the comparison between testicular sperm retrieval (ICSI) and ejaculated sperm (ICSI), we identified one RCT and found no clinically important difference in clinical pregnancy or miscarriage. Therefore, the guideline committee agreed that surgical sperm retrieval should not be offered for those with non-azoospermia and reduced sperm DNA integrity.
Examen	Guideline	038	022	Rec 1.11.3 – we are concerned that if clinicians are relying solely on a normal semen analysis to exclude male factor infertility, then up to 40% of causes of male factor infertility can be missed(4,6), leading to incorrect management, for example IVF where perhaps ICSI or sperm selection techniques would be better(3).	Thank you for your comment. We are unclear what the 40% figure you cite is based on. We have reviewed the references you provided, including reference 4 by Andrabi et al. (2023), which cites Agarwal et al. (2020). The stakeholder comment states that up to 40% of infertile men have semen

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					parameters within the WHO normal reference ranges. However, the cited paper (Agarwal et al. 2020) does not report this figure. Instead, Agarwal et al. (2020) indicate that approximately 15% of infertile men have normal semen parameters, not 40%. Therefore, the proportion of cases that could potentially be missed when relying solely on semen analysis seems to be considerably lower than suggested in the comment. The recommendation states that ICSI should not be used for non–male-factor fertility problems, which is consistent with HFEA guidance stating that ICSI should be reserved for cases with abnormal semen parameters. This ensures that ICSI is used only where there is clear evidence of male-factor infertility, while avoiding unnecessary use of ICSI in couples without male-factor indications.
Ferring Pharmaceuticals	Guideline	4 30 31	011 06-07 015-017	The guidelines seem somewhat contradictory in that they say, *'People with health-related fertility problems are those who do not achieve a pregnancy after 12 months of regular unprotected sexual intercourse'*. However in section 1.8 and again in section 1.9 (Access criteria for IVF) it states, *'Offer IVF treatment for people under 42 years if they have not conceived after 2 years of regular unprotected vaginal intercourse'*.	Thank you for your comment. The guideline recommends (recommendation 1.16.4) that if people have not achieved a pregnancy after 1 year of regular unprotected sexual intercourse they should be offered further assessment and investigations. For some people the investigations show a cause for subfertility, and based on this there are different treatment options depending on the cause,

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				It seems that the guidelines recognise there is a 'health-related fertility problem' after 1 year of not conceiving (as per the WHO definition of infertility), yet treatment isn't offered until 2 years of not conceiving, which seems contradictory, especially given the role of age in determination of success.	including assisted reproductive techniques. However, if subfertility is unexplained by investigations, it is recommended that there is a period of expectant management when conception is attempted through regular unprotected sexual intercourse for another 12 months before assisted reproductive techniques are considered (recommendations 1.38.1 and 1.38.3).
Ferring Pharmaceuticals	Guideline	012	023-025	There is also a recommendation in section 1.2.30 that in women aged 36 or over an earlier referral should be made, but no timeframes are mentioned as part of this recommendation.	Thank you for this comment. The committee considered your and other stakeholders' comments on this issue and agreed to amend the recommendation by replacing 'an earlier referral' with 'referral at presentation'.
Ferring Pharmaceuticals	Guideline Table 3 Recommendations that have been deleted	074	015	The definition of serum AMH levels to predict the likely ovarian response to gonadotrophin stimulation in IVF has been deleted, so there will be no guidance to predict low, normal and high responders using AMH measurement. The "Prevention of ovarian hyperstimulation syndrome (OHSS): British Fertility Society policy and practice guideline" uses serum AMH levels to define potential high responders; the guideline states that serum AMH levels above 22.5 pmol/l have been shown to have an optimum balance of sensitivity and specificity for patients with a predicted high response to gonadotropins, and can guide appropriate management of these patients.	Thank you for your comment. This recommendation was replaced by the new set of recommendations on ovarian reserve testing (recommendations 1.18.3 to 1.18.5). Recommendation 1.18.4 advises to use AMH levels or antral follicle count (AFC) as predictors of ovarian response and likelihood of live birth following assisted conception, and therefore there is guidance on this practice. Most outcomes had no serious inconsistency despite the use of multiple different AMH assays and different

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				Follitropin delta used in doses according to an algorithm including weight and AMH may be associated with a reduction in risk of OHSS (Evidence level 1). Follitropin delta used in doses according to an algorithm based on weight and AMH may be considered for prevention of OHSS. (Grade A). The Guideline Development Committee took into account evidence showing a reduced need for preventive measures and a lower risk of OHSS in patients with AMH> 15 pmol/l who were treated with follitropin delta in doses based on an algorithm incorporating weight and AMH. N. Tsampras, K. Palinska-Rudzka, Y. Alebrahim, L. Craciunas & R. Mathur (2025) Prevention of ovarian hyperstimulation syndrome (OHSS): British Fertility Society policy and practice guideline, Human Fertility, 28:1, 2441827, DOI: 10.1080/14647273.2024.2441827 Full article: Prevention of ovarian hyperstimulation syndrome (OHSS): British Fertility Society policy and practice guideline Ferring will request NICE to include definition of serum AMH levels to predict ovarian response to gonadotrophin stimulation in IVF.	thresholds in included studies, and where there was heterogeneity between studies it was not accounted for by the specific threshold or AMH assay used. As a result, the committee agreed not to recommend specific assays or give guidance on thresholds, and agreed this should be based on clinician judgment and the assay used. Additionally, the guideline now refers to the recently updated ESHRE guideline on Ovarian stimulation for IVF/ICSI which provides guidance on ovarian stimulation, including appropriate treatment to prevent OHSS.
Hertility Health Limited	Evidence review A	General	General	Methods/Scope Inclusion of Digital Pathways Evidence. The protocol for this evidence review should explicitly accommodate evidence from validated digital/at-home	Thank you for your comment. The scope of this guideline is limited to settings where NHS-commissioned health-related fertility advice or

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				diagnostic services (which often use capillary blood samples and advanced algorithms). Excluding this rapidly growing data source will make the final guidance outdated upon publication.	treatment is provided including primary, secondary and tertiary settings, and HFEA-licensed private clinics. Therefore, the protocol for the review on ovarian reserve testing did not cover at-home testing kits.
Hertility Health Limited	Evidence review A	006	017-019	Review question: Introduction NICE's current evidence review aims to determine associations between ovarian reserve markers and outcomes such as spontaneous conception or treatment success. However, the review's scope assumes that these markers are only relevant within fertility treatment contexts. We implore NICE to therefore recognise that fertility testing increasingly occurs in non-clinic settings. With the rapid rise of direct-to-consumer (DTC) fertility and hormone testing, NICE must establish clear guidelines on clinical governance, including testing conducted outside fertility clinics, to safeguard patients. Fertility testing, especially for complex biomarkers like AMH, is not self-explanatory. The potential for misinterpretation in a DTC setting is high and can have the potential to cause unnecessary anxiety and over testing, or delay clinical action. Today, thousands of women and couples use at-home tests to assess their hormones and fertility status before seeking NHS or	Thank you for your comment. The scope of this guideline is limited to settings where NHS-commissioned health-related fertility advice or treatment is provided including primary, secondary and tertiary settings, and HFEA-licensed private clinics. Therefore, the protocol for the review on ovarian reserve testing did not cover direct-to-consumer testing kits.

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				private fertility care. Ignoring this shift risks a major regulatory blind spot.	
Hertility Health Limited	Evidence review A	024 026 027	017-019 009-011 002-007	Summary of the evidence / Outcomes that matter most / Benefits and harms We note the committee's evidence of an association between low AMH levels and a higher likelihood of cycle cancellation due to poor ovarian response. However, the current guidance risks missing individuals most likely to benefit from early, proactive intervention by restricting ovarian reserve testing to those already engaged in fertility treatment. This approach risks missing individuals most likely to benefit from early identification of diminished ovarian reserve. By the time a patient experiences "poor ovarian response" within IVF stimulation, opportunities for proactive intervention have already been lost. Whilst there is discourse regarding AMH as an indicator of ovarian reserve when interpreted in isolation, our clinical data confirms its immense value when used within a comprehensive diagnostic panel which harnesses the power of machine learning alongside clinical review to paint a comprehensive picture.	Thank you for your comment. The evidence review addressed the prognostic effectiveness of ovarian reserve markers, including their ability to predict spontaneous conception. The recommendations made based on this evidence therefore address whether ovarian reserve markers should be used to predict outcomes related to assisted and spontaneous conception. This does not preclude their use in other contexts.

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				Hertility's Position on AMH: ● Integrated Diagnostics: AMH is a robust biomarker of the growing follicle pool and a key indicator of ovarian response potential, but its clinical utility is only maximised when interpreted in the context of a full panel of reproductive and thyroid hormones, biometrics, and a detailed health assessment. ● Clinical Data Context: Hertility's health assessment captures essential lifestyle, medical, and symptomatic information (guided by international criteria like NICE, RCOG, ASRM, and ESHRE). This enables the use of our proprietary clinical decision support tool to provide highly accurate, personalised insights and screen for up to 18 reproductive health conditions. ● Preventative Intervention: Routine preconception or early fertility screening that integrates AMH with contextual data can identify at-risk individuals earlier, enabling realistic family planning discussions and targeted referral before advanced reproductive age or the onset of "poor ovarian response" within IVF stimulation.	

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Hertility Health Limited	Evidence review A	026	029-033	Benefits and harms Hertility supports NICE's position that diagnostic testing should be targeted and evidence-based, and we agree that AMH/AFC should not be used as access criteria for IVF. However, the draft guideline does not go far enough in promoting early fertility assessment, particularly for individuals with known risk factors such as age, BMI, smoking status, comorbidities etc. which may limit reproductive success. Our data shows that over 60% of women testing with Hertility for preconception reasons had previously unrecognised hormone imbalances or undiagnosed gynaecological conditions. This supports earlier, proactive hormone testing as a public health measure, not merely a clinical one, to reduce time to diagnosis, improve fertility literacy, and prevent delayed intervention.	Thank you for your comment. The scope of this update included people with health-related fertility problems and people who may require interventions to preserve fertility because of high risk of fertility problems due to clinical conditions or medical or surgical interventions. The aim of the review on ovarian reserve testing was to ascertain different markers' predictive ability for spontaneous conception and the outcome of assisted reproductive treatment for people with fertility problems. Therefore, this review only included people undergoing ovarian reserve testing to investigate subfertility (defined as not achieving a pregnancy after at least 12 months of regular unprotected sexual intercourse, or after at least 6 cycles of artificial insemination).
Hertility Health Limited	Evidence review A	027	024-029 042-045	Benefits and harms Fertility care remains highly uneven across the UK, with persistent disparities by geography, ethnicity, and socioeconomic status. Validated at-home testing models can bridge these gaps by increasing accessibility for those unable to attend fertility clinics or GP appointments. Further, this can in turn reduce strain on primary care providers.	Thank you for your comment. The scope of this guideline is limited to settings where NHS-commissioned health-related fertility advice or treatment is provided including primary, secondary and tertiary settings, and HFEA-licensed private clinics. Therefore, the protocol for the review on ovarian reserve testing did not cover at-home diagnostic pathways or direct-to-consumer testing kits.

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				NICE guidance should explicitly recognise how validated digital and at-home diagnostic pathways can improve equity in early fertility care. Integrating these models into national guidance would support more inclusive and representative fertility care.	
Hertility Health Limited	Guideline	General	General	Governance gap: With the rapid rise of DTC fertility and hormone testing, NICE must establish clear guidelines on clinical governance for testing conducted outside fertility clinics to ensure patient safety and comprehension. Fertility testing is not self-explanatory; the potential for misinterpretation in a DTC setting is high and can cause unnecessary anxiety or delay clinical action. Further, it is critical that NICE mandates an evidence base for external providers to ensure the data is clinically validated and trustworthy and establish frameworks to ensure consistent laboratory and reporting standards across NHS and regulated private providers.	Thank you for your comment. This was not within the scope of this guideline update and so we are unable to comment on this.
Hertility Health Limited	Guideline	006	011	Guideline 1.2 Initial advice to people concerned about delays in conception. NICE acknowledges that there is some evidence linking low AMH to increased cycle cancellation rates. This recognition highlights the critical need for proactive ovarian reserve testing. Early assessment allows patients	Thank you for your comment. The evidence review on ovarian reserve testing assessed the prognostic effectiveness of ovarian reserve markers, including their ability to predict spontaneous conception. The recommendations made based on this evidence therefore address whether

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				to receive realistic initial advice, potentially mitigating the impact of low ovarian reserve via preventative measures.	ovarian reserve markers should be used to predict outcomes related to assisted and spontaneous conception. It was not within scope to assess evidence on how timing of assessment affects fertility outcomes, and therefore the committee could not make recommendations on this. Although low quality evidence showed that low AMH levels at baseline were associated with an increased risk of cycle cancellation due to poor response, there was very limited evidence on AMH's predictive abilities for clinical pregnancy through spontaneous conception.
Hertility Health Limited	Guideline	008	019	Alcohol consumption This section, which covers preconception advice, should include a stronger recommendation for structured and personalised support for lifestyle changes. Our research (pre-print DOI: 10.22541/au.174093125.50526223/v1) demonstrates that, despite general public health messaging, a significant proportion of people are not following key preconception guidance, particularly regarding alcohol use (47.2% of women actively trying to conceive reported drinking 1-13 units of alcohol per week, and 4.0% reported drinking over 14 units per week). Generic advice is insufficient; the guideline should recommend structured support or digital tools to help patients adhere to recommended reductions in harmful habits.	Thank you for your comment. Initial advice or preconception advice was not within the scope of this guideline update so no evidence on this was reviewed and no new recommendations have been made.

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Hertility Health Limited	Guideline	009	022	Smoking Our internal research (pre-print DOI: 10.22541/au.174093125.50526223/v1) demonstrates that, despite general public health messaging, a significant proportion of people are not following key preconception guidance, including smoking advice (9.1% of women actively trying to conceive said they smoked, and this was higher in women trying to conceive for >12 months compared to <12 months (11.6% vs 6.9%, respectively, p<0.05)). Generic advice is insufficient; the guideline should recommend structured support or digital tools to help patients adhere to recommended reductions in harmful habits, particularly in the preconception period or when actively trying to conceive. The guidance also omits any mention of the use of e-cigarettes, vaping and other tobacco-based products, which is a growing public health concern. Hertility's data on 8,340 women (Abstract ID: 10.1093/humrep/deae108.1027) found that both smoking and vaping negatively affect ovarian reserve markers and that the detrimental effect of vaping is statistically significant in certain age groups (e.g. lower AMH in vapers aged 36-40, p=0.01). While acknowledging the need for more evidence, the potential for harm necessitates mentioning that vaping may negatively	Thank you for your comment. The impact of nicotine-containing products, e-cigarettes and vaping on fertility was not within the scope of this guideline update and no evidence has been reviewed on this, so the committee are unable to make recommendations on this topic. Several stakeholders made a similar comment and we have noted this as a potential topic for future updates.

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				impact fertility in a similar manner to smoking, warranting increased caution and future research recommendations.	
Hertility Health Limited	Guideline	016	017	Rec 1.3.14 With the rapid rise of Direct-to-Consumer (D2C) hormone testing, this recommendation must be expanded to include explicit guidance on D2C counselling. It is critical that any diagnostic results accessed outside a traditional clinical pathway are accompanied by mandatory counselling or clinical review by a registered specialist healthcare professional. This ensures that patients understand their results in the necessary clinical and historical context, mitigating the risks of misinterpretation or inappropriate self-treatment based on isolated biomarker values.	Thank you for this comment. The scope of this guideline is limited to settings where NHS-commissioned health-related fertility advice or treatment is provided including primary, secondary and tertiary settings, and HFEA-licensed private clinics. Therefore, the protocol for the review on ovarian reserve testing did not cover direct-to-consumer testing kits.
Hertility Health Limited	Guideline	031	005	Rec 1.9.2 This recommendation should emphasise that comprehensive, early assessment is key to adequate preparation for fertility treatment. Gaining an early understanding of ovarian reserve and overall reproductive health status supports people in taking proactive and preventative measures (e.g. lifestyle changes, timely treatment of underlying conditions like sub-optimal thyroid function). This approach ensures patients are optimally prepared to maximise the chances of successful ART and avoids the situation where preventable factors lead to	Thank you for your comment. Recommendations relating to key lifestyle factors with the potential to affect fertility are provided in section 1.6-1.15, and the guideline aims to set out advice about these factors for people with concerns about delays in conception as an initial step. The recommendations about ovarian reserve testing are only intended to cover when various ovarian reserve markers should be used to predict outcomes related to assisted and spontaneous conception.

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				exclusion or poor outcomes at the point of specialist referral, when it may be too late to intervene.	
Hertility Health Limited	Guideline	042	001	1.14 Fertility preservation for medical indications This section should stress the importance of a comprehensive assessment of reproductive and overall health before starting the preservation process. This includes assessing ovarian reserve markers, reviewing medical and lifestyle history, and screening for other conditions which may affect outcomes (e.g. thyroid function). This approach ensures patients receive appropriate, personalised counselling regarding their prognosis and potential success rates, enabling fully informed decision-making during a vulnerable time.	Thank you for this comment. The guideline committee agreed that each case should be assessed individually and based on clinical judgement. Additionally, this section of the guideline has been updated by adding the previous recommendation with some minor edits on the factors to be considered when offering fertility preservation such as diagnosis, treatment plan, expected outcome of subsequent fertility treatment etc.
Hertility Health Limited	Guideline	045	015	Recommendations for research The guidance must include a research recommendation on the growing impact of Direct-to-Consumer (D2C) fertility testing on patient pathways and public health spending. Research is required to investigate: a) How D2C results impact patient fertility choices, including early fertility preservation or pre-conception interventions. b) The importance of mandated clinical counselling in conjunction with D2C results to ensure safe interpretation and correct action. c) The subsequent costs to the NHS for specialist fertility treatment versus the costs borne by individuals who face	Thank you for this comment. In this update the guideline committee prioritised 5 other key research recommendations. All recommendations for research are related to the evidence that has been reviewed and where a gap in evidence has been identified. Your suggested topics were not reviewed for this guideline update.

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				significant barriers or lack funding, and how early D2C-enabled intervention can mitigate these costs and improve equity.	
Hertility Health Limited	Guideline	045	015	Recommendations for research Preconception Health and Cost-Effectiveness: Research should investigate the effects of structured preconception lifestyle behaviour interventions (including addressing alcohol, smoking, vaping, and diet) on both spontaneous conception rates and ART outcomes. This research should quantify how proactive, preventative NHS and D2C diagnostic pathways can lead to overall cost reduction for the NHS by decreasing the reliance on expensive, late-stage reactive treatments.	Thank you for this comment. In this update the guideline committee prioritised 5 other key research recommendations. All recommendations for research are related to the evidence that has been reviewed and where a gap in evidence has been identified. Your suggested topics were not reviewed for this guideline update.
Human Fertilisation and Embryology Authority (HFEA)	Guideline	General	General	This comment concerns all references to treatment add-ons throughout the draft guideline. For some treatment add-ons there is not enough evidence to show that they are effective at improving treatment outcomes, and the HFEA supports the view that add-ons without sufficient evidence shouldn't be offered to patients. We support treatment add-on recommendations that align with the HFEA's review of add-ons and current ratings. The HFEA's Scientific and Clinical Advances Advisory Committee (SCAAC) rates some treatment add-ons. We	Thank you for your comment.

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				publish information about treatment add-ons and have a **ratings system** on our website. The ratings indicate whether the treatment add-on is effective at improving the chances of having a baby for most fertility patients. Some treatment add-ons are also rated by the HFEA for other treatment outcomes. In the future, the HFEA may use evidence published by NICE to help inform its ratings of these add-ons. Our **National Patient Survey** indicates that a significant number of patients are having treatment with add-ons and emerging technologies, and that only half of patients had the effectiveness explained to them, let alone the risks. We regularly remind clinics that, according to our Code of Practice, they must give patients a clear idea of what any treatment add-on involves, how likely it is to increase their chance of a successful pregnancy, cost, risks, and link to our public **ratings system**.	
Human Fertilisation and Embryology Authority (HFEA)	Guideline	045-048	045: 015-022, 046-047	Research recommendations – the HFEA notes the recommendations for further research in particular areas and also notes a recent SCAAC review on long term safety/health risks – see June 2025 SCAAC paper Scientific and Clinical Advances Advisory Committee (SCAAC) | HFEA. The HFEA has updated our information on the following pages in light of this review:	Thank you for your comment. The research recommendation this relates to is from 2013 and the evidence on long-term safety of IVF was not reviewed as part of this update. We note the updated information on your website.

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			048:001-020	https://www.hfea.gov.uk/treatments/explore-all-treatments/risks-of-fertility-treatment/ https://www.hfea.gov.uk/donation/donors/donating-your-eggs/ https://www.hfea.gov.uk/treatments/explore-all-treatments/reciprocal-ivf/	
Human Fertilisation and Embryology Authority (HFEA)	Guideline	031-032	030, 20-30, 031:1-7	We welcome the proposed recommendations that three full cycles of IVF should be offered to women under 40 if they have fertility problems and meet certain criteria, as it represents value for money for the NHS. Funding for IVF continues to vary across the UK, and disparities in outcomes still exist. In recent years, Asian and Black patients have had lower birth rates than White patients and patients from a mixed ethnic background. Female same-sex couples and single patients were also less likely than opposite-sex couples to receive NHS funding. While the HFEA does not regulate funding or eligibility criteria, we encourage those who commission fertility services to review their eligibility criteria and consider whether these have an adverse impact on access to treatment.	Thank you for your comment.

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Human Fertilisation and Embryology Authority (HFEA)	Guideline	005	012-014	We support the reference to HFEA as a source of information.	Thank you for your comment.
Human Fertilisation and Embryology Authority (HFEA)	Guideline	008	004	Typo (remove additional 'a' at the start of this line).	Thank you for your comment. The 'a' was meant to be in superscript and was referring to a particular section in the table. We have replaced the 'a' with an asterisk to avoid confusion.
Human Fertilisation and Embryology Authority (HFEA)	Guideline	011	001-006	Should add information about weight loss drugs and fertility/pregnancy as per MHRA guidance https://www.gov.uk/government/news/women-on-skinny-jabs-must-use-effective-contraception-mhra-urges-in-latest-guidance	Thank you for this comment. Based on your and other stakeholders' feedback, the committee agreed to amend the recommendation on prescribed, over-the-counter and recreational drug use to include examples of drugs such as GLP-1 agonists and others.
Human Fertilisation and Embryology Authority (HFEA)	Guideline	014	012	Reflects HFEA's position on unproven treatment add-ons. HFEA patient information states: *The results of a sperm DNA damage test are unlikely to impact on the management of your treatment.*	Thank you for your comment.

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Human Fertilisation and Embryology Authority (HFEA)	Guideline	015	002-004	The recommendation that appropriate genetic counselling is provided for men, trans women and non-binary people who have a specific genetic defect associated with male factor infertility aligns with HFEA Code of Practice guidance eg. Guidance Notes 3.10 and 9.7.	Thank you for your comment.
Human Fertilisation and Embryology Authority (HFEA)	Guideline	016	001	Amend to include updated data on live births per embryo transfer by age. This data is published on the HFEA website. Preliminary data is available in the following report: https://www.hfea.gov.uk/about-us/publications/research-and-data/fertility-treatment-2023-trends-and-figures/ This report provides an update on fertility treatment and outcomes in the UK from 1991 to 2023.Please see the 'About our data' section of the report for further information.	Thank you for your comment. As suggested, figure 2 has now been updated with latest data from HFEA dashboard on live births per embryo transfer by age (from 1991 to 2023).
Human Fertilisation and Embryology Authority (HFEA)	Guideline	030	008-018	We note that the draft guidance places greater emphasis on IVF as a cost-effective first line option (vs ovarian stimulation alone) for people with unexplained infertility, mild endometriosis, or mild male factor infertility after two years of trying to conceive. We note that 1.8.3 recommends that IUI with ovarian stimulation is considered as an alternative first-line treatment option to IVF treatment	Thank you for this comment. NICE produces recommendations on the best available clinical and cost-effectiveness evidence. The economic analyses suggested that IUI as a 'gateway treatment' does result in higher cumulative live birth rates than IVF alone. However, the reduction in IVF treatment does not fully offset the costs of IUI treatment and in most scenarios the increase in live births was not achieved at

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				While clinical decisions are outside our remit, we recognise the importance of ensuring patients have access to clear, evidence-based information to support informed treatment choices.	an acceptable cost (as assessed by the cost-effectiveness threshold). However, the analysis was not without limitations and uncertainty and in some cases IUI with gonadotrophin appeared to be a relatively cost-effective alternative. Therefore, the committee agreed a weaker 'consider' recommendation was reasonable. Please also note that the recommendation referred to in the comment has been revised and 'mild endometriosis' and 'mild male factor fertility problems' have been removed as they are clinically ambiguous and the committee decided not to refer to these terms in the recommendations.
Human Fertilisation and Embryology Authority (HFEA)	Guideline	031		1.9.1 - Refer to this page for the relevant HFEA Code of Practice https://portal.hfea.gov.uk/knowledge-base/read-the-code-of-practice/	Thank you for your comment. We have updated the link.
Human Fertilisation and Embryology Authority (HFEA)	Guideline	033	009-014	We support the recommendation not to offer endometrial receptivity testing as a treatment add-on for embryo transfer. This reflects our position that such tests lack robust evidence of benefit in improving pregnancy or live birth rates. Our website advises that there is currently no clear evidence that these tests improve outcomes, and we	Thank you for this comment.

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				continue to monitor developments in this area. We strongly encourage clinics to ensure that any tests offered are backed by reliable evidence and that patients are given accurate, transparent information before making decisions.	
Human Fertilisation and Embryology Authority (HFEA)	Guideline	033	004-005	We support the recommendation not to offer endometrial scratch as a pre-treatment means of improving IVF outcomes. This aligns with our position on treatment add-ons: we advise caution where there is limited or conflicting evidence of benefit. Endometrial scratch is currently rated amber on our traffic-light system, reflecting that more research is needed, and patients should be fully informed of the uncertainties.	Thank you for this comment.
Human Fertilisation and Embryology Authority (HFEA)	Guideline	034	001-004	The HFEA supports the guideline's recommendation not to use immunological agents (e.g. steroids, IVIG, intralipids) as part of fertility treatment. These interventions are classified by us as add-ons with limited or no proven benefit and, in many cases, potential safety risks. An agreement between the HFEA and other professional and patient bodies (**the 19th October 2023 consensus statement**) states that treatments that have no strong evidence of their safety and/or effectiveness should only be offered in a research setting. Patients should not be	Thank you for this comment.

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				charged extra to take part in research, including clinical trials.	
Human Fertilisation and Embryology Authority (HFEA)	Guideline	036	008-009	We support the recommendation not to offer PGT-A as a routine part of fertility treatment. This is consistent with the HFEA's current view that the evidence does not show a clear benefit in improving live birth rates for most patients. An agreement between the HFEA and other professional and patient bodies (**the 19th October 2023 consensus statement**) states that treatments that have no strong evidence of their safety and/or effectiveness should only be offered in a research setting. Patients should not be charged extra to take part in research, including clinical trials.	Thank you for your comment.
Human Fertilisation and Embryology Authority (HFEA)	Guideline	004 005 029	003-013, 001-003, 009-021	This comment concerns the scope of the guideline, as set out on pages 4-5.The draft scope appears to exclude same-sex couples and single patients who require assisted conception, but do not necessarily have health-related fertility problems. This could create ambiguity, especially as the guideline states it applies "irrespective of sexual orientation, partnership status or gender identity." We recommend clarifying whether these groups are in or out of scope. If excluded, the guideline should state this explicitly and provide a clear rationale, while acknowledging the growing demand for fertility treatments	Thank you for your comment. Based on the guideline scope, consulted on and published in 2022, the guideline states that "The recommendations apply to people who: • have health-related fertility problems, or • may need interventions to preserve fertility because they have a high risk of fertility problems because of clinical conditions, or medical or surgical interventions.

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				in these patient groups.Our Family formation in fertility treatment 2022 report shows that there is increasing use of IVF by same-sex couples and single women and that these groups now account for around 1 in 6 of all IVF and DI treatment.	People with health-related fertility problems are those who: • have a known clinical cause of infertility, or • do not achieve a pregnancy: o after 12 months of regular unprotected sexual intercourse, or o after 6 cycles of artificial insemination." This means that people who do not meet the above criteria are not within the scope of this guideline. The guideline goes on to say that "The guideline applies to all people seeking assessment and treatment for health-related fertility problems who meet these criteria, regardless of their sexual orientation, partnership status or gender identity." The committee recognised that people without health-related fertility problems who will use donor insemination are not currently receiving NHS funding for their initial donor insemination cycles which can cause significant financial barriers and lead to people seeking donor insemination through unregulated routes, which can in turn involve health or other risks. While these initial cycles of donor insemination in the absence of health-related fertility problems are outside the scope of the

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					guideline, the committee wanted to include a recommendation in the beginning of the guideline advising people considering donor insemination to conceive to have treatment in a licensed fertility clinic to ensure clinical safety and legal parenthood, recognising the financial barriers that exist.
Human Fertilisation and Embryology Authority (HFEA)	Guideline	040	003	We support the reference to the HFEA as a source of information.	Thank you for this comment. The committee agreed to remove the recommendation you're referring to, because it is covered by the HFEA Code of Practice.
Human Fertilisation and Embryology Authority (HFEA)	Guideline	041	024	We support the reference to the HFEA as a source of information.	Thank you for this comment. The committee agreed to remove the recommendation you're referring to, because it is covered by the HFEA Code of Practice.
Human Fertilisation and Embryology Authority (HFEA)	Guideline	042	001-027	The HFEA welcomes the proposed broadening of access for those who need fertility preservation.	Thank you for this comment.

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Human Fertilisation and Embryology Authority (HFEA)	Guideline	070	018-021	Update with 2023 figures. This data is published on the HFEA website. Preliminary data is available in the following report: https://www.hfea.gov.uk/about-us/publications/research-and-data/fertility-treatment-2023-trends-and-figures/ This report provides an update on fertility treatment and outcomes in the UK from 1991 to 2023. Please see the 'About our data' section of the report for further information.	Thank you for your comment. We would have updated the figures based on the more recent data provided, however, since the consultation of this draft guideline NICE no longer includes 'Context' sections in the published guidelines.
Leeds Beckett University, on behalf of the Online Sperm Donation Project research team.	Guideline	001, 004-005	General	"People with health-related fertility problems, their families and carers" are specified in the *Who is it for?* section of the guidelines (page 1), and the *Recommendations* section (page 4) states that the guideline recommendations are for people who "have health-related fertility problems". People with health-related fertility problems are then defined on page 4 as: "People with health-related fertility problems are those who: • have a known clinical cause of infertility or • do not achieve a pregnancy: − after 12 months of regular unprotected sexual intercourse or − after 6 cycles of artificial insemination."	Thank you for your comment. The committee are sympathetic to your comment but are bound by the remit of the populations covered by this guideline is stated in the scope document for this guideline, consulted on and published in 2022. The scope of the previous version of the guideline also was "intended for people who have a possible pathological problem (physical or psychological) to explain their infertility" (see the 2013 Full guideline) so this is not new but the definition of the population has been further clarified in the scope of the new guideline. Therefore, people who do not meet the definition of the population inclusion criteria set out in the scope of the guideline are indeed not covered by the guideline. This may include the initial cycles of artificial insemination for

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				Page 5 continues: "The guideline covers all people seeking assessment and treatment of health-related fertility problems who meet these criteria, irrespective of their sexual orientation, partnership status or gender identity." Although this is reassuring, we think that the couching of fertility problems in terms of 'health-related fertility problems' is problematic. This potentially excludes those who might be termed 'situationally infertile', i.e. those who have no health-related fertility problems but need access to gamete donation to form their families. These might be same-sex couples, solo parents by choice or others. Therefore, we feel that this definition of infertility used in the guidance is too narrow and has the potential to discriminate against certain groups of people who want to access clinic provided fertility services. This is an important issue as funding allocation is linked to who is seen as infertile and hence needing treatment, and current criteria discriminate against 'lesbians and single women' (Tippett, 2023, Taylor et al., 2022). The Women's Health Strategy (2022) explicitly recognises that lack of access to fertility treatment for LGBT+ couples and people is a concern and recommends changes so that	people with "situational infertility". The evidence base for recommendations on IUI and IVF considered studies with populations who had either a known health-related impediment to fertility or had not conceived after trying for a certain period of time. Therefore, the clinical and cost-effectiveness evidence underpinning the recommendations on IUI and IVF only apply for people with health-related fertility problems, as defined in the scope and guideline documents. As you note, the guideline's population definition includes people who have either tried to conceive for 12 months through unprotected sexual intercourse or who have tried to conceive through 6 cycles of artificial insemination. These are based on the decisions made by the guideline development group (GDG) who updated the guideline in 2013. From the 2013 Full guideline p77: "The aim was to decide the number of failed AI cycles that would be equivalent to failure to conceive after 12 months of unprotected vaginal intercourse." The GDG's discussions covered a number of ethical and practical issues relating to 'equivalence' including: • the financial cost of AI and disadvantage of those attempting to conceive by that route

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				'Female same-sex couples are able to access NHS-funded fertility services in a more equitable way' (page 68). Other organisations have attempted to address the potential discriminatory consequences of restrictive definitions of infertility. For example, the American Society of Reproductive Medicine has issued a definition of infertility that includes other aspects, 'The inability to achieve a successful pregnancy based on a patient's medical, sexual, and reproductive history, age, physical findings, diagnostic testing, or any combination of those factors… Nothing in this definition shall be used to deny or delay treatment to any individual, regardless of relationship status or sexual orientation' (ASRM, 2023). Therefore, we think a definition that encompasses the 'situationally infertile', would be more appropriate. Such as, 'Infertility is the condition in which a person or couple cannot achieve parenthood without assistance, whether medical, technological, or third-party.' The current definition of infertility has the advantage of clinical precision, but it embeds assumptions about heterosexual intercourse and biological dysfunction that exclude many who require assistance to reproduce. By contrast, the more inclusive definition reframes infertility	• the time to conception and disadvantage of those attempting to conceive by vaginal intercourse. Further discussion explaining the group's decision is documented in the 2013 Full guideline document p77-78. They agreed that 6 cycles of artificial insemination and 12 months of unprotected sexual intercourse was of reasonable 'equivalence'. The current guideline committee did not find a reason to change this. In relation to your comment about people with difficulty accessing clinic-based care and turning to informal/self-arranged/non-clinical/online-based sperm donation. The committee are aware of this issue and discussed how lack of NHS funding for people with 'situational infertility' can lead to unsafe routes for trying to conceive. While acknowledging that the remit of the guideline, as defined in the 2022 scope, does not cover situations where fertility treatment is needed in the absence of a health-related reason, they wanted to make a recommendation to advise people who are thinking about using donor sperm to conceive to have treatment in a licensed fertility clinic to ensure clinical safety and legal parenthood. They recognised the disadvantage and difficulty of financial access to fertility treatments in these scenarios.

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				as a matter of capability and need rather than disease. This avoids pathologising people, recognises the legitimacy of 'situational infertility', and ensures equal treatment of single people, LGBTQ+ families, and others who fall outside the heteronormative model. Importantly, it aligns with equality law obligations to avoid indirect discrimination and better supports reproductive justice by focusing on fair access to reproductive opportunities, rather than restricting support to those who can demonstrate a medical need. In addition, defining "people with health-related fertility problems" as those who do not become pregnant after 12 months of regular unprotected sexual intercourse or after 6 cycles of artificial insemination has inequitable financial implications for same-sex and mixed-sex couples. As monogamous same-sex couples are biologically unable to become pregnant 'after 12 months of regular unprotected sexual intercourse', they are therefore required to first undertake '6 cycles of artificial insemination' to qualify for funded treatment. Given that unprotected sexual intercourse between mixed-sex couples incurs no financial cost, but a single cycle of artificial insemination can cost between £800–2000, plus the cost of donor sperm (~£1,000 for one vial), consultations and health tests, same-sex couples are expected to pay in excess of	Thank you for sharing information about your research project.

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				£10,000 before being eligible for NHS funding (Taylor et al., 2022). Lobbying and campaign groups have come to refer to this as a 'tax' on the LGBTQ+ community, and we support the suggestion that this part of the guideline should be revised to make it more equitable (British Pregnancy Advisory Service, 2021; Fertility Justice Campaign, 2024). **Our research** Research conducted by the Online Sperm Donation Project team found that often those who found it hard to access clinic-based fertility services turned to the internet to find online sperm donation (OSD). This is sperm donation that's arranged via connection websites and social media groups. Sometimes, this is known as 'informal', 'self-arranged', 'private' or 'non-clinical' sperm donation. While this may be a first choice for some people, others used this option as a 'last resort'. The Human Fertilisation and Embryology Authority cautions against using online sperm donation as a route to parenthood (HFEA, 2025) on a number of grounds: the legal ambiguity of legal parent status; no cap on the usage of the donor; lack of genetic screening of donors; and lack of any support and counselling. Our research	

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				uncovered a mixture of positive and negative experiences with OSD. For some people, forming a family in this way was a 'first choice', however others felt they had no other option: 'All the recipients who took part in [the OSD] studies mentioned that the lack of funding for, and/or the associated costs of, clinical treatment were prohibitive to them, and that this was a contributing factor in their decision to undertake OSD.' (Taylor-Phillips et al., forthcoming). A number of same-sex couples in our studies also mentioned the inequitable criteria to qualify for NHS funding, namely the need to self-fund six cycles of artificial insemination. For example, one LGBTQ+ recipient said the following in her first interview with us: "we've got so much institutional homophobia…we want this child! We're in a stable relationship, we're financially stable, we've got a great support system. Why can't we get any support from anyone? Why do straight couples only have to try for a year for free?... It makes me really upset, because we [queer people] exist!" Statements like these were not uncommon, and there was a general perception among LGBTQ+ participants that the guidelines and institutions they would rely on for fertility treatment did not treat them equally and were not welcoming.	

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				Information about the OSDP The Online Sperm Donation Project, led by Dr Rhys Turner-Moore at Leeds Beckett University and funded by the Economic and Social Research Council, is the largest study ever on online sperm donation. Ten researchers from five organisations are collaborating on the project. The Online Sperm Donation Project is a four-year research project (2022-2026) on online sperm donation. In the first part of the research, we explored the families and relationships in online sperm donation, what influences people's experiences, and what the impacts are. To find out about this, we have: • interviewed people who recently started looking for a sperm donor online (which some people call 'recipients') and in some cases their partners (if they had one); • interviewed donors who are donating their sperm online and in some cases their partner (if they had one). Where a recipient later became pregnant with their sperm, we were sometimes able to speak with them, as well;	

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				• followed people's online sperm donation journeys over time by interviewing them again after a year or two years; • interviewed people who owned and managed the connection websites and social media groups about their experiences; • looked at the information available on connection websites and social media groups for site members; • joined connection websites and social media groups for a year as a researcher to understand how people communicate and make connections. For further information, please see the project website: https://www.theosdproject.com/	
Leeds Teaching Hospital Trust – Fertility Preservation Service MDT	Guideline	014	003	Would this apply if there is an expected cause of azoospermia / severe oligozoospermia e.g. post bone marrow transplantation? We would suggest adding caveat i.e., unless there is an established cause of azoospermia, undertake the repeat test	Thank you for this comment. The guideline committee discussed this and agreed that a repeat test would needed as the parameter levels may vary and a one-off test may not be sufficient to confirm azoospermia or very low sperm concentration.
Leeds Teaching Hospital Trust – Fertility	Guideline	014	014	Should we be offering this now in the post chemotherapy males who have unexpected subfertility?	Thank you for your comment. The committee considered the stakeholder comment regarding the role of Y chromosome microdeletion

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Preservation Service MDT					testing in post-chemotherapy males presenting with unexpected subfertility and agreed that testing should be offered to those with unexpected subfertility (i.e. idiopathic azoospermia or unexplained severe oligozoospermia [sperm concentration <1 million per ml]) after chemotherapy. If fertility potential was known to be normal prior to chemotherapy and subsequently became impaired, it is reasonable to attribute this change to the chemotherapy itself. In such cases, genetic testing is not indicated. If fertility potential was not assessed prior to chemotherapy, then impaired fertility detected afterwards cannot be assumed to be solely due to chemotherapy. A pre-existing problem may have been present, and in this context Y chromosome microdeletion testing may be appropriate. Certain chemotherapy regimens are not expected to have a lasting or significant impact on fertility. Therefore, if markedly impaired fertility is observed following such treatment, it is less likely that chemotherapy alone is responsible and Y chromosome microdeletion testing may be appropriate.

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Leeds Teaching Hospital Trust – Fertility Preservation Service MDT	Guideline	030	011	'mild' endometriosis. Suggest the definition/classification should ideally be referenced, with a link to the 'terms used in this guideline' in the same way that the definition of 'mild male factor fertility problems' is referenced/defined. Suggest also offer definition of severe /other grades, as will support the rest of the guidelines, e.g., section 1.9.3. Suggest that the 'terms used in this guideline' definition of 'mild male factor fertility problems' is unhelpful without referencing or linking to the studies mentioned or offering a definition e.g. "semen values lower than ..." As both 'mild endometriosis' and 'mild male factor fertility problems' are used to relation to access treatment, ambiguity is unhelpful and could affect treatment offered e.g. IVF or IUI or expectant management.	Thank you for this comment. The recommendation referred to in the comment has been revised and 'mild endometriosis' and 'mild male factor' have been removed, and the committee decided not to refer to these terms in the recommendations as they are clinically ambiguous. They also discussed that it was difficult to define mild endometriosis and mild male factor. The guideline recommendations no longer refer to 'mild' or 'severe' endometriosis, or 'mild male factor fertility problems' because the committee agreed they can be clinically ambiguous. In the case of endometriosis, these types of terms also do not appropriately reflect the complexity of potential fertility problems in relation to endometriosis. Instead, the committee agreed to include a section titled Endometriosis, where fertility treatment options for women and people with endometriosis are covered, with cross-reference to the NICE guideline on endometriosis.
Leeds Teaching Hospital Trust – Fertility Preservation Service MDT	Guideline	042	005	We welcome this recommendation but would suggest NICE be clearer re this as this is very open to differing interpretation - this guidance provides the valuable opportunity for equal access to fertility preservation. As per standard fertility treatment this is likely different for	Thank you for this comment. The guideline committee did not want to be too prescriptive about the age limit for fertility preservation and agreed that eligibility for fertility preservation should be assessed individually and based on clinical

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				men and women also, i.e., upper age limit for egg freezing for women.	judgement. Additionally, this section of the guideline has been updated by adding the previous recommendation with some minor edits on the factors to be considered when offering fertility preservation such as diagnosis, treatment plan, expected outcome of subsequent fertility treatment etc.
Leeds Teaching Hospital Trust – Fertility Preservation Service MDT	Guideline	042	015	We would suggest that this is revised to clarify that this includes those men and women who had already received medical treatment that is likely to make them infertile i.e., those who have already received treatment and are as a result now at high risk of becoming infertile. An example would be women requiring urgent oncology treatment who do not have time to freeze eggs prior to treatment and may have a narrow window of opportunity post treatment to preserve her fertility.	Thank you for this comment. The guideline committee agree that a discussion about fertility preservation should be held at the earliest opportunity for those who require urgent treatment and this has now been added to the recommendation. The committee did not think that the guideline can recommend fertility cryopreservation for those who have already received gonadotoxic treatment because of uncertainties in the quality and safety of the material. However, they recognised that there may be situations based on clinical and professional judgment where this could be reasonable. The committee's discussion on this has been included in the Benefits and harms section of the evidence review R on Fertility preservation.
Leeds Teaching Hospital Trust – Fertility	Guideline	042	023	In reference to the 5 yearly follow up - this is not appropriate for all e.g. young men or women should in our opinion be reviewed earlier and whilst there is flexibility suggested by NICE, we suggest this needs expanding	Thank you for this comment. As it is outlined in the Benefits and harms section of the evidence review R on Fertility preservation, the guideline

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Preservation Service MDT				and further clarity regarding the timing and frequency of fertility surveillance in those at risk of infertility post treatment. We would request / welcome more guidance regarding the measures to monitor fertility and with what measures, i.e. in males a repeat semen analysis but the role of AMH / other ovarian reserve markers would be helpful in this context to again ensure more consistent care and service provision for patients requiring fertility preservation. The 5-year recommendation is in our view not supported by robust evidence of what follow up care should consist of, it's frequency and the length of storage (which may differ depending on type of preservation used). Clarification on referral pathways is also needed as the guidance does not suggest who should be accountable, the minimum content of reviews or risk management requirements / safety. Whilst 5 years is suggested flexibly, consent renewals to lawfully continue storage for paediatric populations is complex considering transition to adult services at 16/18. This requires consideration as current drafted detail could be criticised as inadequate. Cross-reference to cancer pathways and detail of accountability / shared-care responsibilities could be more	committee were aware that the consent to store cryopreserved material must be renewed with the person every 10 years for NHS-funded storage to lawfully continue. In addition to the legal requirement, the committee emphasised the importance of more robust follow-up procedures to discuss the need for continued storage. Balancing considerations such as minimising unnecessary storage of materials, the resources needed to organise follow-ups, and risk of losing touch with people, the committee agreed follow-ups at least every 5 years would be reasonable but leaving flexibility. This could happen more often in some cases, or every 5 years in other cases. The committee were unable to go into a lot of detail in terms of follow-up schedule or content in different scenarios. The committee discussed the evidence on ovarian tissue cryopreservation and agreed that the evidence showed ovarian tissue retrieval and cryopreservation was feasible and effective, and that this fertility preservation option would be particularly relevant for girls before puberty, when oocyte and embryo retrieval would not be possible. The recommendation on ovarian tissue cryopreservation has been updated and it now refers to the NICE interventional procedures guidance on removal, preservation and reimplantation of ovarian

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				explicit throughout. In particular, for people with stored ovarian/testicular tissue who are at risk of becoming lost to follow-up and for whom fertility needs materialise many years after fertility preservation has occurred. Good evidence exists showing there is significant variation in provision of care, therefore it would be helpful to add minimum standards around this, e.g. reporting requirements, transition to adult services to reduce this variability (see Newton HL, Picton HM, Friend AJ, Hayden CM, Brougham M, Cox R, Grandage V, Kwok-Williams M, Lane S, Mitchell RT, Skinner R, Wallace WH, Yeomanson D, Glaser AW; Children's Cancer and Leukaemia Group Late-effects Working Group. Inconsistencies in fertility preservation for young people with cancer in the UK. Arch Dis Child. 2022 Mar;107(3):265-270. https://pubmed.ncbi.nlm.nih.gov/34544694/) Suggest if tissue preservation is included, cross-check recommendations to ensure no discrepancies to existing NICE guidelines on fertility tissue (https://www.nice.org.uk/guidance/ipg772). Long-term safety of ART using stored tissue could be added. Patients who had cancer and then wish to use tissue may be at risk of re-introducing disease if tissue is implanted. The guidelines could set a UK standard for	tissue for restoring fertility after gonadotoxic treatment (IPG772). The committee also discussed that testicular tissue cryopreservation was still experimental and that there was very limited evidence available, and they agreed that this was particularly relevant for boys before and during puberty. Given the experimental nature of this procedure and the lack of evidence on the primary outcomes (live birth and clinical pregnancy), they decided they could not comment on the use of testicular tissue cryopreservation as a fertility preservation option. However, they made a research recommendation in the hope of generating further research on the success and safety of testicular tissue cryopreservation. In terms of research recommendations in this update, the committee prioritised 5 other key research recommendations. However, the research recommendations suggested in the comment may be considered in the future update if the committee considers them to be relevant. In terms of other issues raised in the comment such as offering advice on continuity of information when people move or change name/gender etc., the guideline is not

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				testing so that care is standardised, or it could refer/signpost to best evidence on this. Otherwise centres may improvise. Add detail on who pays for long term storage or tissue use to avoid further ambiguity. Whilst ovarian or testicular tissue is mentioned, it is included with significantly less detail than other methods. However, for pre-pubertal children, it is the ONLY option. The current framing somewhat undervalues its significance. The guidance also does not offer advice on continuity of information when people move or change name/gender. Suggest including a recommendation on record-linkage and traceability, especially for those storing tissue (likely to be over a decade between preservation and use). As testicular tissue cryopreservation is still experimental and there remains very limited evidence on the efficacy of ovarian tissue storage and outcomes, capturing data centrally (including tissue storage/procurement, transition to adult services, tissue use, endocrine/fertility outcomes, adverse events, malignant contamination) is essential. Suggest:	intended to cover every eventuality related to fertility material preservation. In relation to long-term safety of ART using stored tissue, this was not part of the scope of this guideline update.

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				• Add recommendation for providers to participate in the national fertility-preservation tissue United Kingdom of Stored Ovarian and Testicular Tissue (UKSTORE) as per NICE guidelines (https://www.nice.org.uk/guidance/ipg772), including updating records at key points (tissue use, consent renewal, endocrine hormone recovery, disposal, births) within 12 months. • Add a recommendation to prioritise research on outcomes following ovarian or testicular tissue use, e.g. " What is the clinical effectiveness and safety of using ovarian or testicular tissue following tissue preservation for children and adults undergoing treatment for cancer and other conditions or situations which are likely to impair their fertility?" (add after Report R: Fertility preservation 4.1.1) • What are the psychosocial, psychological and quality-of-life outcomes following ovarian or testicular tissue storage and use, and what design and frequency of reproductive follow-up care will best support young people with stored ovarian or testicular tissue between childhood and reproductive outcomes?	

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Malebox Health Ltd	Evidence review S	General	General	Malebox believes the DNA fragmentation Evidence review (S) should be revisited. The "review aims to examine the clinical and cost effectiveness of treating DNA fragmentation (identified from screening ejaculated sperm) on reproductive outcomes, and subsequently whether testing is worthwhile." The review identified that "The committee were aware of evidence suggesting an association between sperm DNA fragmentation and poor embryo quality (Borges 2019; Li 2024)" therefore Malebox believe that although evidence for routine use of DNA fragmentation may not be sufficient there is still a case for using DNA fragmentation as a diagnostic tool in certain cases with persistent unexplained infertility to inform clinical decisions/ pathways. The risk of a blanket recommendation against the use of DNA fragmentation is that further research into factors that affect DNA fragmentation stagnates and thus clinically relevant associations are not identified. Malebox believes that this would be unproductive at a point where male fertility rates are declining.	Thank you for your comment. Evidence Review S aims to examine the effectiveness of treating DNA fragmentation, and subsequently whether testing is worthwhile. The guideline committee agreed that based on the evidence showing no clear benefits of treating sperm DNA fragmentation, there was no justification for routine testing of sperm DNA fragmentation. In other words, since treatment does not improve clinical outcomes, the DNA fragmentation test does not lead to any actionable steps. For this reason, the committee did not recommend its use even in certain cases with persistent unexplained infertility. In addition, the committee were concerned that sperm DNA assays are expensive tests which can take weeks to get results for. Based on the potential advantages of saving lost time in time-sensitive fertility pathways, and without effective treatments to rationalise testing from a potential cost-saving perspective, the committee agreed that testing for sperm DNA integrity (fragmentation) should not be carried out. The committee acknowledged the need for further research to identify and validate the best assay or test, define a threshold for high DNA fragmentation, and

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					clarify its association with subfertility. However, given all these unknowns, the committee agreed it would be premature to draft a fully specified and implementable research recommendation that would be able to deliver conclusive results (please see page 22, line 42-49).
Malebox Health Ltd	Guideline	005 – 006	019-029, 001-005	The mental health implications of fertility are well documented with Fertility network UK finding that 90% of men who are infertile suffer from depression. 42% experience suicidal feelings (https://fertilitynetworkuk.org/let-down-lack-of-support-for-fertility-patients-before-during-and-after-treatment/). Malebox strongly supports that counselling for all patients being a part of the diagnosis journey that should be included within this guideline.	Thank you for your comment. The guideline recommends offering counselling to all people experiencing fertility problems before, during and after investigations and treatment (recommendations 1.2.2-1.2.4).
Malebox Health Ltd	Guideline	044	013 - 018	Due to delays in reproductive treatments in the UK, we have become aware of a point in the fertility journey that has become neglected - this is the wait from diagnosis to treatment. There is significant evidence to suggest that male fertility can be improved in many cases through simple lifestyle programmes and changes in order to provide for individuals: • Smoking cessation - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5416813/ • Weight	Thank you for your comment. In Evidence Review S, we have stated that no evidence was found for lifestyle advice (including weight loss, healthy diet, exercise, smoking cessation, reducing alcohol intake, and so on) (Please see 'Summary of evidence' section [page 18, line 30]). As there is no evidence to justify the beneficial effect of lifestyle advice, the committee agreed, based also on their clinical knowledge and experience, that it is not reasonable to recommend lifestyle advice in people with a fertility

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				• loss - https://www.ncbi.nlm.nih.gov/pubmed/28661897 • Physical exercise - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5582143/ • Diet - https://pubmed.ncbi.nlm.nih.gov/28333357/ • Stress - https://doi.org/10.1093/humrep/dei062 By promoting improvement of fertility whilst waiting for treatment we believe there will be an increased natural conception due to improvement of the male factor which has been shown to contribute to 30-50% of fertility struggles (https://pmc.ncbi.nlm.nih.gov/articles/PMC4424520/). Which will in turn reduce the cost of fertility treatments within the UK health care system. Further providing support and advice during this period will contribute towards providing more holistic care through the entire journey.	problem that may be associated with sperm DNA fragmentation. We have checked the references provided by the stakeholder, but they do not meet inclusion criteria because they are: (1) Observational study (Smoking cessation - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5416813/) (2) Narrative review (Weight loss - https://www.ncbi.nlm.nih.gov/pubmed/28661897 (3) Cross-sectional study (Physical exercise - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5582143/ (4) Systematic review of observational studies (Diet - https://pubmed.ncbi.nlm.nih.gov/28333357/ (5) Before and after study design conducted in healthy participants (Stress - https://doi.org/10.1093/humrep/dei062 (6) Review of population-based studies or epidemiologic studies (https://pmc.ncbi.nlm.nih.gov/articles/PMC4424520/)

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Merck Serono Ltd	Guideline	General	General	Related to the comment above, the draft guidance does not provide any guidance regarding egg donation routes for patients that cannot conceive with their biological eggs. We propose this is included in the guidance.	Thank you for your comment. This was not within the scope of this guideline update and so we are unable to comment on this.
Merck Serono Ltd	Guideline	General	General	The draft guidance does not provide any guidance on IVF for same sex couples or single parents. We propose this is included in the guidance.	Thank you for your comment. It should be noted that the guideline only covers fertility treatments in the context of health-related fertility problems, regardless of the person's sexual orientation or relationship status. The guideline makes recommendations about IVF for people who have not conceived through artificial insemination, this would likely include female same sex couples and single women/people with female reproductive organs.
Merck Serono Ltd	Guideline	032	005-007	Rec 1.9.7 Related to the comment above, the evidence supporting the reduction of IVF cycles from 3 to 1 for people aged 40 and 41, was not fully clear. People over 40 could benefit from >1 cycle of IVF if they have adequate AFC/AMH and FSH as 1 cycle may not be enough to produce an optimised number of oocytes. Also it would be valuable to add an option for an egg donation pathway.	Thank you for this comment. As with the previous 2013 guideline, the updated guideline only recommended 1 full cycle of NHS funded IVF to people aged 40-41. This was based on the best available evidence of clinical and cost-effectiveness evidence. The full economic analysis is described in Appendix I of Evidence Review J. See the Results section and p167, lines 15-24.

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				Can you please provide more clarity on the cost-effectiveness evidence supporting this restriction to 1 cycle and please consider revising 1.9.7. to allow 3 cycles of IVF in relevant scenarios where 3 cycles are cost-effective in this age group.	AFC/AMH and FSH were not utilised as predictors in the prediction models (as these were not available in the linked HFEA dataset used to develop the prediction models) which underpinned the economic analysis and therefore recommendations were not based on ovarian reserve, independent of age.
Merck Serono Ltd	Guideline	062	026-032	This section states that *some* scenarios of IVF access were not cost-effective for this age group. This implies that the remaining scenarios in the 40-41 age group were cost-effective. However, the draft guideline wording states that only a *limited number* of scenarios were cost-effective. Can we please ask for further clarification in this section and for further detail on which scenarios of IVF access were cost-effective for people aged 40-41.	Thank you for this comment. This is outlined in the full write-up of the economic analysis in Appendix I of Evidence Review J. In particular see the Results section and p167, lines 15-24. This section is intended to give a broad overview to the rationale that underpins guideline recommendations and is not used to go into this level of detail.
Mid Cheshire Hospitals NHS Foundation Trust	Guideline	General	General	Could NICE acknowledge the Government guide of charging for overseas visitors and include a statement in their guidelines that not all overseas visitors are eligible for fertility treatment and then reference the overseas visitors charging regulations. 1. Would it be challenging to implement of any of the draft recommendations? **No** **2.** Would implementation of any of the draft recommendations have significant cost	Thank you for your comment. This is not within the remit of this guideline.

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				implications? **Possibly if overseas visitors were unidentifed.**	
NHS Black Country ICB	Guideline	009	022	Noted absence of references made to the effects of vaping on fertility. This is a current criteria in BC ICB clinical commissioning policy and raises concerns to omit from future guidance/policy.	Thank you for your comment. The impact of nicotine-containing products, such as e-cigarettes and vaping, on fertility was not within the scope of this guideline update and no evidence has been reviewed on this, so the committee are unable to make recommendations on this topic. Several stakeholders made a similar comment and we have noted this as a potential topic for future updates.
NHS Black Country ICB	Guideline	012	013-018	Could this potential cause inequity and inflate waiting times for this service, whereby patients who have conceived naturally and then miscarried and those that have never conceived, actually have equal access to treatment. Should we not be prioritising access to those who have never conceived at all?	Thank you for your comment. The committee's view is that there is no inequity in treating people equally who are childless after a year of trying without conceiving, or who are childless after a year of trying but having had a miscarriage (or ectopic pregnancy). Both of these scenarios warrant further assessment and treatment for subfertility.
NHS Black Country ICB	Guideline	029	018	This recommendation of 12 cycles (6+6) IUI in total is more than the ICB's current offer where 6 failed cycles of IUI would proceed directly to IVF. Has a cost- benefit analysis being consider as part of this recommendation.	Thank you for your comment. These recommendations are originally from 2013 and no new evidence was analysed for this update. The recommendation to have 12 cycles of artificial insemination before IVF treatment for those without

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					contraindications (such as a known clinical cause of infertility) has been in place since 2013. We won't be able to comment on local decisions.
NHS Black Country ICB	Guideline	030	004-007	What is the definition of 'mild' endometriosis or 'mild' male factor fertility problems. Lack of clarity for patient and clinician, leaves recommendation open to interpretation.	Thank you for your comment. The definitions of 'mild' endometriosis and 'mild' male factor fertility problems are clinically ambiguous. There are no standard definitions; therefore, the committee decided not to refer to these terms in the recommendations. The terms 'mild' endometriosis and 'mild' male factor fertility problems have been removed throughout the guideline.
NHS Black Country ICB	Guideline	031	024	This is a significant increase to the offer of recommended up to 6 cycles of IVF. In the current financial climate, the majority of ICB's will struggle to implement this. This unfairly raises patient expectations and puts the ICB under further pressure to justify rationing of IVF treatment.	Thank you for this comment. The guideline committee were aware that the implementation of recommendations had to be considered as part of their deliberations. The updated guideline recommends that 3 cycles of IVF are still offered as per previous NICE guidance but a weaker 'consider' recommendation is made for an additional 3 cycles. The weaker recommendation reflects the more uncertain evidence of clinical and cost-effectiveness for 4-6 cycles. The committee did not think that many patients would want more than 3 cycles if previous attempts were

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					unsuccessful but noted that expectations are already unmet in many areas of the NHS where NICE recommendations are not adhered to.
NHS Black Country ICB	Guideline	032	001	The ICB current offer of one full cycle of IVF is not compatible with this recommendation and again raises patient's expectations.	Thank you for this comment. NICE makes recommendations on the best available clinical and cost effectiveness evidence. Economic analysis suggested that more than 1 cycle of IVF would be cost-effective for most people, although access to NHS treatment was no longer recommended for those aged 42 years.
NHS Black Country ICB	Guideline	032	005	The current BC ICB commissioning policy criteria does not offer IVF treatment beyond 40. Based on the graph on page 16, we would be offering a treatment which has a success rate of between 10-20%. Would this be considered an appropriate use of resources? This would prove very challenging to implement in the current financial climate.	Thank you for this comment. The revised NICE guideline is more restrictive with respect to IVF access on the NHS, with it no longer being offered to women age 42 years. Economic analysis reported in Appendix I of Evidence review J did suggest that 1 cycle of IVF would be an appropriate use of resources in this age group.
NHS Black Country ICB	Guideline	038	016	This would not be part of the current ICB offer past one cycle of IVF. Again, implications of cost.	Thank you for this comment. NICE recommends 3 full IVF cycles for women and people with female reproductive organs under 40 years of age and therefore this recommendation about considering ICSI for couples in whom a previous IVF treatment cycle has resulted in failed or very poor

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					fertilisation is valid. We are aware many ICBs do not follow this guidance.
NHS Black Country ICB	Guideline	041	019	Further explicit guidance around 'egg sharing' 'shared motherhood' within same sex couples would be welcomed. There is an noticeable increase in demand to fund this IVF treatment option for same sex female couples, which has further cost and legal implications.	Thank you for your comment. This is not within the scope of the guideline but may be considered in future updates if considered a priority. The committee agreed to remove the recommendation from 2004 about egg-sharing because it was not considered relevant for NHS practice and benefit-in-kind egg sharing is covered in HFEA Code of Practice. HFEA also has information about reciprocal IVF.
NHS Cheshire and Merseyside ICB	Guideline			We are concerned about the affordability of an increase in the number of recommended cycles up to as many as 6. Like many ICBs we have recently completed a public consultation as part of plans to reduce the number of available cycles to 1 as this is deemed the affordable number in current financial climate. Guidance recommending 3+3 cycles will not be deliverable.	Thank you for this comment. NICE produces recommendations on the best available clinical and cost-effectiveness evidence. As per the previous NICE guideline it is recommended that 3 cycles are offered. The committee considered that the evidence for this recommendation was even better supported this time. Reflecting weaker evidence, a 'consider' recommendation is also made for a further 3 cycles,

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					which should include a discussion about the probability of success and implications of further treatment. The committee discussed that many people who have experienced several failed IVF cycles do not want to proceed with further IVF cycles, so the number of people opting for further cycles would likely not be high.
NHS Cheshire and Merseyside ICB	Guideline			**Risk of widening inequalities** Like many ICBs we have recently held a public consultation in reducing to one cycle of based on affordability. There has been a gradual move towards ICBs being aligned in the number of cycles offered with approx. 70% now only offering one cycle. Although this is a lower level of access it has reduced the inequity and "postcode lottery" between different parts of the country which is a major source of concern for potential patients and featured significantly in the feedback we have received. If the guidance increases to 3 +3 it will leave ICBs in a difficult position regarding affordability and could potentially lead to increasing inequalities in access across the country particularly because ICBs have different levels of financial challenge. In the Northwest the 3 ICBs all have more challenging financial positions as well as having lower overall fertility rates and higher rates of conditions underlying infertility.	Thank you for this comment. NICE produces recommendations on the best available clinical and cost-effectiveness evidence. As per the previous NICE guideline it is recommended that 3 cycles are offered. The committee considered that the evidence for this recommendation was even better supported this time. Reflecting weaker evidence, a 'consider' recommendation is also made for a further 3 cycles. Furthermore, it is recommended that a discussion of the probability of success and the implication of more treatment accompanies the consideration of any further 3 cycles if the person has not conceived after the first 3 full cycles. The committee discussed that many people who have experienced several failed IVF cycles do not want to

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				In addition there is more in the Northwest meaning less ability to self fund.	proceed with further IVF cycles, so the number of people opting for further cycles would likely not be high. Please see the Equalities and health inequalities assessment form (available in the History tab of the guideline website), where we discuss the inequalities issues in relation to geographical locations.
NHS Cheshire and Merseyside ICB	Guideline	012	011	1.2.28 This paragraph talks about non binary people but then uses the pronoun her on line 11	Thank you for this comment. This has been amended to be 'their partner'.
NHS Devon ICB	Guideline	008-009	019-022 & 001-010	Point 1.10.5.1 from the current guideline "People should be informed that the consumption of more than 1 unit of alcohol per day reduces the effectiveness of assisted reproduction procedures, including IVF" has been deleted because: it was "not considered to be useful, and advice on alcohol is already covered in section on 'Initial advice'." (from Table 3 p74 line 15, this recommendation p79) The initial advice guidance refers to spontaneous conception and does not include the fact stated in the current guideline that alcohol consumption can reduce the success of assisted conception including IVF.	Thank you for this comment. The guideline committee agreed that the recommendations in the Initial advice section on alcohol are useful and suitable for fertility patients in general.
NHS Devon ICB	Guideline	009	011-024	Point 1.10.5.2 from the current guideline "People should be informed that maternal and paternal smoking can adversely affect the success rates of assisted reproduction procedures, including IVF treatment" has	Thank you for your comment. The guideline committee agreed that the recommendations in the Initial advice section on

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				been deleted because: it was "not considered to be useful, and advice on smoking is already covered in section on 'Initial advice'." (from Table 3 p74 line 15, this recommendation p79-80) The initial advice guidance refers to spontaneous conception and does not include the fact stated in the current guideline that smoking can reduce the success of assisted conception including IVF.	smoking are useful and suitable for fertility patients in general.
NHS Devon ICB	Guideline	009	025-029	Point 1.10.5.3 from the current guideline "People should be informed that maternal caffeine consumption has adverse effects on the success rates of assisted reproduction procedures, including IVF treatment." Has been because: it was "not considered to be useful and advice on caffeine use is already covered in section on 'Initial advice'." (from Table 3 p74 line 15, this recommendation p80) The initial advice guidance refers to spontaneous conception and does not include the fact stated in the current guideline that caffeine consumption can reduce the success of assisted conception including IVF.	Thank you for your comment. The committee's view was that this was based on an old evidence review which was not updated and might no longer be particularly useful and accurate. The committee thought the information on caffeine use in the 'Initial advice' section was sufficient and further information on its association with IVF outcomes was not needed.
NHS Devon ICB	Guideline	010	001-018	Point 1.10.4.1 from the current guideline "Women should be informed that female BMI should ideally be in the range 19 to 30 before commencing assisted reproduction, and that a female BMI outside this range is likely to reduce the success of assisted reproduction procedures" has been deleted because: it was "not considered to be	Thank you for your comment. This recommendation was based on an old evidence review which was not updated and the committee thought it was not particularly useful and has been used to deny treatment even though BMI has not been an

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				useful and could be misused to deny treatment, and advice around BMI is already covered in section on 'Initial advice'". (from Table 3 p74 line 15, this recommendation p79) The initial advice guidance refers to spontaneous conception and does not include the fact stated in the current guideline that BMI outside of the stated range can reduce the success of assisted conception. We also feel that removing this point ignores the evidence and does not help to target resources to patients who are most likely to benefit from assisted conception, and to maximise an individual's chance of success.	access criterion for IVF treatment in the guideline. The committee agreed that BMI advice should focus on health optimisation rather than being used as a strict eligibility criterion. General advice around BMI and fertility covered in the section on 'Initial advice' was thought to be sufficient.
NHS Devon ICB	Guideline	012	013-018	This recommendation about miscarriage contradicts the definition of "people with health-related fertility problems" as those who "do not achieve a pregnancy" as defined on p4 line 10. The recommendation is not evidence-based and risks introducing inequity as it does not also consider those who had an ectopic pregnancy, for example.	Thank you for this comment. The committee agreed with this and amended the recommendation to include ectopic pregnancy.
NHS Devon ICB	Guideline	012	024	Change to text has not been highlighted or marked as amended 2026. In the current guidance it is "known clinical cause of infertility", in the draft it is "known or suspected clinical cause of infertility". In Table 4 the use of "suspected" in this recommendation (1.2.30) appears to be the reason for also adding "suspected" to 1.2.27 and 1.2.28 (Table 4 p88 line 3, these recommendations p92)	Thank you for your comment. Not highlighting or marking this change as an amendment was an omission. We have corrected this now.

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NHS Devon ICB	Guideline	016	017-020	Point 1.3.15 states that anti-Müllerian hormone (AMH) or antral follicle count (AFC) should be used as predictors of ovarian response but no longer gives thresholds for a low or high predicted response. We are concerned that this will lead to inequity for patients because different regions and/or providers will adopt different thresholds for low or high predicted responses. The previous guidance was able to give thresholds based on less evidence than that reviewed in Evidence Review A and did so despite highlighted issues regarding lack of standardisation of AMH assays and lack of consistency of thresholds investigated by individual studies.	Thank you for this comment. As outlined in the Benefits and harms section of the evidence review A on Ovarian reserve testing, the guideline committee could not include specific thresholds on ovarian reserve in the recommendations as there were no consistent thresholds reported in the evidence. They also discussed that this should be guided by clinical judgement.
NHS Devon ICB	Guideline	016	021-022	Point 1.3.16 states that FSH should not be used as a predictor of ovarian response or the outcome of assisted conception. Literature indicates that an FSH of more than thresholds that range between 10-20 IU/L can be helpful to predict poor ovarian response. Many of the studies considered in Evidence Review A had inclusion criteria of FSH < 10 -15 IU/L, indicating that this measurement can be helpful to identify patients with obviously elevated FSH who are highly unlikely to respond to gonadotrophin stimulation. Agree that the evidence shows that AMH and AFC are then helpful to be used as predictors of ovarian reserve for patients with a normal FSH level.	Thank you for your comment. Studies using FSH thresholds as inclusion criteria were all investigating the prognostic ability of other ovarian reserve markers (AMH and/or AFC) and therefore used these thresholds to control for potential confounding. FSH can be used to aid in diagnosing premature ovarian insufficiency, the diagnosis of which can determine access to fertility treatments and ART; a separate NICE Clinical Knowledge Summary recommends a specific FSH threshold of >30 IU/L for this purpose: https://cks.nice.org.uk/topics/menopause/diagnosis/diagnosis-of-premature-ovarian-insufficiency/. The committee also acknowledged that FSH can be used to

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					aid in predicting ovulation dysfunction, however the evidence review only intended to address the ability of ovarian reserve markers to predict outcomes related to assisted and spontaneous conception, and the evidence showed FSH did not have prognostic ability in this context. The recommendations made based on this evidence therefore only address their predictive ability in this regard. This does not preclude the use of FSH testing in other contexts.
NHS Devon ICB	Guideline	030	001-018	The initial advice section covering age, BMI, smoking, alcohol, caffeine is helpful for unstimulated IUI which is recommended for people not having vaginal intercourse. Now that stimulated IUI is recommended for people with unexplained fertility problems, mild endometriosis and mild male factor fertility problems trying to conceive through vaginal intercourse, it is unclear if the lifestyle factors listed above are also relevant for this group.	Thank you for this comment. The initial advice on lifestyle factors applies to the whole population of the guideline, not only for people using unstimulated IUI. Please note that the information about the success rate of IUI after 6 or 12 cycles (in Table 2 and recommendation 1.4.2) has been updated with latest HFEA data. This data includes both unstimulated and stimulated IUI. Please also note that the recommendation referred to in the comment has been revised and 'mild endometriosis' and 'mild male factor fertility problems' have been removed as they are clinically ambiguous and the committee decided not to refer to these terms in the recommendations.

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NHS Devon ICB	Guideline	031	024-028	The recommendation to offer up to 6 cycles of IVF for people < 40 is substantially different from current NHS practice. It would be extremely challenging to put into practice. Nationally, ICBs already struggle to offer the 3 cycles recommended by the current guidance. Given financial resource and capacity constraints it is unlikely that the NHS would be able to universally follow this recommendation. We are therefore concerned that this change would increase inequity for patients across the country and be unhelpful in terms of managing patient expectations. We note that in half of the scenarios (mild & severe endometriosis, severe cervical and combined) considered in the economic model, the IVF Predict model is used which is based on fresh embryo transfer only, not full cycles.	Thank you for this comment. The guideline committee were aware that the implementation of recommendations had to be considered as part of their deliberations. Whilst 3 cycles of IVF are still recommended to be offered as per previous NICE guidance, a weaker 'consider' recommendation was made for an additional 3 cycles. The committee did not think that many patients would want more than 3 cycles if previous attempts were unsuccessful but noted that expectations are already unmet in many areas of the NHS where NICE recommendations are not currently adhered to. Furthermore, it is recommended that a discussion of the probability of success and the implication of more treatment accompanies the consideration of any further 3 cycles if the person has not conceived after the first 3 full cycles. Appendix I of Evidence Review J notes that the OPIS pre-IVF prediction model was preferred for base case analyses but the IVF Predict model did include some conditions as predictors that were not included in the OPIS pre-IVF prediction model. However, where it was possible to do a comparison the OPIS model tended to

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					produce higher cumulative live birth rates than IVF Predict and therefore we do not think the limitation you have highlighted will have led cost-effectiveness to be over-estimated.
NHS Devon ICB	Guideline	031	018-019	The IVF access criteria no longer state that 6 or more of the cycles of Artificial Insemination (AI) should be by **Intrauterine Insemination (IUI)**. It is unclear why this has been removed. We suggest that this it should be retained as a part of the eligibility criteria for IVF treatment. The data in Table 2 (p8 row 3) demonstrate that IUI is more effective than intracervical insemination (ICI). Additionally, the removal of this requirement creates an inconsistency with IUI recommendations: 1.7.1 recommends that people unable to have vaginal intercourse should be offered 12 cycles of IUI for before considering IVF and 1.7.2 recommends that patients trying to conceive by donor insemination should be offered 6 cycles of NHS funded IUI following 6 cycles of unsuccessful, self-funded AI before considering IVF.	Thank you for your comment. The committee agreed to reinstate in the recommendation that 6 or more cycles should be by IUI.
NHS Devon ICB	Guideline	031	005-006	Point 1.9.2 states that ovarian reserve should be taken into account when discussing the option of IVF treatment. We are concerned that the lack of thresholds provided in point 1.3.15 will lead to inequity for patients because different regions and/or providers will adopt different thresholds for low or high predicted responses.	Thank you for this comment. As it is outlined in the Benefits and harms section of the evidence review A on Ovarian reserve testing, the guideline committee could not include specific thresholds on ovarian reserve in the recommendations as there were no consistent thresholds reported in the

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					evidence. They also discussed that this should be guided by clinical judgement.
NHS Devon ICB	Guideline	032	001-004	1.9.6 risks being misinterpreted because it states that previous full IVF cycles should count towards the total number of full cycles offered by the NHS but also that previous self-funded IVF treatment should not preclude NHS-funded IVF treatment. This does not account for a scenario where a patient has self-funded the same number or more cycles than the number offered by the NHS (for example, what if a patient under 40 had self-funded 6 or more cycles?)	Thank you for this comment. Based on stakeholder feedback, the committee amended the wording of the recommendation to make it clearer. In the cited example the patient would not be eligible for NHS funded treatment. The economic analysis shows diminishing returns to the effectiveness of IVF (regardless of who funds it) with increasing cycles.
NHS Devon ICB	Guideline	037	007 - 017	For people aged < 40 the draft guidance recommends up to 6 cycles of IVF however embryo transfer strategies for cycles 4-6 are not discussed. It is therefore unclear what the recommended embryo transfer strategies are in cycles 4, 5, and 6.	Thank you for your comment. This section of the guideline has not been updated this time, but embryo transfer strategies has been identified as a potential future topic for update and we will take note of your suggestion.
NHS Devon ICB	Guideline	041	004-010	3 x changes to terminology have not been highlighted or marked as amended 2026. In the current guidance it is "Indications for oocyte donation", in the draft it is "Medical indications for oocyte donation" In the current guidance it is "premature ovarian failure", in the draft it is "premature ovarian insufficiency". In the current guidance it is "ovarian failure following chemotherapy or radiotherapy",	Thank you for pointing out the unmarked sections as amended. Where changes have been considered to be editorial, rather than change to meaning, these have not been marked as changes. However, we realise we have accidentally omitted some of these markings from the draft guideline.

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				in the draft it is "ovarian insufficiency following chemotherapy or radiotherapy".	
NHS England	Evidence Review T	014 029 030	014 – 016 042 – 050 001 - 003	The NHS England Genomics Unit notes the recommendation in the Guideline that states that men, trans women and non-binary people with male reproductive organs who have idiopathic azoospermia should be tested for Y chromosome microdeletion. The Evidence Review T states that the committee recognised that this will result in more genetic testing than the NHS currently offers but that the cost of this additional testing would be significantly lower than the costs for ineffective surgical sperm retrieval. In Evidence Review T, the committee concluded that the recommendation for unrestricted Y chromosome microdeletion testing is a change to current NHS practice but that this would not result in a significant resource impact and overall across the pathway could be cost saving. No health economic analysis was conducted in making this recommendation but the NHS in England need to understand what the additional level of Y chromosome testing will be required to expand the scope of this test from the current eligibility criteria as set out in the National Genomics Test Directory and provided here:	Thank you for your comment. The committee discussed that determining whether a patient has non-obstructive azoospermia (NOA) or obstructive azoospermia (OA) is not always clear from examination and hormone profile, and in such cases the only way to confirm the diagnosis is by attempting surgical sperm retrieval. The chances of successful surgical sperm retrieval for people with Y chromosome AZFa and AZFb microdeletions is almost non-existent, and such patients need to be identified before they are put through an unnecessary and invasive procedure that has significant cost implications. Therefore, to avoid unnecessary surgical sperm retrieval with no chance of success, the committee agreed that testing for Y chromosome microdeletion should be performed as routine clinical practice to investigate idiopathic azoospermia. The committee now restricted the recommendation 1.17.7 to those with idiopathic azoospermia or a sperm concentration of less than 1 million per ml because in clinical practice Y chromosome microdeletion would not be offered to people with known causes of azoospermia

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				Patients with non-obstructive azoospermia or severe oligospermia where testicular sperm extraction (TESE)/microdissection TESE (mTESE) is considered and outcome of testing will inform eligibility for (m)TESE and success of sperm retrieval (https://www.england.nhs.uk/wp-content/uploads/2018/07/Surgical-sperm-retrieval-for-male-infertility.pdf) Testing for Y chromosome microdeletions should not routinely be performed before ICSI (https://www.nice.org.uk/guidance/cg156/chapter/Recommendations)	and testing those with higher sperm concentrations (>1 million per ml) might not be cost effective as the majority of Y chromosome microdeletions occur in those with sperm concentrations less than or equal to 1 million per ml (Kohn 2019). By restricting the recommendation to those with a sperm concentration of less than 1 million per ml, the committee believes that the new recommendation may reduce the number of tests rather than increase them, as tests are currently performed for individuals with sperm counts of up to 5 million/ml.
NHS England	Guideline	General	General	People with a learning disability and autistic people experience significant health inequalities such as those as highlighted in LeDeR reports (Learning from Lives and Deaths of people with learning disability and autistic people) https://www.kcl.ac.uk/research/leder and so it is important that consideration is given to their particular needs and to ensuring equality of access, experience and outcomes in healthcare services.	Thank you for your comment. The guideline makes reference to the foundational NICE guidelines, including NICE guideline on patient experience in adult NHS services. Considerations around a person's individual needs and how communication and care should be tailored is covered in this guideline and should underpin all care across NHS services. Please also see the equalities and health

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				• We suggest including a reference to making reasonable adjustments to care on the basis of disability. This is a legal requirement in the Equality Act 2010 and is important to help you make the right diagnostic and treatment decisions for an individual. You can ask the person and their carer or family member what reasonable adjustments should be made. Adjustments aim to remove barriers, do things in a different way, or to provide something additional to enable a person to receive the assessment and treatment they need. Possible examples include; allocating a clinician by gender, taking blood samples by thumb prick rather than needle, providing a quiet space to see a patient away from excess noise and activity. Resources are available such as NHS England » Sensory-friendly resource pack and NDTi | Green Light Toolkit 2022. • Ensuring information and advice is in formats that is accessible and can easily be understood is essential In line with the NHS England » Accessible information standard • Be aware of diagnostic overshadowing: This occurs when the symptoms of physical ill health are mistakenly either attributed to a mental health or behavioural problem or considered inherent to the person's learning disability or autism diagnosis.	inequalities assessment forms (in the History tab of the guideline website) which highlight the need to consider people with disabilities and other equalities issues.

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				People with a learning disability or autistic people have the same illnesses as everyone else, but the way they respond to or communicate their symptoms may be different and not obvious. More information can be found in this guidance:. NHS England » Clinical guide for front line staff to support the management of patients with a learning disability and autistic people – relevant to all clinical specialties	
NHS England	Guideline	014	017-021	The NHS England Genomics Unit notes the recommendation to test for cystic fibrosis transmembrane conductance regulator genetic mutations in men, trans women and non-binary people with male reproductive organs who have idiopathic suspected obstructive azoospermia and/or vasal abnormality on examination. We would suggest that this recommendation references the eligibility criteria for testing as per the National Genomics Test Directory as if this changes then the Guideline will keep pace with any update in the Test Directory. The current criteria is: Infertility associated with obstructive azoospermia, AND	Thank you for this comment. The guideline committee agreed not to refer to the National Genomic Test Directory as they thought that there may be different clinical reasons beyond the criteria set in the directory.

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				a. CBAVD (or isolated CUAVD) diagnosed from expert clinical examination, OR b. CBAVD identified at incidental herniotomy	
NHS England	Guideline	040	005 - 009	The Genomics Unit in NHS England note the recommendation for screening sperm donors that states that units should follow the UK guidelines for the medical and laboratory procurement and use of sperm, oocyte and embryo donors (2019). Please could NICE be more directive in their recommendation about who should have genetic testing and what genetic testing should be provided? The UK guidelines for the medical and laboratory procurement and use of sperm, oocyte and embryo donors (2019) recommend that all donors should be screened for chromosomal abnormalities. Could NICE review if this is a requirement for all potential sperm donors as there is evidence that there is a low diagnostic yield (~1/200 oocyte donors PMID: 39486504; ~1/500 sperm donors PMID: 16484311) and whilst there is a significantly increased risk of IVF failure and early miscarriage of being a translocation carrier there is a low	Thank you for your comment. The committee agreed to remove this recommendation because it is within the remit of HFEA Code of Practice. Genetic testing in the context of sperm donation is not within the scope of this guideline.

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				risk of later pregnancy complications and very low risk of a live born with an unbalanced chromosome complement (Barber, 2010, PMID: 20482539). Could NICE state what the legal requirement is for screening potential sperm donors? The HFEA Code of Practice edition 9.4 October 2023 states: "donors of gametes and embryos should be screened in accordance with screening guidelines and timeframes set out in current professional guidance produced by the relevant professional bodies" but then also states on the HFEA website that they do not require UK fertility clinics to carry out expanded carrier screening for gamete (egg or sperm) donors. Expanded carrier screening testing involves identifying whether the individual unknowingly carries gene variants associated with common genetic conditions, such as cystic fibrosis, that may be passed on to their children. It would be helpful to have clear recommendations on who should be offered genetic testing, what they should be tested for (including the health economic evidence of benefit that support these recommendations) and as part of the recommendation to indicate what elements are a	

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				legal requirement for genetic testing for potential sperm donors.	
NHS England	Guideline	041	015 - 018	The Genomics Unit in NHS England note the recommendation for screening oocyte donors that states that donors should be screened for both infectious and genetic diseases in accordance with the UK guidelines for the medical and laboratory procurement and use of sperm, oocyte and embryo donors (2019). The UK guidelines for the medical and laboratory procurement and use of sperm, oocyte and embryo donors (2019) recommend that all donors should be screened for chromosomal abnormalities. Could NICE review if this is a requirement for all potential oocyte donors as there is evidence that there is a low diagnostic yield (~1/200 oocyte donors PMID: 39486504; ~1/500 sperm donors PMID: 16484311) and whilst there is a significantly increased risk of IVF failure and early miscarriage of being a translocation carrier there is a low risk of later pregnancy complications and very low risk of a live born with an unbalanced chromosome complement (Barber, 2010, PMID: 20482539).	Thank you for your comment. The committee agreed to remove this recommendation because it is within the remit of HFEA Code of Practice. Genetic testing in the context of oocyte donation is not within the scope of this guideline.

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				Could NICE state what the legal requirement is for screening potential oocyte donors? The HFEA Code of Practice edition 9.4 October 2023 states: "donors of gametes and embryos should be screened in accordance with screening guidelines and timeframes set out in current professional guidance produced by the relevant professional bodies" but then also states on the HFEA website that they do not require UK fertility clinics to carry out expanded carrier screening for gamete (egg or sperm) donors. Expanded carrier screening testing involves identifying whether the individual unknowingly carries gene variants associated with common genetic conditions, such as cystic fibrosis, that may be passed on to their children. It would be helpful to have clear recommendations on who should be offered genetic testing, what they should be tested for (including the health economic evidence of benefit that support these recommendations) and as part of the recommendation to indicate what elements are a legal requirement for genetic testing for potential egg donors.	

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NHS Greater Manchester ICB	Guideline	005	004	NHS Greater Manchester would like to add that the first principles of care should be to equalize access to fertility both geographically and by protected characteristic. This will be particularly important for same sex couples, trans gendered people, older women and disabled people and people with long term health conditions.	Thank you for your comment. Aim to reduce health inequalities is principle 9 in NICE's principles (Our principles | NICE) and is at the core of NICE's work. Our recommendations also aim to improve equitable access to care. The key issue to bear in mind is that the guideline only covers assessment and treatment for health-related fertility problems and as such does not exclude people based on their sexual orientation or relationship status and the guideline's recommendations do not determine treatments based on the person's sexual orientation or relationship status. The scope of the guideline, consulted on and published in 2022, defined the guideline's population remit as: "**Groups that will be covered in the update** • People with health-related fertility problems • People who may require interventions to preserve fertility because of high risk of fertility problems due to clinical conditions or medical or surgical interventions

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					In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination. The guideline will be applicable to all people seeking assessment and treatment of health-related fertility problems who meet these criteria, irrespective of their sexual orientation, partnership status or gender reassignment. This includes single people, people in heterosexual relationships, people in same sex relationships, people who are non-binary, undergoing or have undergone gender transition and people using a surrogate." In relation to fertility preservation, the guideline has now expanded the population for whom fertility preservation should be offered to include people with medical indications for fertility preservation, not just people who are preparing for cancer treatment. Medical indications

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					for fertility preservation could include gender-affirming treatments that are likely to impair fertility. Please see the Equalities and Health Inequalities Assessment forms which we have published after every phase of the guideline development, found under the "History" tab on the guideline's website for further discussion on equalities considerations.
NHS Greater Manchester ICB	Guideline	005	015	NHS Greater Manchester would like to add to ensure that information is accessible in preferred formats and health literate to enable informed choices. This will be particularly important to people with learning disabilities, people with communication barriers such as deaf and blind people, people experiencing mental ill health and neurodiverse people as well as people for whom English is not their first language.	Thank you for your comment. We agree this is very important. The guideline refers to the NICE foundational guidelines on Patient experience in adult NHS services and Shared decision making which cover general recommendations on the principles of person-centred care, such as communication, providing information and shared decision making.
NHS Greater Manchester ICB	Guideline	007	004	The title of the graph should be changed from 'Cumulative pregnancy rate over 12 cycles by age' to 'Cumulative pregnancy rate over 12 menstrual cycles by age' as this would match the description in lines 5-8.	Thank you for your comment. The heading of the figure has been amended as suggested.
NHS Greater Manchester ICB	Guideline	007	005	This is a general comment that is relevant to various sections of the revised guidance and relates to NICE's processes and methods. Much of the evidence this guideline is based on is relatively old (e.g. this section is from 2016), a lot of it is international evidence (e.g. the clinical prediction models). NHS Greater Manchester	Thank you for this comment. Where possible, we have used the most up to date evidence to inform the guidance, however, it should be noted that not all sections of the guideline were part of the scope of this update. In terms of the 2016 data in

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				feels it is worth reflecting on the influences on high profile guidance to the NHS, would the NHS be better served if it was able to develop the necessary evidence itself.	Figure 1 you're referring to, we think presenting this data is reasonable and we would not expect there to be significant changes to the spontaneous pregnancy rate by 12 menstrual cycles by age even if newer data was available. The clinical prediction models used to estimate the treatment effectiveness of IVF were developed using HFEA UK data and are reported in scientific peer reviewed journals.
NHS Greater Manchester ICB	Guideline	008	010	The table is using data from 2015-2019. Shouldn't more timely data be used? The table needs to clearer and state whether the IUI cycles are stimulated or unstimulated.	Thank you for your comment. We have updated the data in Table 2 around IUI using latest data from HFEA dashboard. The table now includes more age categories ranging from 18 years to over 44-year-olds. The data included in the table includes both unstimulated and stimulated cycles.
NHS Greater Manchester ICB	Guideline	010	016	NHS Greater Manchester feels that 'advising' women, trans men and non-binary people to increase their body weight (where their BMI is less than 18.5 kg/m2) may be interpreted by commissioning organisations as women, trans men and non-binary people **must** have a body weight 18.5 kg/m2 to access IVF and thus restrict IVF to these women, trans men and binary people. Is this NICE's intention? If so, it should be more clearly worded – if not then be explicit about this..	Thank you for this comment. Recommendation 1.9.4 is about advising women and people with female reproductive organs about their chances of conception, and it is not part of an access criteria for IVF. The recommendations in the section 1.10 on IVF access do not include BMI or body weight

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				NHS Greater Manchester would like to add BMI should be proportionate to ethnic make-up.	as an access criteria for IVF treatment, i.e. NICE does not recommend that to be used as an access criteria. Regarding BMI and ethnicity. We assume you're referring to ethnicity-specific BMI thresholds. The recommendations about BMI and chance of conception were not updated as part of this update so no new evidence was reviewed and ethnicity-specific BMI thresholds related to chance of conception for are not provided. NICE guideline on overweight and obesity NG246 recommends differing BMI thresholds for cardiometabolic risk for people with a South Asian, Chinese, other Asian, Middle Eastern, Black African or African–Caribbean background (see section Identifying and assessing overweight, obesity and central adiposity in NG246).
NHS Greater Manchester ICB	Guideline	010	027	NHS Greater Manchester are unclear where patients should be directed to for advice about workplace exposure to hazards that may reduce infertility. Shouldn't patients be directed to their employer or workplace occupational health teams for specific advice. Alternatively, please include a link for healthcare professionals to signpost patients to for specific advice regarding workplace hazards.	Thank you for this comment. The recommendation 1.11.1 on Occupation has been updated to include that, if necessary, people might be directed to their workplace occupation health team.

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NHS Greater Manchester ICB	Guideline	012	002	Does this section of the guidance recommend faster access to specialist care for different cohorts? Recommendations are for some cohorts to try 1 year of unprotected vaginal sexual intercourse, others cohorts 6 cycles (i.e. 6 months) of IUI.	Thank you for your comment. The 2013 guideline committee aimed to decide the number of cycles of artificial insemination that would be considered reasonably equivalent to trying to conceive for 12 months of unprotected vaginal intercourse. They considered a number of ethical and practical issues relating to 'equivalence'. They agreed that for people trying to conceive through unprotected vaginal sexual intercourse, the initial time period should be 12 months before further clinical assessment and investigation. For people using artificial insemination to conceive, the 2013 guideline committee agreed that the reasonable equivalence would be 6 cycles of artificial insemination before further clinical assessment and investigation, considering, for example, the costs, availability of donor sperm and success rates of artificial insemination. The 2013 guideline committee's deliberations and considerations are documented in the 2013 Full guideline document. Please also see the updated figures for cumulative probability of conceiving a clinical pregnancy after 6 or 12 cycles of intrauterine insemination in Table 2 of the guideline. These decisions by the 2013 guideline committee are the basis for the recommendations and purely from a time perspective, this can mean that some people may

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					access IVF treatment quicker than others. However, this also reflects the fact that while heterosexual couples with unexplained subfertility have a chance of conception with expectant management, female same sex couples do not have a chance.
NHS Greater Manchester ICB	Guideline	013	026	NHS Greater Manchester is unclear whether the labs in Greater Manchester are able to undertake the testing as outlined by the World Health Organisation.	Thank you for your comment. This is a local issue and we are unable to comment on this.
NHS Greater Manchester ICB	Guideline	014	012	NHS Greater Manchester feel that it would be better for a single clear list of genetic tests, especially for information for patients and providers, which should and shouldn't be undertaken,	Thank you for this comment. This was not within the scope of this update.
NHS Greater Manchester ICB	Guideline	016	001	The data used is 10 years old and NHS GM feel that more timely data should be used.	Thank you for your comment. Figure 2 has been amended to include updated HFEA data on live births per embryo transfer by age (from 1991 to 2023).
NHS Greater Manchester ICB	Guideline	017	002	NHS Greater Manchester would like to add the following to this section:- Recognition of ethnic diversity and propensity to menstrual problems should be considered. (endometriosis by example)	Thank you for your comment which we have acknowledged in the Equalities and health inequalities assessment form. This section of the guideline was not updated and no new evidence was reviewed in relation to regularity of menstrual cycles so no new recommendations were made on this topic.

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				Recognition of age diversity and propensity to menstrual problems should be considered. Recognition of prescribed drugs and impact on fertility , particularly for disabled women and women with mental ill health.	
NHS Greater Manchester ICB	Guideline	021	024	NHS Greater Manchester does not fund clinical trials and therefore this would not form part of our commissioned pathway.	Thank you for this comment. We cannot comment on local decisions.
NHS Greater Manchester ICB	Guideline	029	010	Does this section of the guidance recommend faster access to specialist care for different cohorts? Heterosexual couples are asked to try to conceive for 2 years which would take as long as 24 cycles of IUI but other couples/single women are offered 12 cycles of IUI which is at odds with heterosexual couples trying to conceive. Please provide the evidence that supports offering 12 cycles of IUI. NHS Greater Manchester feels that this section needs to be clearer as it can be open to interpretation.	Thank you for your comment. The 2013 guideline committee aimed to decide the number of cycles of artificial insemination that would be considered reasonably equivalent to trying to conceive for 12 months of unprotected vaginal intercourse. They considered a number of ethical and practical issues relating to 'equivalence'. They agreed that for people trying to conceive through unprotected vaginal sexual intercourse, the initial time period should be 12 months before further clinical assessment and investigation. For people using artificial insemination to conceive, the 2013 guideline committee agreed that the reasonable equivalence would be 6 cycles of artificial insemination before further clinical assessment and investigation,

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					considering, for example, the costs, availability of donor sperm and success rates of artificial insemination. The 2013 guideline committee's deliberations and considerations are documented in the 2013 Full guideline document. Please also see the updated figures for cumulative probability of conceiving a clinical pregnancy after 6 or 12 cycles of intrauterine insemination in Table 2 of the guideline. These decisions by the 2013 guideline committee are the basis for the recommendations and purely from a time perspective, this can mean that some people may access IVF treatment quicker than others. However, this also reflects the fact that, while heterosexual couples with unexplained subfertility have a chance of conception with expectant management, female same sex couples do not have a chance. The recommendations you're referring to in this comment have been amended to bring more clarity.
NHS Greater Manchester ICB	Guideline	030	006	Why are we asking people who may be over the age of 37 to try and conceive for 2 years when the evidence states that success declines with age. Should this be lowered to 35? NHS Greater Manchester would like to suggest having a rider that if the woman is reaching late 30's that they do not need to wait for 2 years as they may "age" out of being able to access IVF	Thank you for your comment. Cost-effectiveness of the optimal period of expectant management before treatment for people with unexplained fertility problems was not analysed as part of this guideline update so the 2013 recommendation stands.

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NHS Greater Manchester ICB	Guideline	031	028	Under what circumstances should the patient be offered an additional 3 cycles. Patients are going to interpret the guidance as patients can access 6 cycles of IVF. 70% of ICB's across England offer one full cycle, therefore how will this work in practice (i.e. offering 3 cycles plus an additional 3 when 70% of ICB's currently offer 1). This is misleading patients, may raise expectations and they will interpret the guidance differently as they do now. Please provide the UK based evidence that suggests that 3 cycles plus a further 3 is effective. Could NICE insert a line that the number of cycles commissioned is determined by local commissioning organisations. This would help to manage expectations. Additionally NICE states that the impact of offering 6 cycles may be minimal; however has consideration been given to people who may now come back (after being discharged) asking for more cycles as initial cycles previously commissioned have failed. This is likely more of a short term impact and would be a risk to NHS Greater Manchester as an organisation.	Thank you for this comment. Thank you for this comment. The recommendation to consider a further 3 full cycles of IVF states that any consideration of further cycles should include a discussion of the probability of success and the implications of further treatment. This will be dependent on individual circumstances, informed by clinical and professional judgement and shared decision making. The committee did not think that many patients would want more than 3 cycles if they had not previously conceived but noted that expectations are already unmet in many areas of the NHS where NICE recommendations are not currently adhered to. The UK based evidence that suggests that 3 cycles plus a further 3 is effective comes from the HFEA data that was used to develop the OPIS pre-IVF prediction model (see Appendix I of Evidence Review J, p106). The effectiveness is illustrated in Figures 17 and Figures 20. The guideline committee were aware that the implementation of recommendations had to be considered as part of their deliberations. The committee

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					acknowledged that a short-term one-off impact of the type described (people who may come back after being discharged) was possible but believed that the numbers would be small. Therefore, they did not think this was a reason to amend their recommendations.
NHS Greater Manchester ICB	Guideline	032	003	Please provide the evidence that supports the statement in this paragraph. The 2 sentences in the paragraph appear to be contradictory and the paragraph is therefore difficult to understand, so could this be reworded. Could an example be provided for clarity.	Thank you for this comment. Based on stakeholder feedback, the recommendation referred to in the comment has been revised to make it clearer.
NHS Greater Manchester ICB	Guideline	037	005	The 2013 recommendations around embryo transfers need to be reviewed. There is now good evidence from NHSE that only a handful of ICBs currently commission 3 cycles – so this section does not apply to the majority of the NHS. What are the embryo transfer recommendations if fewer than 3 cycles are commissioned? Similarly what is the embryo transfer recommendations for cycle 4,5 and 6.	Thank you for your comment. This section of the guideline has not been updated this time but embryo transfer strategies has been identified as a potential future topic for update and we will take note of your suggestion.
NHS Hertfordshire and West Essex ICB	Guideline		General	1.5 Question regarding letrozole not being included as a treatment option for hypothalamic pituitary ovarian dysfunction PCOS	Thank you for this comment. NICE is currently developing a guideline on PCOS adapting the International evidence-based guideline for the assessment and management of polycystic ovary

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					syndrome. The scope of this guideline includes management of infertility in the context of PCOS. The recommendations related to PCOS have stood down in anticipation of the new guideline.
NHS Hertfordshire and West Essex ICB	Guideline	Whole	Whole	The terminology used to describe women, trans men or non binary people with female reproductive organs in every sentence makes it very difficult to actually read the clinical guidance. Some explanation at the top the guidance of this and using more simpler terms throughout the policy would make this guidance easier for clinicians to read.	Thank you for your comment. NICE uses gender inclusive language when possible to be inclusive of people who do not identify with the sex they were registered with (or assigned) at birth. Sometimes this means we need to be specific on who is covered by a recommendation. We do appreciate that spelling out the populations covered in full can make recommendations longer. However, we believe this is necessary for clarity here - particularly as this guideline covers so many different subgroups. The specific wording that we have used in this recommendation is line with the Style Guide's section on sex and gender, which is based on extensive user research. However, we are also aware that the language we use around sex and gender is rapidly evolving, and your feedback has been passed to our colleagues who work on the Style Guide for consideration.
NHS Hertfordshire and West Essex ICB	Guideline			Definition and diagnoses around male factor infertility is wooly and results in inequity of access. When compared to what women have to demonstrate in order to be eligible	Thank you for your comment. Some revisions have been made to the recommendations on investigations for male factor

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				and clinically successful, practice is very varied when it comes to men.	fertility problems and we hope these will bring more clarity. The committee also agreed to remove the term 'mild male factor fertility problems' from the guideline recommendations because it was thought to be unhelpful, poorly defined, and clinically ambiguous. NICE will develop and publish flowcharts / visual summaries for some treatment pathways, for example for male factor fertility problems, which will hopefully clarify some of the uncertainties.
NHS Midlands and Lancashire - Clinical Support Unit	Evidence Review A	024 - 28	001 – et seq.	This section summarises current evidence on ovarian reserve testing. The grades of evidence vary from low to high (the majority are mostly low). However, even some evidence graded as "low" has been incorporated into the recommendations – this gives the impression that the recommendations were drafted according to current practice rather than driven by good quality evidence. It would have been much preferred for NICE to concentrate on the best quality evidence to date and use this to drive its recommendations then leaving the "low" quality evidence to drive the discussion about disinvestment for those remaining interventions.	Thank you for your comment. As you have identified, there was a range in the quality of the evidence available to assess the predictive ability of ovarian reserve markers. Where possible, the committee prioritised the highest quality evidence to base their recommendations on, including the recommendation to use AMH and AFC as markers of ovarian reserve. There was moderate to high quality evidence available for both AMH and AFC which showed an independent association between these markers and live birth or clinical pregnancy as an outcome of IVF, and this was supplemented by the additional lower quality evidence. Where moderate or high quality evidence is not available, NICE committees can still consider the available evidence and use their

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					own experience and expertise to weigh up any potential risks and benefits before making recommendations. These considerations are always detailed in the 'Committee's discussion and interpretation of the evidence' section of each evidence review. It is not always possible or sensible to restrict the making of recommendations to cases where high quality evidence is available.
NHS Midlands and Lancashire - Clinical Support Unit	Evidence Review A	024 - 28	001 – et seq.	The committee acknowledged that "live birth" is a critical outcome and clinical pregnancy rate was also useful. However, the live birth outcome is the most important to the NHS and families. With the complete lack of economic analysis/modelling, it might be useful to reconsider this section in terms of live birth only. Should this be done, the overall evidence base will dwindle but at least this might point to the need for necessary research recommendations. Otherwise, the NICE recommendations are based on limited real-world outcomes with no chance of deciding whether these tests are cost-effective. Would it be possible to get some audit data to at least get a feel for how these tests perform in the real world?	Thank you for your comment. The committee agreed that live birth is the most important outcome and reflected this in their discussions of the evidence by prioritising this outcome where reported. However, it can be difficult for studies to capture live birth as an outcome due to logistical issues arising from loss to follow-up, which can also result in increased risk of bias for studies reporting this outcome. As a result, it is common for studies to report pregnancy rates as a proxy for live birth, as it is still a measure of effectiveness that captures improved fertility. The committee wanted to ensure a balanced approach that did not disadvantage well-conducted studies that provided important information on improvements to fertility, while still ensuring live birth was regarded as the most important outcome.

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NHS Midlands and Lancashire - Clinical Support Unit	Evidence Review A	024 - 28	001 – et seq.	We note that NICE have avoided quoting reference ranges for AMH tests because these are specific to the particular manufacturer or brand. This is concerning because how do we know that these tests are valid? Is there a gold standard and how do the other tests compare to this? If no solid work has being performed to support the interchangeability of these tests, the NHS could be paying considerable money for activity based on AMH tests of questionable validity and reliability. Is another research recommendation appropriate? Should NICE be specifying a particular brand ?	Thank you for your comment. The committee noted that most outcomes had no serious inconsistency despite the use of multiple different AMH assays in included studies, and where there was heterogeneity between studies it was not accounted for by the specific threshold or AMH assay used. This suggests that the effectiveness of AMH as a predictive marker is not dependent on the assay used, and therefore specific assays were not recommended.
NHS Midlands and Lancashire - Clinical Support Unit	Evidence Review K	056	020 - 048	This is the review section which underpins recommendation 1.8.3 which suggests offering up to 4 cycles of IUI with ovarian stimulation before IVF treatment. The review states that this is based on an NMA which led the committee to recognise that IVF is the most cost effective treatment. However, the review clearly states that IUI is a weaker alternative and there would be "some increase in costs" although these would be limited. We feel this is very vague and it makes it difficult to accept this particular recommendation. We would like to see much more detail on this particularly regarding the accurate costs involved. Otherwise, this feels as though the committee didn't base its decision on solid evidence. As a minimum, commissioners will need much better estimates of the likely numbers in order to facilitate their	Thank you for this comment. NICE produces recommendations on the best available clinical and cost-effectiveness evidence. The economic analyses suggested that IUI as a 'gateway treatment' does result in higher cumulative live birth rates than IVF alone. However, the reduction in IVF treatment does not fully offset the costs of IUI treatment and in many scenarios the increase in live births was not achieved at an acceptable cost (as assessed by the cost-effectiveness threshold). However, the analysis was not without limitations and uncertainty and in some cases IUI with gonadotrophin appeared to be a cost-effective alternative. Therefore, the committee agreed a weaker 'consider' recommendation was reasonable.

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				financial planning following implementation of the revised guideline.	To support implementation NICE produces Resource Impact tools but these focus on areas where a significant resource impact is expected. Furthermore, limitations and uncertainties would make it very difficult to provide an estimate of numbers. The committee acknowledged that some people may prefer the less invasive treatment of IUI to IVF but unless these people go on to have IVF despite their preferences, then costs are likely to be lower than for IVF.
NHS Midlands and Lancashire - Clinical Support Unit	Evidence Review R	052 et seq	021 et seq	The review describes the evidence to support ovarian tissue cryopreservation to be "very low quality" for all of the 6 specified case series. We are shocked that NICE have made a recommendation on the basis of such poor evidence. In order to justify this recommendation, we need to see high quality data with properly worked out health economics. Otherwise, the NHS is unable to fund interventions on the basis of an apparent whim.	Thank you for this comment. There was a total of 34 studies relevant to ovarian tissue cryopreservation included in the evidence review. The 6 studies referred to in the comment relate to studies where different multiple materials, including ovarian tissue, were preserved. The recommendations are often based not only on the evidence but also on the committee's clinical experience and expertise. In this case, the committee agreed that ovarian tissue retrieval and cryopreservation was feasible and effective and would be the only option available in certain circumstances, for example, before puberty.

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					To reflect very serious risk of bias and very serious heterogeneity among the studies for ovarian tissue cryopreservation, the committee agreed to make a 'consider' rather than an 'offer' recommendation, that is ovarian tissue cryopreservation should be considered in girls before puberty when oocyte or embryo cryopreservation is not feasible.
NHS Midlands and Lancashire - Clinical Support Unit	Guideline	004	004	Recommendations are for "health related fertility problems". This is the essence of the whole document and we think that this message should be repeated throughout. This could help alleviate some of the problems associated with queries about fertility which the ICB receives as the health-related focus is frequently forgotten/misunderstood by the enquirers.	Thank you for your comment. We have tried to make it clear from the start of the guideline that the focus of the guideline is on health-related fertility problems.
NHS Midlands and Lancashire - Clinical Support Unit	Guideline	009	022	Whilst it is laudable that recommendation 1.2.12 supports people to stop smoking, we suggest that both partners should be confirmed non-smokers. This is because smoking increases the risk of infertility in women and men. Nicotine alone is known to affect development of the foetus and long term safety data on e-cigarettes are unknown. Because of these concerns and issues , all forms of smoking (which includes cigarettes, e-cigarettes or NRT) should be a barrier to treatment. NICE are very firm in making respondents disclose any links to the tobacco industry, they should be equally firm in making smoking a barrier to treatment.	Thank you for your comment. The impact of nicotine-containing products, e-cigarettes and vaping on fertility was not within the scope of this guideline update and no evidence has been reviewed on this, so the committee are unable to make recommendations on this topic. Several stakeholders made a similar comment and we have noted this as a potential topic for future updates.

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NHS Midlands and Lancashire - Clinical Support Unit	Guideline	009	022	In addition, the recommendation should reference the impact of passive/second-hand smoking on children – if NICE will not make smoking a barrier to fertility treatment, then they must make a recommendation on passive smoking and how this affects the potential newborn and existing children.	Thank you for your comment. The impact of passive/second-hand smoking on fertility or children was not within the scope of this guideline update and no evidence has been reviewed on this, so the committee are unable to make recommendations on this topic.
NHS Midlands and Lancashire - Clinical Support Unit	Guideline	014	008	Whilst we appreciate the sensitivities around gender identity, we feel the terms " men, trans women and non-binary people with male reproductive organs" is somewhat cumbersome. Have NICE taken into account the recent Supreme Court ruling on biological sex? Could this term be condensed to simply "men"? If not, because this definition appears throughout, the document becomes more difficult to read. Alternatively, would it be considered appropriate to add the current phrase to the list of definitions and use the term "men" only in the recommendations?	Thank you for your comment. NICE uses gender inclusive language when possible to be inclusive of people who do not identify with the sex they were registered with (or assigned) at birth. Sometimes this means we need to be specific on who is covered by a recommendation, which we have done in this instance. We do appreciate that spelling out the populations covered in full can make recommendations longer. However, we believe this is necessary for clarity here - particularly as this guideline covers so many different subgroups. The specific wording that we have used in this recommendation is line with the Style Guide's section on sex and gender, which is based on extensive user research. However, we are also aware that the language we use around sex and gender is rapidly evolving, and will pass on your feedback to our colleagues who work on the Style Guide for consideration.

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NHS Midlands and Lancashire - Clinical Support Unit	Guideline	016	015 - 022	On rereading the section, it is apparent that NICE are using the 3 tests (AMH, AFC & FSH) and how these should be used for 3 different outcomes:- ie **outcome 1**) predictor of spontaneous pregnancy (without medical intervention), **outcome 2**) response to ovarian stimulation and **outcome 3**) predictor of clinical pregnancy following medical intervention. Unfortunately, it is not clear from 1.3.14 – 16 what these recommendations are. In order to improve this, we suggest that the section is completely remodelled according to the 3 outcomes above and the revised recommendations appear under these headings. For example:- 1) **predictor of spontaneous pregnancy without medical intervention** Recommend do not use AMH. 2) **response to ovarian stimulation** Recommend normal range of AMH …… etc. And, perhaps, present these data in a table with the list of outcomes in the first column and the 3 ovarian tests in subsequent columns with a tick or cross to indicate which test is appropriate (or not) for each specified outcome.	Thank you for your comment. The committee considered your comment but did not think further changes are needed. It is stated within the recommendations in which contexts the markers of ovarian reserve should and should not be used.
NHS Midlands and	Guideline	016	015 - 022	For the sake of clarity, it may be worth emphasising or stating that FSH no longer has a role in fertility	Thank you for your comment.

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Lancashire - Clinical Support Unit				management or at least for the 3 outcome measures mentioned above. In addition, policy readers will also need to understand how to handle disparate AMH/AFC results i.e. if one is high and the other is low – how should the clinician proceed?	The available evidence showed that FSH did not have predictive ability for response to or the outcome of fertility treatment. However, there was no evidence on its ability to predict spontaneous conception, and so no recommendation was made in this regard. The contexts in which FSH should not be used as a predictive marker as per the available evidence are stated in the recommendation. The committee agreed not to make recommendations about how to interpret the results of ovarian reserve testing as they agreed this would be down to clinical judgment.
NHS Midlands and Lancashire - Clinical Support Unit	Guideline	016	015	1.3.14 recommends that AMH should not be used alone as a predictor of clinical pregnancy. However, the rationale section states that the committee agreed that AMH should not be used. The current wording of 1.3.14 is confusing. Suggest the word "alone" is removed.	Thank you for this comment. The committee amended the recommendation by removing the word 'alone'.
NHS Midlands and Lancashire - Clinical Support Unit	Guideline	022	017/018	This section involves surgical sperm retrieval in men with obstructive azoospermia. One criterion "the obstructive interval if known (for example, the time from vasectomy to seeking reversal)" implies that NICE are recommending sperm retrieval in men with a vasectomy reversal. However, vasectomy reversal is generally unavailable on the NHS and this is the case for all the ICBs in north West England who all have "non-reversal" policies. It would be	Thank you for your comment. The committee considered this and removed "(for example, the time from vasectomy to seeking reversal)" from recommendation 1.25.1, but agreed not to remove the bullet because the obstructive interval could be an important factor when deciding which treatment to offer. For example, based on the committee's clinical

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				inequitable for men who have had a reversal procedure done privately to then receive treatment for subfertility on the NHS. We strongly suggest that this whole bullet point be deleted.	knowledge and experience obstructive intervals of less than 15 years are considered favourable to successful surgical reconstruction, although the length of obstruction may be less of an issue in situations where the partner with female reproductive organs is relatively young, with good ovarian reserve (please see 'Benefits and harms' section of Evidence Review W, page 13-15).
NHS Midlands and Lancashire - Clinical Support Unit	Guideline	032	001-005	This amended wording adds "previous self-funded IVF treatment should not preclude NHS funded IVF treatment". However, this could easily be misinterpreted and could appear to contradict the first sentence (which says that the total number of cycles must be taken into account when assessing NHS treatment). We suggest that this second sentence should be extended to read "previous self-funded IVF treatment should not preclude NHS funded IVF treatment although the number of private cycles received will count when assessing the number of NHS eligible cycles" – or words to that effect.	Thank you for your comment. The recommendation wording has been revised based on your feedback.
NHS Midlands and Lancashire - Clinical Support Unit	Guideline	042	002 - 019	Recommendations 1.14.1 to 1.14.5 are concerned with fertility preservation for people undergoing treatments which might impact their fertility. CG 156 previously called this cryopreservation for those undergoing cancer treatment. Thus, the indications have been extended to include all treatment which might impact fertility – this is to be welcomed and it has always been our impression that	Thank you for this comment. The recommendations on fertility preservation now also cover medical conditions that will likely impair fertility. The committee does not think this will lead to a significant increase in the requirements for fertility preservation services and in many places this is already being done. The guideline committee agreed that they

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				this was the intention of the original CG 156 guideline committee. However, all 3 of the new recommendations have added yet another indication which is "have a **medical condition**" which might impair fertility. The inclusion of "medical condition" represents a seismic increase in the number of indications for cryopreservation. What are these medical conditions? Could these be premature ovarian insufficiency, endometriosis or polycystic ovarian syndrome for example? Should these conditions be included, the demand for cryopreservation would rise exponentially. Where is the evidence that cryopreservation for these indications is cost-effective? 1. Our perception is that this is not what NICE intended. 2. If this is correct, then we would respectfully suggest that this section be reworded as follows:- 3. Change 1.14.1 to "discuss fertility preservation as an option with people before they receive treatment (medicines or surgery) which could impair their fertility". 4. Change 1.14.4 to "offer sperm cryopreservation to men…….. before they receive treatment	can't provide an exhaustive list of all medical conditions and medical/surgical interventions that potentially warrant fertility preservation, this needs to be based on clinical judgment. Evidence review R section on the committee's interpretation and discussion of the evidence includes the committee's discussion about examples of potential medical indications where fertility cryopreservation may be relevant.

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				(medicines or surgery) which is known to impair fertility". 5. Change 1.14.5 to "offer oocyte cryopreservation to women…. before they receive treatment (medicines or surgery) which is known to impair fertility". 6. The title would need to be changed to "Cryopreservation before treatment known to affect fertility". 7. If our perception is wrong, then NICE would need to list all of the relevant "medical conditions" within the recommendations and provide the evidence base to support this.	
NHS Midlands and Lancashire - Clinical Support Unit	Guideline	042	015	Recommendation 1.14.5 states "offer oocyte **or embryo** cryopreservation to women"….. "Preparing for medical treatment". Our impression is that this will be mainly women about to undergo cancer treatment which might impair fertility. We are therefore puzzled as to why this would include "embryo" preservation. This would suggest that the woman has undergone IVF in order to create the embryo. Are NICE saying that any woman about to undergo chemotherapy is therefore eligible for IVF? Otherwise, we suggest that "embryo" is deleted.	Thank you for this comment. The recommendation does not imply that embryo cryopreservation should be offered to everyone but for some couples/people it may be a relevant option. For example, if a couple is in a stable relationship and would like to create embryos.

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NHS Midlands and Lancashire - Clinical Support Unit	Guideline	042	020	Recommendation 1.14.6 states "consider **ovarian tissue cryopreservation** when oocyte cryopreservation isn't feasible". We are surprised that NICE are recommending ovarian tissue cryopreservation when the evidence base is known to be poor. Our view is that this intervention should be a research recommendation and 1.14.6 should be deleted until the evidence base is much stronger.	Thank you for this comment. As outlined in the Benefits and harms section of the evidence review R on Fertility preservation, the committee agreed that the evidence showed ovarian tissue retrieval and cryopreservation was feasible and effective. The wording of the recommendation ('consider') reflects the quality of the evidence base, compared to the stronger recommendation ('offer') on sperm, egg or embryo cryopreservation. They also noted that ovarian tissue preservation would be the only option available in certain circumstances, for example, before puberty. Therefore, they agreed that ovarian tissue cryopreservation should be considered as a fertility preservation option when oocyte or embryo cryopreservation is not feasible. This recommendation has been expanded by referring to the NICE interventional procedures guidance on removal, preservation and reimplantation of ovarian tissue for restoring fertility after gonadotoxic treatment.
NHS Midlands and Lancashire - Clinical Support Unit	Guideline	046	006	Research recommendation "Safety and effectiveness of testicular tissue cryopreservation" – suggest this should also include cost effectiveness.	Thank you for your comment. This has been added as per your suggestion.

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NHS Midlands and Lancashire - Clinical Support Unit	Guideline	062	006 - 015	This section is the "why the committee made the recommendation" on access to IVF. The recommendation for 3 – 6 cycles of IVF is based on prediction models which estimated both effectiveness and cost effectiveness. The committee acknowledges that the economic analysis did have its limitations. We are told that for 3 cycles, using the model, the observed ICERs were lower than those detailed in the previous 2013/17 guideline which used a maximum threshold of £30,000 per QALY. It is hard to accept that the cost effectiveness of 3 cycles of IVF has somehow shifted from being only just cost-effective to very cost-effective in the matter of a few years. 1. Clearly there is a difference in the models and this should be explored and explained in depth. 2. What does the published literature around the world tell us about the cost effectiveness of IVF? 3. How does this compare to the proposed model? 4. In order to give it credibility, it is very important to see how this model performs using real-world data. There may even need to be a wider societal debate as to whether £20,000 per QALY is an acceptable threshold in this context. 5. Perhaps a hint of the potential fallibility of this model is given in the accompanying review "[J]	Thank you for this comment. Whilst the guideline recommends that 3 cycles of IVF are offered, it is only recommended that an additional 3 cycles can be "considered", reflecting less strong evidence for clinical and cost-effectiveness. 1. Differences in the models are discussed in depth in Appendix I of Evidence Review J. This also explains that since the previous guideline there are now prediction models available that estimate cumulative live birth rates, and this explains some of the improved estimate of the cost-effectiveness of IVF. 2. No economic studies were identified for Evidence Review J (with its focus on prediction models). We are not aware of any published economic evidence comparing cumulative cycles of IVF to expectant management using a cost-utility approach 3. Not applicable 4. The OPIS prediction models which underpins the estimates of IVF treatment effectiveness is based on "real-world" UK data 5. Given the stated limitations of the prediction models, we also included analyses using the IVF Predict model which was used in the previous guideline. This prediction model was not developed to predict

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				Fertility prediction models and IVF access" in figure 37 (page 133). Figure 37 shows the cost effectiveness of up to 6 cycles according to age. In this diagram, IVF is cost-effective in women aged 34 but not cost-effective (at the higher threshold) for cycles 2, 3 & 4 in women aged 35 – 6. Bizarrely, it becomes cost-effective again for cycles 2, 3 & 4 in women aged 37 – 39. Clearly, this aberration requires thorough investigation and explanation. Otherwise, we have no confidence in this model and it's important to bear in mind that this intervention will be used for thousands of women costing the NHS millions of pounds.	cumulative live birth rates. The "aberration" described was an artefact of the IVF Predict model grouping women in various age bands and the counter-intuitive result observed (in this and other analyses) is discussed in Evidence Review J, Appendix I (p104, lines 17-34)
NHS Midlands and Lancashire - Clinical Support Unit	Guideline	062	016 - 025	This section "explains" why NICE recommended offering a further 3 cycles to women who have failed to respond to the first three. The section acknowledges there were some uncertainties in the evidence particularly for cycles 4 – 6 which related to selection bias in the datasets, very small numbers of women and considerable sampling uncertainty around the point estimates. Almost incomprehensibly, therefore, the committee agreed that although the evidence was not sufficiently robust to offer the additional 3 cycles, they still agreed that they could be considered.	Thank you for this comment. The full write-up of the health economic analysis is in Appendix I of Evidence Review J. NICE produces recommendations on the best available clinical and cost-effectiveness evidence. As per the previous NICE guideline it is recommended that 3 cycles are offered. The committee considered that the evidence for this recommendation was even better supported this time. However, reflecting the weaker evidence that you

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				1. Based on such poor data, it is hard to accept how the committee have made this recommendation. 2. Clinically, women receiving greater than 3 cycles will be at greater risk of ovarian hyperstimulation syndrome (OHS). 3. It is crucial that real-world data on women receiving >3 cycles are examined in detail to appreciate the prevalence of OHS in these patients. 4. To rely on economic modelling alone in this situation is not acceptable for potentially life-threatening events. 5. This is made more complex because the majority of women in England do not receive 3 cycles (let alone >3). 6. We understand that the guideline committee had no NHS commissioners to advise them – if this had been the case, perhaps these issues would have been discussed? 7. In addition, it would have been useful to see the literature on other places in the world where women are routinely offered >3 cycles. 8. Finally, perhaps the main problem with these economic analyses is the utility value of a live birth. The disutility or dysphoria associated with	allude to, a 'consider' recommendation is also made for a further 3 cycles. We refer you to the wording of recommendations in the NICE Guidelines Manual (https://www.nice.org.uk/process/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869) – see section 9.3 **Reflect the strength of the recommendation:** *In 'strong' recommendations (see the section on strength of recommendations) for actions that should (or should not) be offered, use directive language such as 'offer' (or 'do not offer'), 'advise', or 'ask about'. In keeping with the principles of shared decision making, people may choose whether or not to accept what they are offered or advised.* *If there is a closer balance between benefits and harms (activities or interventions that could be used), use 'consider' reflecting that the recommendation is 'weak'* In reference to your specific numbered points:

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				the inability to have a child may be more important. 9. We do not think it is appropriate to make this recommendation based on a model of limited (at best) value. 10. As a minimum, the ICB will require reliable estimates of the numbers and costs to help with their financial planning.	1. A weaker recommendation was made to consider an additional 3 cycles of IVF in those who have not achieved a live birth in previous attempts. This reflected that the evidence for cost-effectiveness evidence supporting these additional cycles was subject to greater uncertainty. Furthermore, the guideline also recommends that any consideration of an additional 3 cycles should be made in the context of a discussion of the probability of success and the implications of more treatment. 2. We are not aware that the risk of ovarian hyperstimulation syndrome increase with successive IVF cycles but rather depends on patient-specific factors and stimulation protocols used in each cycle. The health economic analysis does take OHSS as an adverse effect of IVF into account. 3. We are not aware that this data is available but see also the response to point 2. Also, it is recommended that any consideration of more than 3 cycles is done alongside a discussion of the probability of success and the implications of more treatment. 4. The guideline committee makes recommendations based on all the evidence presented to them alongside their professional experience and

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					expertise. It is not the case that they relied on economic evidence alone. 5. This is an implementation issue for ICBs rather than NICE, but we recognise that those who commission services for the NHS often must make difficult decisions. 6. Although commissioners are difficult to recruit to NICE guidelines, the position was advertised and there was a commissioner on the committee (Please see Committee membership list in the History tab of the guideline website) 7. NICE makes evidence based recommendations on the best available clinical and cost-effectiveness evidence. This will often align with international practice but there is no requirement for it to do so or for that to be a key component of the committee's deliberations. However, there are other countries (e.g. Belgium and France) where more than 3 cycles are publicly funded. 8. It is acknowledged that use of the QALY has important limitations in assessing the cost effectiveness of assisted reproduction techniques. Sensitivity analysis was undertaken to encompass a wide range of assumptions with respect to the QALY gain from a live birth. Many commentators

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					argue that the QALY inadequately captures the full benefits of live birth (Keller 2022, Skedgel 2023). 9. See previous responses. 10. NICE will provide a resource impact tool when the guideline is published.
NHS Midlands and Lancashire Clinical Support Unit (MLCSU)	Guideline			We are aware that the guideline committee comprised embryologists, gynaecologists, andrologists, fertility experts and lay representatives. Just under half of the members had affiliations to patient-led fertility charities. We are extremely surprised that there were no NHS commissioners on the guideline committee (we would have expected there to be 3 or 4). We are aware that there was one county council "commissioner" on the panel but county councils do not commission NHS fertility services. It is fair to say that issues related to fertility services (e.g. patient enquiries, complaints, freedom of information requests, individual funding requests, policy development work etc.) take up a disproportionate amount of the ICB's time. The fact that the ICBs (or representatives from the former CCGs) were excluded from the guideline committee is very puzzling.	Thank you for this comment. The committee is recruited to have the necessary expertise and experience to produce practice-based guidelines based on the best available clinical and cost effectiveness evidence. A competitive application process is used to identify the best candidates (see https://www.nice.org.uk/get-involved/our-committees/how-to-apply-to-join-a-committee). Commissioners are difficult to recruit and NICE guideline committees often operate without an NHS commissioner, although GPs or other practicing clinicians are sometimes able to address the commissioning perspective. However, recognising the importance of funding issues pertaining to this guideline a commissioner was recruited. The county council "commissioner" is currently involved in public health commissioning but the member also has

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				Our impression, therefore, is that the committee was very "Provider" orientated. It is 12 years since CG 156 was published and it is a reasonable expectation that a balance would have been achieved between new recommendations driven by high quality evidence and consideration given to disinvestment in those areas where the evidence base is known to be or continues to be poor. Had there been NHS commissioners (who have the responsibility of remaining within budget despite various competing pressures) on the committee , perhaps this balance would have been different ?	an extensive commissioning experience within the NHS, including related to reproductive care and has a strong interest in fertility having also served on the previous NICE fertility guideline.
NHS North West London ICB	Guideline			1.14.5 Consider ovarian tissue cryopreservation in girls or people with female reproductive organs before puberty The evidence to support the use of ovarian tissue for the purposes of IVF/live births remains experimental. We feel that this may give young patients unhelpful expectations	Thank you for this comment. As outlined in the Benefits and harms section of the evidence report R on Fertility preservation, the committee agreed that the evidence showed ovarian tissue retrieval and cryopreservation is feasible and effective. They also noted that it would be the only option available in certain circumstances, for example, before puberty. Therefore, they agreed that ovarian tissue cryopreservation should be considered as a fertility preservation option when oocyte or embryo cryopreservation is not feasible.

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NHS North West London ICB	Guideline	009		1.2.9 Nicotine containing products and E-cigarettes We are disappointed that there is an absence of guidance on the use of e-cigarettes in the guidance. We would like the committee to provide guidance on whether e-cigarette use negatively impacts on fertility and/or IVF	Thank you for your comment. The impact of nicotine-containing products, e-cigarettes and vaping on fertility was not within the scope of this guideline update and no evidence has been reviewed on this, so the committee are unable to make recommendations on this topic. Several stakeholders made a similar comment and we have noted this as a potential topic for future updates.
NHS North West London ICB	Guideline	030		I 1.8.3 'before IVF treatment, consider up to 4 cycles of IUI with ovarian 17 stimulation using gonadotrophins or offer IVF. It is unclear in the policy which cohort of patients should be offered IUI and which should be offered. Lack of clarity makes this policy difficult to implement. Some detail are required	Thank you for this comment. The committee considered there was sufficient evidence, albeit weaker, that IUI with ovarian stimulation with a gonadotrophin could be cost effective, so the committee agreed that it could be considered as an alternative first-line treatment option before IVF. The committee acknowledged that some people may prefer the less invasive treatment of IUI to IVF. Decision on treatment would be based on shared decision making.
NHS North West London ICB	Guideline	031		1.9.5 'consider further 3 cycles of IVF treatment' It is unclear when patients should be considered to have further 3 cycles. Lack of clarity means that this policy is difficult to implement. Whilst it is noted that ICERs have now improved for IVF, ICBs also need consider affordability. Our ICB current funds one cycle of IVF, and	Thank you for this comment. The recommendation to consider a further 3 full cycles of IVF states that any consideration of further cycles should include a discussion of the probability of success and the implications of further treatment. This will

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				thus offering 6 cycles may be difficult to adopt in the current financial constraints	depend on individual circumstances, informed by clinical and professional judgement and shared decision making. The committee did not think that many patients would want more than 3 full cycles of IVF if they had not previously conceived but noted that expectations are already unmet in many areas of the NHS where NICE recommendations are not currently adhered to.
NHS North West London ICB	Guideline	079		The removal of recommendations that BMI should be between 19-30 is unhelpful as obesity is clearly a contributing factor to unsuccessful IVF, therefore it does not support patients' in their IVF journey. As high BMI carries a high risk of complications during pregnancy, having pre-conception advice is essential	Thank you for this comment. Preconception advice on body weight is captured in the Obesity and Low body weight sections of the guideline.
NHS North West London ICB	Guideline	095		1.9.1.1 Offer 6 cycles of unstimulated IUI for people who not have conceived after 6 cycles of donor insemination - We note that the guidance now only relates to health related fertility issues. However it is questioned why same sex couples would be considered subfertile after 6 cycles of IUI rather than 12. This is incongruent with the rest of the guidance	Thank you for your comment. The 2013 guideline committee aimed to decide the number of cycles of artificial insemination that would be considered reasonably equivalent to trying to conceive for 12 months of unprotected vaginal intercourse. They considered a number of ethical and practical issues relating to 'equivalence'. They agreed that for people trying to conceive through unprotected vaginal sexual intercourse, the initial time period should be 12 months before further clinical assessment and investigation. For

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					people using artificial insemination to conceive, the 2013 guideline committee agreed that the reasonable equivalence would be 6 cycles of artificial insemination before further clinical assessment and investigation, considering, for example, the costs and success rates of artificial insemination. The 2013 guideline committee's deliberations and considerations are documented in the 2013 Full guideline document. Please also see the updated figures for cumulative probability of conceiving a clinical pregnancy after 6 or 12 cycles of intrauterine insemination in Table 2 of the guideline.
NHS SCW	Economic model IVF			Economics model for IVF - Economics inputs tab - With regard to the cost inputs, the cost of IVF of ICSI used are lower than the guide price suggested in the 25/26 NHS Payment Scheme workbook (see Tab 8 'other guide prices) which are between £3,740 and £4,223 for IVF and between £4,223 and £4,826 for ICSI (one fresh plus one frozen cycle).	Thank you for your comment. This was most likely because this workbook was released after the development of our model. We have updated all model unit costs where more recent sources now exist.
NHS SCW	Guideline	General	General	Whilst welcoming the use of inclusive of language, repeated use of the phrase 'men, trans women and non-binary people with male reproductive organs' in the guideline is difficult to read in the context of complex recommendations. Suggest this could be rephrased to 'people with female reproductive organs' to improve readability.	Thank you for your comment. NICE uses gender inclusive language when possible to be inclusive of people who do not identify with the sex they were registered with (or assigned) at birth. Sometimes this means we need to be specific on who is covered by a recommendation, which we have done in this instance. We do appreciate that spelling out the

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					populations covered in full can make recommendations longer. However, we believe this is necessary for clarity here - particularly as this guideline covers so many different subgroups. The specific wording that we have used in this recommendation is line with the Style Guide's section on sex and gender, which is based on extensive user research. However, we are also aware that the language we use around sex and gender is rapidly evolving, and your feedback has been passed to our colleagues who work on the Style Guide for consideration.
NHS SCW	Guideline	General	General	Whilst welcoming the use of inclusive of language, repeated use of the phrase 'women, trans men and non-binary people with female reproductive organs' in the guideline is quite difficult to read in the context of complex recommendations. Suggest this could be rephrased to 'people with female reproductive organs' to improve readability.	Thank you for your comment. NICE uses gender inclusive language when possible to be inclusive of people who do not identify with the sex they were registered with (or assigned) at birth. Sometimes this means we need to be specific on who is covered by a recommendation, which we have done in this instance. We do appreciate that spelling out the populations covered in full can make recommendations longer. However, we believe this is necessary for clarity here - particularly as this guideline covers so many different subgroups. The specific wording that we have used in this recommendation is line with the Style Guide's section on sex and gender, which is based on extensive user

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					research. However, we are also aware that the language we use around sex and gender is rapidly evolving, and your feedback has been passed to our colleagues who work on the Style Guide for consideration.
NHS SCW	Guideline	094-095		**4th row in table - 2026 Rec 1.7.1.** An additional group of patients with conditions that require specific consideration in relation to methods of conception who may require IUI are patients who have undergone electroejaculation due to spinal injuries – these could be considered as an additional example in recommendation 1.7.1.	Thank you for this comment. This recommendation has been revised by the committee and these examples have been removed.
NHS SCW	Guideline	012	13-18	**Rec 1.2.29.** We note that the rationale for including this recommendation is that it is 'not in the spirit of the previous version of the guideline' but feel there should be a more robust clinical rationale for this recommendation.	Thank you for your comment. The committee's view is that people who are childless after a year of trying without conceiving, or who are childless after a year of trying but having had a miscarriage (or ectopic pregnancy) both need further assessment and treatment for subfertility.
NHS SCW	Guideline	012	013-018	**Rec 1.2.29.** It may be useful to refer to 2023 national guidance from RCOG (Green-top guideline No.17) on recurrent miscarriage so patients who experience recurrent miscarriage are referred for investigations rather than continue on a subfertility pathway inappropriately (assisted conception treatment is not recommended as a treatment option for recurrent miscarriage).	Thank you for your comment. Recurrent miscarriage is not within the scope of this guideline update, and based on our current methodology, we would not refer to an external guideline without assessing its quality and relevance, including formal appraisal with AGREE II where appropriate.

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					Therefore, recommendations on recurrent miscarriage could not be made in this guideline. The committee acknowledged that it is a standard practice to consider miscarriage before any fertility treatment and suggested to follow the recommended time frame and not to restart it after the miscarriage or ectopic pregnancy (please see the amended recommendation 1.16.6).
NHS SCW	Guideline	016	017-020	**Rec 1.3.15.** NICE should include thresholds at which AMH and AFC are considered good predictors of live birth following assisted conception, otherwise it will not be possible to implement this recommendation consistently and there is a risk clinical practice will not be based on the available evidence.	Thank you for this comment. As outlined in the Benefits and harms section of the evidence review A on Ovarian reserve testing, the guideline committee could not include specific thresholds on ovarian reserve in the recommendations as there were no consistent thresholds reported in the evidence. They also discussed that this should be guided by clinical judgement.
NHS SCW	Guideline	022	013-020	**Rec 1.4.7.** NICE should indicate how the factors listed in bullet points can be used to decide which treatment is offered, otherwise it will not be possible to implement this recommendation consistently and there will be a risk clinical practice will not be based on the available evidence.	Thank you for your comment. The committee considered this comment but did not think changes to the recommendation was needed. This recommendation is intended for clinicians and requires professional judgement when deciding which treatment to offer based on these factors. A full rationale with justification and explanation is provided in the rationale

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					and impact section associated with the recommendation and Evidence Review W (please see 'Benefits and harms' section, page 13-15).
NHS SCW	Guideline	023	3-5	**Rec 1.4.9.** This 'consider' recommendation in relation to micro-TESE for non-obstructive azoospermia is confusing in the context of the previous two recommendations to offer surgical sperm retrieval to people with obstructive and non-obstructive azoospermia (1.4.7 and 1.4.8 respectively), neither of which mention any specific techniques. Does this mean **all other** techniques should be 'offered' to people with non-obstructive azoospermia? Does it mean micro-TESE should **not** be offered to people with obstructive azoospermia? Please provide clarification.	Thank you for your comment. Evidence Review W showed that surgical sperm retrieval increases chance of clinical pregnancy in people with obstructive azoospermia. However, there was no evidence on the techniques for surgical sperm retrieval in obstructive azoospermia, so the committee did not specify a technique in the recommendation 1.25.1. In other words, all forms of surgical sperm retrieval can be offered to people with obstructive azoospermia, taking into account the factors outlined in the recommendation 1.25.1. Recommendations 1.25.2 and 1.25.3 are about non-obstructive azoospermia. As outlined in the benefits and harms section of Evidence Review Y, the committee discussed that the evidence was not sufficient to make a strong recommendation about a specific technique for surgical sperm retrieval for non-obstructive azoospermia. However, the committee acknowledged that although there is no randomised controlled trial evidence, evidence from non-randomised studies support micro-TESE (microscopic testicular sperm

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					extraction) for surgical sperm retrieval in people with non-obstructive azoospermia, and based on their clinical knowledge and experience, less tissue is removed during a surgical sperm retrieval with micro-TESE. Therefore, the committee recommended that the use of micro-TESE could be considered in people with non-obstructive azoospermia (please see recommendation 1.25.3) which aligns with existing European Association of Urology (EAU) guideline.
NHS SCW	Guideline	030	011-017	**Rec 1.8.3.** We note that this recommendation excludes people trying to conceive via artificial insemination (AI). As those trying to conceive via AI include same sex couples, who are a protected group under the Equality Act 2010, it would be important to ensure the equity of this recommendation has been considered and documented in the context of the overall offer to same sex couples versus that to heterosexual couples. We note the 2013 full guideline provided details of how the committee determined how same sex and heterosexual couples received equivalent treatment and suggest this should be documented for the update as well.	Thank you for this comment. The 2013 guideline committee's decisions around 'equivalence' between those conceiving through vaginal sexual intercourse or through artificial insemination still stand and are documented in the 2013 Full guideline document. This issue has not been updated. Section 1.38 which you're referring to is covering people attempting to conceive through unprotected vaginal intercourse. People attempting to conceive through artificial insemination are covered in section 1.37. Equalities considerations have been carefully considered, please see the Equalities and health inequalities impact assessment forms from every major phase of the guideline development process, available on the guideline's website under the History tab.

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NHS SCW	Guideline	030	011-017	**Rec 1.8.3.** Evidence review K, which supports this recommendation, states IUI as a gateway treatment prior to IVF does not lead to lower costs because first line IVF is the cheapest strategy and this recommendation could therefore lead to an increase in costs. In the context of the already very limited availability of NHS fertility treatment in most areas where current NICE guidelines are not fully implemented in the vast majority of areas, it therefore appears very unlikely this recommendation will be affordable and therefore implemented by ICBs. We would suggest affordability should be a factor that is taken into consideration when NICE make their recommendations, particularly in cases like this where the recommendation is to 'consider' and therefore does not have strong evidence to support it.	Thank you for this comment. NICE produces recommendations on the best available clinical and cost-effectiveness evidence. The economic analyses suggested that IUI as a 'gateway treatment' does result in higher cumulative live birth rates than IVF alone. However, the reduction in IVF treatment does not fully offset the costs of IUI treatment and in most scenarios the increase in live births was not achieved at an acceptable cost (as assessed by the cost-effectiveness threshold). However, the analysis was not without limitations and uncertainty and in some cases IUI with gonadotrophin appeared to be a relatively cost-effective alternative. Therefore, the committee agreed a weaker 'consider' recommendation was reasonable.
NHS SCW	Guideline	031	011-017	**Rec 1.9.3.** Please clarify whether people who experience a miscarriage during the expectant management period prior to IVF (i.e. 2 years of regular unprotected vaginal intercourse or 12 cycles of artificial insemination) would be required to 'start again' or whether these pregnancies should be discounted as per recommendation 1.2.29 in the draft guidance. Currently in many areas these patients are often required to 'start again' because it has been demonstrated that they can conceive, and IVF alone is not a treatment for miscarriage.	Thank you for this comment. The committee discussed this and agreed to revise the recommendation 1.16.6 so that it also includes the expectant management period before IVF treatment beyond the first year, or the 12 cycles of artificial insemination before IVF treatment.

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NHS SCW	Guideline	031	005-006	**Rec 1.9.2.** In order to facilitate implementation of this recommendation, NICE will need to include thresholds at which AMH and AFC are considered good predictors of live birth following assisted conception.	Thank you for this comment. As it is outlined in the Benefits and harms section of the evidence review A on Ovarian reserve testing, the guideline committee could not include specific thresholds on ovarian reserve in the recommendations as there were no consistent thresholds reported in the evidence. They also discussed that this should be guided by clinical judgement.
NHS SCW	Guideline	031	018-019	**Rec 1.9.3.** Currently CG156 recommends offering IVF in women who have not conceived after complicas of artificial insemination where 6 or more are by intrauterine insemination. The new draft guidance simply recommends offering IVF after 12 cycles of artificial insemination. Please specify the rationale for this change. It may be preferable to maintain the previous recommendation of requiring at least 6 IUI as it can then be ascertained that patients have undergone at least some AI cycles under optimum circumstances (i.e. at the correct time in their cycle, using good quality sperm etc.). As recommendation 1.7.2 allows 6 NHS funded IUI for this group, this should have limited impact on patients.	Thank you for your comment. The committee agreed to reinstate in the recommendation that 6 or more cycles should be by IUI.
NHS SCW	Guideline	031	028	**Rec 1.9.5.** As noted in the rationale section of the draft NICE guidance, very few ICBs in England offer up to 3 full cycles of IVF for women aged under 40 as per the current NICE guideline. The new recommendation to consider	Thank you for this comment. The guideline committee were aware that the implementation of recommendations had to be

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				funding up to 6 full IVF cycles is therefore not likely to be implemented by any ICBs in the current financial climate. Including this recommendation in the final guidance is going to raise patient expectations and lead to more NHS resources being used to deal with queries and complaints. Whilst we appreciate NICE recommendations are based on the evidence, the affordability needs to be taken into consideration. Making recommendations which are known to have a very limited chance of being implemented undermines the value of NICE guidelines. The recommendation to extend IVF provision to up to 6 cycles seems particularly inappropriate in the current financial climate considering the rationale sections states there are 'particular uncertainties' about the evidence to support funding of cycles 4 to 6.	considered as part of their deliberations. Whilst 3 cycles of IVF are still recommended to be offered as per previous NICE guidance, a weaker recommendation was made for an additional 3 cycles. The committee did not think that many patients would want more than 3 cycles if previous attempts were unsuccessful but noted that expectations are already unmet in many areas of the NHS where NICE recommendations are not currently adhered to. Furthermore, it is recommended that a discussion of the probability of success and the implication of more treatment accompanies the consideration of any further 3 cycles if the person has not conceived after the first 3 full cycles. A weaker recommendation was made to consider an additional 3 cycles of IVF in those who have not achieved a live birth in previous attempts. This reflected that the cost-effectiveness evidence supporting these additional cycles was subject to greater uncertainty.
NHS SCW	Guideline	032	005-007	**Rec 1.9.7.** We note that the current NICE guideline requires people aged 40-42 to have no evidence of low ovarian reserve (recommendation 1.11.1.4). Please clarify why this recommendation has now been removed for the recommendation relating to people aged 40-41.	Thank you for your comment. Based on evidence review A, the committee agreed that taking into account ovarian reserve is relevant for all

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					patients considering IVF treatment, not only those aged 40+. This is reflected in recommendation 1.39.2.
NHS SCW	Guideline	079		**3rd row in table - 2013 Rec 1.10.1.1.** We would not agree that the 2013 recommendation 1.10.1.1 is covered by the 'initial advice' section of the draft guidance, which only relates the impact of age on fertility, not the impact of age on the outcome of IVF treatment. This is a useful statement to keep in the guideline; our engagement with specialists indicates patients are often not well informed about factors which might influence the outcomes of fertility treatment. We would also argue that ICBs using age to prioritise treatment for patients who are most likely to succeed in the context of a limited NHS budget does not constitute 'misuse' of this information.	Thank you for this comment. The impact of age on IVF 'success' in terms of live births per embryo transfer by age is captured in the updated Figure 2 in the new guideline. And recommendation 1.18.2 captures age as the main predictor for fertility (both through spontaneous conception and IVF). The guideline already gives evidence-based guidance on restricting IVF provision based on age.
NHS SCW	Guideline	079		**4th row in table - 2013 Rec 1.10.2.1.** The 2013 recommendation 1.10.2.1 is a useful statement to keep in the guideline; our engagement with specialists indicates patients are often not well informed about factors which might influence the outcomes of fertility treatment.	Thank you for your comment. The committee thought the information is widely understood by clinicians and is routinely discussed during treatment planning, so the committee felt it might not add value as a standalone recommendation.
NHS SCW	Guideline	079		**6th row in table - 2013 Rec 1.10.4.1.** We would not agree that 2013 recommendation 1.10.4.1 is covered by the 'initial advice' section of the draft guidance, which only relates to the impact of BMI on fertility, not the impact of BMI on the outcome of IVF treatment. This is a useful	Thank you for the comment. The committee agreed that BMI advice should focus on health optimisation rather than being used as a strict eligibility criterion. Even in the 2013 guideline, BMI was

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				statement to keep in the guideline; our engagement with specialists indicates patients are often not well informed about factors which might influence the outcomes of fertility treatment. We would also argue that ICBs using BMI to prioritise treatment for patients who are most likely to succeed in the context of a limited budget does not constitute 'misuse' of this information. In addition, we would note: • The majority of clinicians we have engaged with are supportive of limiting NHS funded treatment to people with a BMI range of 19-30. • The HFEA Commissioning Guide (page 10) recommends NHS treatment is limited to people with a BMI range of 19-30. • BMI criteria are in place in all ICBs across the country – see the DHSC webpage on NHS funded IVF in England.	not part of the recommended access criteria for IVF, but we are aware that BMI is and has been sometimes used as such. This is not according to the NICE guideline. General advice on BMI and fertility in the 'Initial advice' section was considered to be sufficient.
NHS SCW	Guideline	079		**8th row in table - 2013 Rec 1.10.5.2.** We would not agree that 2013 recommendation 1.10.5.2 is covered by the 'initial advice' section of the draft guidance, which only relates to the impact of smoking on fertility, not the impact of smoking on the outcome of IVF treatment. This is a useful statement to keep in the guideline; our engagement with specialists indicates patients are often not well informed about factors which might influence the outcomes of fertility treatment.	Thank you for this comment. The committee think this is sufficiently covered in the section on 'Initial advice', considering impact of smoking on fertility as the overall capacity to achieve pregnancy (whether trying to conceive naturally or through IVF).

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NHS SCW	Guideline	087		**5th row in table - 2013 Rec 1.16.1.3.** Please clarify why NICE no longer recommends girls/ women should only undergo oocyte/ egg cryopreservation if they are well enough, it will not worsen their condition, and enough time is available before the start of their treatment.	Thank you for this comment. The committee thought this is part of basic good clinical judgments and care. However, the committee did agree to reinstate the 2013 recommendation around factors to take into account when deciding on cryopreservation, including diagnosis, prognosis etc. (see recommendation 1.53.2).
NHS SCW	Guideline	094		**4th row in table - 2026 Rec 1.7.1.** We believe the 2013 recommendations have been misinterpreted in the text in the right hand column. The 2013 recommendations 1.9.1.1 and 1.9.1.2 are not suggesting people unable to have sexual intercourse because of a disability/psychosexual problem have access to 12 cycles of NHS funded artificial insemination (AI). This is confirmed in the 2013 full guideline of CG156 (in the second bullet point at the bottom of page 78) which states in relation to people with a disability/ psychosexual problems: *"In these cases, the GDG was of the opinion that most of the points covered in the discussion in relation to women in same-sex couples trying to conceive with AI (above) applied in this setting. Specifically, the GDG felt that the same criteria (that is, 6 unsuccessful cycles of IUI with partner sperm) applied to people in this group for referral for formal investigation and possible treatment."*	Thank you for your comment. We recognise that the 2013 recommendations may have caused some confusion and in this update, we have tried to clarify these recommendations. The key issue to bear in mind is that the guideline only covers assessment and treatment for health-related fertility problems. People who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychosexual problem are considered to have a health-related fertility problem and are therefore covered by this guideline.

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				Of note, this interpretation has been widely implemented meaning in many areas 6 NHS funded cycles of IUI are only funded following 6 self-funded cycles of AI for both same sex couples and people with physical disabilities/ psychosexual problems. We suggest this change is reviewed in light of the above as it is actually a significant change to the current recommendations.	
NHS SCW	Guideline	094		**4th row in table - 2026 Rec 1.7.1.** Offering 12 cycles of IUI to people unable to have intercourse because they have a disability/psychosexual problem appears to be inequitable compared to the 6 cycles available to other people trying to conceive through AI. Same sex couples fall in the latter group and are also unable to have vaginal sexual intercourse. They are therefore essentially in the same position as the people with disability/ psychosexual problem, yet they are required to demonstrate their subfertility prior to NHS treatment. The reasons for this need to be explained, especially as both groups will fall under protected groups under the Equality Act 2010. Furthermore, patients undergoing donor insemination for medical reasons are only offered up to 6 cycles of IUI using donor sperm as per recommendations 1.12.1, 1.12.2 and 1.12.10. This appears inequitable compared to people with disability/ psychosexual problems who are offered 12 cycles of AI using partner or donor sperm.	Thank you for your comment. The scope of the guideline, consulted on and published in 2022, defined the guideline's population remit as: "Groups that will be covered in the update • People with health-related fertility problems • People who may require interventions to preserve fertility because of high risk of fertility problems due to clinical conditions or medical or surgical interventions In this guideline, people with health-related fertility problems are those who have a known health-related

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					impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination. The guideline will be applicable to all people seeking assessment and treatment of health-related fertility problems who meet these criteria, irrespective of their sexual orientation, partnership status or gender reassignment. This includes single people, people in heterosexual relationships, people in same sex relationships, people who are non-binary, undergoing or have undergone gender transition and people using a surrogate." The key issue to bear in mind is that the guideline only covers assessment and treatment for health-related fertility problems and as such does not exclude people based on their sexual orientation or relationship status and the guideline's recommendations do not determine treatments based the person's sexual orientation or relationship status. Please also see the equalities and health inequalities impact assessments (found in the History tab of the guideline website) which explored this issue further.

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NHS Surrey Heartlands ICB - Surrey County Council Public Health Team	Guideline	009	022 – 1.2.12	We welcome the reference to NICE Guideline 209 on Tobacco; however, we believe the wording should be strengthened to address all products containing nicotine, rather than focusing solely on smoking cessation. Emerging evidence suggests that nicotine and other chemicals found in such products may affect sperm and egg quality, interfere with implantation, and lead to poorer embryo development. • Montjean D, Godin Pagé MH, Bélanger MC, Benkhalifa M, Miron P. An Overview of E-Cigarette Impact on Reproductive Health. Life (Basel). 2023 Mar 18;13(3):827. doi: 10.3390/life13030827. PMID: 36983982; PMCID: PMC10053939. • Szumilas K, Szumilas P, Grzywacz A, Wilk A. The Effects of E-Cigarette Vapor Components on the Morphology and Function of the Male and Female Reproductive Systems: A Systematic Review. Int J Environ Res Public Health. 2020 Aug 24;17(17):6152. doi: 10.3390/ijerph17176152. PMID: 32847119; PMCID: PMC7504689. While we recognise the importance of a harm-minimisation approach - acknowledging that smoking cessation can be challenging and that some patients may benefit from nicotine replacement therapy (NRT) or e-cigarettes - this must be balanced against the potential	Thank you for your comment. The impact of nicotine-containing products, such as e-cigarettes and vaping, on fertility was not within the scope of this guideline update and no evidence has been reviewed on this, so the committee are unable to make recommendations on this topic. Several stakeholders made a similar comment and we have noted this as a potential topic for future updates.

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				risks and associated costs, such as failed treatment cycles. Patients seeking fertility treatment should ideally provide evidence that they are non-smokers, or that they are actively participating in a recognised smoking cessation programme if they are trying to stop smoking. The draft guideline should explicitly define what is meant by "smoking" in the context of fertility care. Our experience is that patients often assume that e cigarettes or nicotine replacement products are acceptable. A clear definition should state whether combustible tobacco products, e cigarettes, heated tobacco devices and cannabis are all considered forms of smoking that adversely affect fertility and count against eligibility. 1. Minimum period of abstinence: Evidence shows that smoking cessation improves fertility outcomes and reduces miscarriage rates. The NICE draft does not give a timeframe for abstinence. The ICB policy requires both partners to demonstrate at least six months of non smoking before treatment , aligning with guidance in other regions. National guidance should recommend a minimum abstinence period (e.g., six months) to give the	

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				ovaries and endometrium time to recover, and to encourage lasting behavioural change. 2. Verification of non smoking status: To avoid inequity, the guideline should suggest objective measures to confirm abstinence, such as carbon monoxide breath testing or cotinine testing. This would support consistent application across fertility centres. 3. Passive smoking considerations: The ICB policy emphasises advising patients about the negative effects of passive smoking . Including this in national guidance would ensure that partners or family members who smoke are also counselled, as passive exposure is known to reduce fertility.	
NHS Surrey Heartlands ICB - Surrey County Council Public Health Team	Guideline	012	013 – 1.2.29	The section on miscarriage would benefit from firmer wording to emphasise the need for timely and comprehensive investigation of recurrent miscarriages. Fertility treatment should not be initiated until potential causes have been identified and addressed, to ensure both clinical effectiveness and value for money for the commissioning organisation.	Thank you for your comment. The committee agreed that it is a standard practice to consider recurrent miscarriage before any fertility treatment and suggested to follow the recommended time frame and not to restart it after the miscarriage or ectopic pregnancy. However, recurrent miscarriage was not within the scope of the guideline update, therefore, we would rather not include investigations of recurrent miscarriage.
NHS Surrey Heartlands ICB - Surrey	Guideline	022	011 – 1.4.7	Greater clarity is needed within the guideline on the application of the listed factors when deciding eligibility for treatment of obstructive azoospermia in men, trans	Thank you for this comment.

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County Council Public Health Team				women, and non-binary individuals with male reproductive organs. The existing text is open to wide interpretation and would benefit from more prescriptive wording to ensure consistency of clinical decision-making.	As outlined in the Benefits and harms section of the evidence review W on Surgical interventions for obstructive azoospermia, the evidence did not show clear differential benefits in favour of surgical correction compared to surgical sperm retrieval or vice versa, therefore the committee thought that other factors should be taken into account when deciding between these treatments. These factors have been listed in the recommendation and more detail around them is provided in the above section of the evidence review. The committee agreed that it was also down to clinical judgement.
NHS Surrey Heartlands ICB - Surrey County Council Public Health Team	Guideline	030	Line 11 – 1.8.3	We are referring here to Evidence K on **Fertility problems: assessment and treatment**. The committee noted that **"*using IUI as a gateway treatment prior to IVF did not lead to lower costs overall, as IVF as a first line treatment was always the cheapest strategy, even in the sensitivity analysis where the costs of IVF were increased above their baseline value.*"** Therefore, the wording of this section - particularly the two bullet points on (a) IUI and (b) IVF - should be strengthened to reflect both affordability and clinical effectiveness. This is especially relevant for patients with	Thank you for this comment. We think the points addressed in this comment are reflected in the different strength of the recommendations for IUI and IVF. We refer you to the wording of recommendations in the NICE Guidelines Manual (https://www.nice.org.uk/process/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869) – see section 9.3 **Reflect the strength of the recommendation:**

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				mild endometriosis or mild male factor fertility problems, where IVF may objectively represent a more effective first-line treatment option.	*In 'strong' recommendations (see the section on strength of recommendations) for actions that should (or should not) be offered, use directive language such as 'offer' (or 'do not offer'), 'advise', or 'ask about'. In keeping with the principles of shared decision making, people may choose whether or not to accept what they are offered or advised.* *If there is a closer balance between benefits and harms (activities or interventions that could be used), use 'consider' reflecting that the recommendation is 'weak'.*
NHS Surrey Heartlands ICB - Surrey County Council Public Health Team	Guideline	031	005 – 1.9.2	Anti-Müllerian hormone (AMH) and antral follicle count (AFC) are the strongest predictors of ovarian reserve and, alongside a woman's age, the best predictors of live birth. References to ovarian reserve should therefore clearly specify the AMH and AFC levels that predict a good chance of live birth.	Thank you for this comment. As outlined in the Benefits and harms section of the evidence review A on Ovarian reserve testing, the guideline committee could not include specific thresholds on ovarian reserve in the recommendations as there were no consistent thresholds reported in the evidence. They also discussed that this should be guided by clinical judgement.
NHS Surrey Heartlands ICB - Surrey County	Guideline	031	007 – 1.9.3	There appears to be a significant difference between the proposed number of IUI cycles in the 2026 draft guideline - which recommends offering 12 cycles - and the previous 2013 guidance, which suggested 6 cycles followed by a further 6 before IVF treatment is considered, which gave	Thank you for your comment. We do not think there is a significant difference between the new guideline and the 2013 guideline. Twelve cycles of IUI are only recommended if there are no

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Council Public Health Team				clinician an opportunity to understand how the patient respond to this type of treatment. Could you please provide the rationale for this change ?	contraindications and earlier in the guideline, it is made clear that further clinical assessment and investigations should be offered to those who have not conceived after 6 cycles of artificial insemination.
NHS Surrey Heartlands ICB - Surrey County Council Public Health Team	Guideline	031	024 – 1.9.5	The work of NICE in ensuring that people with fertility problems are provided with evidence-based interventions to ensure that they maximise their chances to achieve pregnancy and birth, particularly at a time when the total fertility rate in the UK is declining (1.41 children per woman currently), should be commended. We recognise that NICE focuses primarily on clinical effectiveness; however, we would like to draw attention - as many colleagues across the system are likely to do - to the issues of patient expectations and system affordability. We have concerns regarding the proposed recommendation to offer up to six full cycles of IVF (three plus a further three). Many local healthcare systems are currently unable to fund the existing recommendation of three full cycles, and nationally, NHS-funded cycles represent only around 27% of all IVF cycles undertaken in the UK. This ongoing tension between national recommendations and local affordability places patients in a difficult position	Thank you for this comment. We recognise the difficult decisions ICBs must make on the allocation of scare resources, and the committee did discuss implementation. However, the committee considered that the recommendations they made were in line with the best available clinical and cost-effectiveness evidence.

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				and contributes to inequities in access. In addition, while we acknowledge the evidence demonstrating improved cumulative pregnancy rates with each additional cycle, it is important to balance these findings against the economic realities faced by commissioners and providers.	
NHS Surrey Heartlands ICB - Surrey County Council Public Health Team	Guideline	038	020 – 1.11.2	This section related to couples in whom a previous IVF treatment cycle has failed. We feel that it is important that the upcoming NICE guideline provides a clearer definition of what constitutes a failed cycle because without it, commissioners, providers, and patients can all interpret "failed cycle" differently which may result in the following inconsistencies: **Access and eligibility**: some patients may be offered more or fewer funded cycles depending on how "failure" is counted. **Equity:** regional variation emerges if different Integrated Care Boards (ICBs) or clinics apply different interpretations. **Data and evaluation:** outcomes become harder to measure, compare, and improve if cycles are classified inconsistently, particularly in ICB spanning across large geographical footprints.	Thank you for your comment. This recommendation is about failed fertilisation, not failed cycle. The committee discussed this comment and concluded that the guideline is not intended as a text book so not everything needs to be defined in it.

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				Transparency for patients: people undergoing treatment need clarity on what support they are entitled to and what constitutes a completed, failed, or abandoned cycle. The draft guideline uses the term "full cycle" and offers up to three full cycles of IVF for people under 40 (with the possibility of three additional cycles) . It defines a full cycle as one episode of ovarian stimulation and transfer of any resultant fresh and frozen embryos . It also states that a cancelled cycle is one where no egg collection is undertaken; cancelled cycles due to low ovarian response should be taken into account when assessing suitability for further IVF . However, the draft guideline does not define failed cycles or explain how miscarriages, failed fertilisation or abandoned cycles should be counted. This omission makes it difficult to interpret recommendations. The guideline should define "failed cycle" to avoid ambiguity. For example: • **Failed fertilisation or poor response** – cycles where ovarian stimulation does not lead to egg retrieval or embryos fail to fertilise should be counted as full cycles, consistent with our policy . • **Clinical pregnancy loss** – cycles that result in miscarriage should be counted as completed cycles , because they consume similar NHS	

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				resources and may have psychological impacts that warrant a pause before further treatment. • **Live birth** – the definition should clarify whether a cycle culminating in live birth ends eligibility for further NHS funded treatment (our policy precludes access if the couple already has a living child). • **Cancelled cycles:** We support the existing definition that a cancelled cycle is one where no egg collection occurs . Guidance should state whether cancelled cycles count towards the total number offered; our policy counts cancelled cycles due to poor response as full cycles . • **Alignment between local and national policies:** The draft guideline's proposal to offer three (and potentially up to six) full cycles contrasts with our local policy of funding up to two cycles for women under 40. **Clear definitions of failed, cancelled and completed cycles are essential to ensure equity if national funding recommendations change. The guideline should provide a rationale for including or excluding self funded cycles .**	

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NHS Surrey Heartlands ICB - Surrey County Council Public Health Team	Guideline	042	001 – 1.14	Fertility preservation for medical indications. Would you be able to provide a rationale regarding the maximum length of time gametes should be cryopreserved for.	Thank you for your comment. The guidance does not provide recommendations about maximum storage period. The UK the maximum legal storage limit for cryopreserved gametes (eggs and sperm) for use in treatment is 55 years.
NHS Surrey Heartlands ICB - Surrey County Council Public Health Team	Guideline	079	006	There should be greater consistency in the guidance regarding the management of risk factors. Individuals with a high Body Mass Index (BMI) should be advised and supported to achieve weight loss prior to referral for fertility treatment. Clinicians in primary care should ensure that eligible patients are receiving appropriate support through a structured weight loss plan, with follow-up and review, and are referred to local weight management services where appropriate.	Thank you for your comment. Advice around BMI in relation to fertility is covered in the section on 'Initial advice'. We have also added a cross-reference to the NICE guideline on overweight and obesity management which provides guidance on, for example, how to identify and assess overweight and obesity, how to discuss results, and different interventions.
NHS Surrey Heartlands ICB - Surrey County Council Public Health Team	Guideline	095 096	004	**Reference to 1.7.1** We believe that the 2013 recommendations have been misinterpreted in the text in the right-hand column. Recommendations 1.9.1.1 and 1.9.1.2 from 2013 do not suggest that these patient groups should have access to 12 cycles of NHS-funded artificial insemination (AI). If that were the case, up to 12 cycles of AI would be recommended for same-sex couples, as they fall within	Thank you for your comment. We recognise that the 2013 recommendations may have caused some confusion and in this update, we have tried to clarify these recommendations. The scope of the guideline, consulted on and published in 2022, defined the guideline's population remit as: "Groups that will be covered in the update • People with health-related fertility problems

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				the scope of these recommendations — which is clearly not intended. **We suggest that this section be reviewed in light of the above, as the proposed wording represents a significant departure from the current interpretation, which has generally been understood as six cycles of self-funded AI followed by six NHS-funded IUI for all patient groups covered by these recommendations.** Also: Offering 12 cycles of IUI to those unable to have intercourse due to disability or psychosexual problems is inequitable compared to the 6 cycles available to others using AI. Same-sex couples - also unable to have vaginal intercourse - are treated the same way but must prove subfertility first. This distinction should be justified, as both groups are protected under the Equality Act 2010. Additionally, patients needing donor insemination for medical reasons get only 6 cycles of donor IUI (per recommendations 1.12.1, 1.12.2, and 1.12.10), versus 12 cycles (partner or donor sperm) for those with disabilities/psychosexual issues.	• People who may require interventions to preserve fertility because of high risk of fertility problems due to clinical conditions or medical or surgical interventions In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination. The guideline will be applicable to all people seeking assessment and treatment of health-related fertility problems who meet these criteria, irrespective of their sexual orientation, partnership status or gender reassignment. This includes single people, people in heterosexual relationships, people in same sex relationships, people who are non-binary, undergoing or have undergone gender transition and people using a surrogate." The key issue to bear in mind is that the guideline only covers assessment and treatment for health-related fertility problems and as such does not exclude people based on their sexual orientation or relationship status

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					and the guideline's recommendations do not determine treatments based on the person's sexual orientation or relationship status. People who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychosexual problem are considered to have a health-related fertility problem and are therefore covered by this guideline. Please also see the equalities and health inequalities impact assessments (found in the History tab of the guideline website) which explored this issue further.
NHS Sussex ICB	Guideline	General	General	Whilst it welcomes the use of inclusive of language, repeated use of the phrase 'men, trans women and non-binary people with male reproductive organs' in the guideline is difficult to read in the context of complex recommendations. Suggest this could be rephrased to 'people with female reproductive organs' to improve readability.	Thank you for your comment. NICE uses gender inclusive language when possible to be inclusive of people who do not identify with the sex they were registered with (or assigned) at birth. Sometimes this means we need to be specific on who is covered by a recommendation. We do appreciate that spelling out the populations covered in full can make recommendations longer. However, we believe this is necessary for clarity here - particularly as this guideline covers so many different subgroups. The specific wording that we have used in this recommendation is line with the Style Guide's section on

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					sex and gender, which is based on extensive user research. However, we are also aware that the language we use around sex and gender is rapidly evolving, and your feedback has been passed to our colleagues who work on the Style Guide for consideration.
NHS Sussex ICB	Guideline	General	General	Whilst welcoming the use of inclusive of language, repeated use of the phrase 'women, trans men and non-binary people with female reproductive organs' in the guideline is quite difficult to read in the context of complex recommendations. We suggest this could be rephrased to 'people with female reproductive organs' to improve readability.	Thank you for your comment. NICE uses gender inclusive language when possible to be inclusive of people who do not identify with the sex they were registered with (or assigned) at birth. Sometimes this means we need to be specific on who is covered by a recommendation. We do appreciate that spelling out the populations covered in full can make recommendations longer. However, we believe this is necessary for clarity here - particularly as this guideline covers so many different subgroups. The specific wording that we have used in this recommendation is line with the Style Guide's section on sex and gender, which is based on extensive user research. However, we are also aware that the language we use around sex and gender is rapidly evolving, and your feedback has been passed to our colleagues who work on the Style Guide for consideration.
NHS Sussex ICB	Guideline	094-095	4th row	**2026 Rec 1.7.1.** A further group of patients with conditions that require specific consideration in relation to methods of conception who may require IUI, are patients	Thank you for this comment.

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			in table	who have undergone electroejaculation due to spinal injuries – these could be considered as an additional example in recommendation 1.7.1.	The guideline committee agreed that this was covered by the Management of ejaculatory failure recommendation.
NHS Sussex ICB	Guideline	Page 9	General	When referencing that smoking is likely to reduce fertility, we feel that vaping should also be included. Secondary care consultants often will not onward refer to the ACU until both partners have stopped smoking/vaping.	Thank you for your comment. The impact of nicotine-containing products, such as e-cigarettes and vaping, on fertility was not within the scope of this guideline update and no evidence has been reviewed on this, so the committee are unable to make recommendations on this topic. Several stakeholders made a similar comment and we have noted this as a potential topic for future updates.
NHS Sussex ICB	Guideline	012	013-018	**Rec 1.2.29.** We acknowledge that the rationale for including this recommendation is that it is 'not in the spirit of the previous version of the guideline' but believe there should be a more robust clinical rationale for this recommendation.	Thank you for your comment. The committee's view is that people who are childless after a year of trying without conceiving, or who are childless after a year of trying but having had a miscarriage (or ectopic pregnancy) both need further assessment and treatment for subfertility.
NHS Sussex ICB	Guideline	012	013-018	**Rec 1.2.29.** It could be useful to refer to 2023 national guidance from RCOG (Green-top guideline No.17) on recurrent miscarriage so patients who experience recurrent miscarriage are referred for investigations rather than continue on a subfertility pathway inappropriately	Thank you for your comment. Recurrent miscarriage is not within the scope of this guideline update, and we would not refer to an external guideline without assessing its quality and relevance, including formal appraisal with AGREE II where

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				(assisted conception treatment is not recommended as a treatment option for recurrent miscarriage).	appropriate. Therefore, we would rather not include recurrent miscarriage or refer to recommendations on recurrent miscarriage in this guideline. The committee acknowledged that it is a standard practice to consider miscarriage before any fertility treatment and suggested to follow the recommended time frame and not to restart it after the miscarriage or ectopic pregnancy (please see the updated recommendation 1.16.6).
NHS Sussex ICB	Guideline	016	017-020	**Rec 1.3.15.** We suggest NICE should include thresholds at which AMH and AFC are considered good predictors of live birth following assisted conception, otherwise it will not be possible to implement this recommendation consistently and there is a significant risk clinical practice will not be based on the available evidence.	Thank you for this comment. As outlined in the Benefits and harms section of the evidence review A on Ovarian reserve testing, the guideline committee could not include specific thresholds on ovarian reserve in the recommendations as there were no consistent thresholds reported in the evidence. They also discussed that this should be guided by clinical judgement.
NHS Sussex ICB	Guideline	022	013-020	**Rec 1.4.7.** We suggest NICE should indicate how the factors listed in bullet points can be used to decide which treatment is offered, otherwise it will not be possible to implement this recommendation consistently and there	Thank you for this comment. As outlined in the Benefits and harms section of the evidence review W on Surgical interventions for obstructive azoospermia, the evidence did not show

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				will be a significant risk clinical practice will not be based on the available evidence.	clear differential benefits in favour of surgical correction compared to surgical sperm retrieval or vice versa, therefore the committee thought that other factors should be taken into account when deciding between these treatments. These factors have been listed in the recommendation and more detail around them is provided in the above section of the evidence review. The committee agreed that it was also down to clinical judgement.
NHS Sussex ICB	Guideline	023	003-005	**Rec 1.4.9.** This 'consider' recommendation in relation to micro-TESE for non-obstructive azoospermia is confusing in the context of the previous two recommendations to offer surgical sperm retrieval to people with obstructive and non-obstructive azoospermia (1.4.7 and 1.4.8 respectively), neither of which mention any specific techniques. Does this mean **all other** techniques should be 'offered' to people with non-obstructive azoospermia? Does it mean micro-TESE should **not** be offered to people with obstructive azoospermia? Please provide clarification.	Thank you for your comment. Evidence Review W showed that surgical sperm retrieval increases chance of clinical pregnancy in people with obstructive azoospermia. However, there was no evidence on the techniques for surgical sperm retrieval in obstructive azoospermia, so the committee did not specify a technique in recommendation 1.25.1. In other words, all forms of surgical sperm retrieval can be offered to people with obstructive azoospermia, taking into account the factors outlined in the above recommendation. Recommendations 1.25.2 and 1.25.3 are about non-obstructive azoospermia. As outlined in the benefits and harms section of Evidence Review Y, the committee discussed that the evidence was not sufficient to make a

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					strong recommendation about a specific technique for surgical sperm retrieval for non-obstructive azoospermia. However, the committee acknowledged that although there is no randomised controlled trial evidence, evidence from non-randomised studies support micro-TESE (microscopic testicular sperm extraction) for surgical sperm retrieval in people with non-obstructive azoospermia, and based on their clinical knowledge and experience, less tissue is removed during a surgical sperm retrieval with micro-TESE. Therefore, the committee recommended that the use of micro-TESE could be considered in people with non-obstructive azoospermia (please see recommendation 1.25.3) which aligns with existing European Association of Urology (EAU) guideline.
NHS Sussex ICB	Guideline	030	011-017	**Rec 1.8.3.** We recognise that this recommendation excludes people trying to conceive via artificial insemination (AI). As those trying to conceive via AI include same sex couples, who are a protected group under the Equality Act 2010, it would be important to ensure the equity of this recommendation has been considered and documented in the context of the overall offer to same sex couples versus that to heterosexual couples. We note the 2013 full guideline provided details of how the committee determined how same sex and heterosexual couples received equivalent treatment and	Thank you for your comment. The recommendation you're referring to is specifically for people trying to conceive through unprotected vaginal sexual intercourse. Equalities considerations are discussed in more detail in the Equalities and health inequalities assessment forms, which can be found in the History tab of the guideline website. The 2013 guideline committee's decisions and deliberations around the 'equivalence' between

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				suggest this should be documented for the update as well.	expectant management for those trying to conceive through sexual intercourse and the number of cycles of artificial insemination for those not conceiving through sexual intercourse still stand are documented in the 2013 Full guideline.
NHS Sussex ICB	Guideline	030	011-017	**Rec 1.8.3.** Evidence review K, which supports this recommendation, states IUI as a gateway treatment prior to IVF does not lead to lower costs because first line IVF is the cheapest strategy and this recommendation could therefore lead to an increase in costs. In the context of the already very limited availability of NHS fertility treatment in most areas where current NICE guidelines are not fully implemented in the vast majority of areas, it therefore appears very unlikely this recommendation will be affordable and therefore implemented by ICBs. We would suggest affordability should be a factor that is taken into consideration when NICE make their recommendations, particularly in cases like this where the recommendation is to 'consider' and therefore does not have strong evidence to support it.	Thank you for this comment. NICE produces recommendations on the best available clinical and cost-effectiveness evidence. The economic analyses suggested that IUI as a 'gateway treatment' does result in higher cumulative live birth rates than IVF alone. However, the reduction in IVF treatment does not fully offset the costs of IUI treatment and in most scenarios the increase in live births was not achieved at an acceptable cost (as assessed by the cost-effectiveness threshold). However, the analysis was not without limitations and uncertainty and in some cases IUI with gonadotrophin appeared to be a relatively cost-effective alternative. Therefore, the committee agreed a weaker 'consider' recommendation was reasonable.
NHS Sussex ICB	Guideline	031	005-006	**Rec 1.9.2.** In order to facilitate implementation of this recommendation, NICE will need to include thresholds at which AMH and AFC are considered good predictors of live birth following assisted conception.	Thank you for this comment. As outlined in the Benefits and harms section of the evidence review A on Ovarian reserve testing, the guideline committee could not include specific thresholds on ovarian reserve in the recommendations

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					as there were no consistent thresholds reported in the evidence. They also discussed that this should be guided by clinical judgement.
NHS Sussex ICB	Guideline	031	011-017	**Rec 1.9.3.** Please clarify whether people who experience a miscarriage during the expectant management period prior to IVF (i.e. 2 years of regular unprotected vaginal intercourse or 12 cycles of artificial insemination) would be required to 'start again' or whether these pregnancies should be discounted as per recommendation 1.2.29 in the draft guidance. Currently in many areas these patients are often required to 'start again' because it has been demonstrated that they can conceive, and IVF alone is not a treatment for miscarriage.	Thank you for this comment. The committee discussed this and agreed to revise the recommendation 1.16.6 so that it also includes the expectant management period before IVF treatment beyond the first year, or the 12 cycles of artificial insemination before IVF treatment.
NHS Sussex ICB	Guideline	031	018-019	**Rec 1.9.3.** Currently CG156 recommends offering IVF in women who have not conceived after 12 cycles of artificial insemination where 6 or more are by intrauterine insemination. The new draft guidance simply recommends offering IVF after 12 cycles of artificial insemination. Please specify the rationale for this change. It may be preferable to maintain the previous recommendation of requiring at least 6 IUI as it can then be ascertained that patients have undergone at least some AI cycles under optimum circumstances (i.e. at the correct time in their cycle, using good quality sperm etc.). As recommendation 1.7.2 allows 6 NHS funded IUI for this group, this should have limited impact on patients.	Thank you for your comment. The committee agreed to reinstate in the recommendation that 6 or more cycles should be by IUI.

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NHS Sussex ICB	Guideline	031	028	**Rec 1.9.5.** As noted in the rationale section of the draft NICE guidance, very few ICBs in England offer up to 3 full cycles of IVF for women aged under 40 as per the current NICE guideline. The new recommendation to consider funding up to 6 full IVF cycles is therefore not likely to be implemented by any ICBs in the current financial climate. Including this recommendation in the final guidance is going to raise patient expectations and lead to more NHS resources being used to deal with queries and complaints. Whilst we appreciate NICE recommendations are based on the evidence, the affordability needs to be taken into consideration. Making recommendations which are known to have a very limited chance of being implemented undermines the value of NICE guidelines. The recommendation to extend IVF provision to up to 6 cycles seems particularly inappropriate in the current financial climate considering the rationale sections states there are 'particular uncertainties' about the evidence to support funding of cycles 4 to 6.	Thank you for this comment. The guideline committee were aware that the implementation of recommendations had to be considered as part of their deliberations. The updated guideline recommends that 3 cycles of IVF are still offered as per previous NICE guidance but a weaker 'consider' recommendation is made for an additional 3 cycles. The weaker recommendation reflects the more uncertain evidence of clinical and cost-effectiveness for 4-6 cycles. The committee did not think that many patients would want more than 3 cycles if previous attempts were unsuccessful but noted that expectations are already unmet in many areas of the NHS where NICE recommendations are not adhered to.
NHS Sussex ICB	Guideline	032	005-007	**Rec 1.9.7.** We note that the current NICE guideline requires people aged 40-42 to have no evidence of low ovarian reserve (recommendation 1.11.1.4). Please clarify why this recommendation has now been removed.	Thank you for your comment. Based on evidence review A, the committee agreed that taking into account ovarian reserve is relevant with all patients considering IVF treatment, not only those aged 40+. This is reflected in recommendation 1.39.2.

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NHS Sussex ICB	Guideline	079	3rd row in table	**2013 Rec 1.10.1.1.** We do not agree that the 2013 recommendation 1.10.1.1 is covered by the 'initial advice' section of the draft guidance, which only relates the impact of age on fertility, not the impact of age on the outcome of IVF treatment. This is a useful statement to keep in the guideline; our engagement with specialists indicates patients are often not well informed about factors which might influence the outcomes of fertility treatment. We would also argue that ICBs using age to prioritise treatment for patients who are most likely to succeed in the context of a limited NHS budget does not constitute 'misuse' of this information.	Thank you for this comment. The impact of age on IVF 'success' in terms of live births per embryo transfer by age is captured in the updated Figure 2 in the new guideline. And recommendation 1.18.2 captures age as the main predictor for fertility (both through spontaneous conception and IVF). The guideline already gives evidence-based guidance on restricting IVF provision based on age.
NHS Sussex ICB	Guideline	079	4th row in table	**2013 Rec 1.10.2.1.** The 2013 recommendation 1.10.2.1 is a useful statement to keep in the guideline; our engagement with specialists indicates patients are often not well informed about factors which might influence the outcomes of fertility treatment.	Thank you for your comment. The committee thought the information is widely understood by clinicians and is routinely discussed during treatment planning, so the committee felt it might not add value as a standalone recommendation.
NHS Sussex ICB	Guideline	079	6th row in table	**2013 Rec 1.10.4.1.** We do not agree that 2013 recommendation 1.10.4.1 is covered by the 'initial advice' section of the draft guidance, which only relates to the impact of BMI on fertility, not the impact of BMI on the outcome of IVF treatment. This is a useful statement to keep in the guideline; our engagement with specialists indicates patients are often not well informed about	Thank you for the comment. The committee agreed that BMI advice should focus on health optimisation rather than being used as a strict eligibility criterion. Even in the 2013 guideline, BMI was not part of the recommended access criteria for IVF, but we are aware that BMI is and has been sometimes used

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				factors which might influence the outcomes of fertility treatment. We would also argue that ICBs using BMI to prioritise treatment for patients who are most likely to succeed in the context of a limited budget does not constitute 'misuse' of this information. In addition, we would note: • The majority of clinicians we have engaged with are supportive of limiting NHS funded treatment to people with a BMI range of 19-30. • The HFEA Commissioning Guide (page 10) recommends NHS treatment is limited to people with a BMI range of 19-30. BMI criteria are in place in all ICBs across the country – see the DHSC webpage on NHS funded IVF in England.	as such. This is not according to the NICE guideline. General advice on BMI and fertility in the 'Initial advice' section was considered to be sufficient.
NHS Sussex ICB	Guideline	079	8th row in table	**2013 Rec 1.10.5.2.** We do not agree that 2013 recommendation 1.10.5.2 is covered by the 'initial advice' section of the draft guidance, which only relates to the impact of smoking on fertility, not the impact of smoking on the outcome of IVF treatment. This is a useful statement to keep in the guideline; our engagement with specialists indicates patients are often not well informed about factors which might influence the outcomes of fertility treatment.	Thank you for this comment. The committee think this is sufficiently covered in the section on 'Initial advice', considering impact of smoking on fertility as the overall capacity to achieve pregnancy (whether trying to conceive naturally or through IVF).
NHS Sussex ICB	Guideline	087	5th row	**2013 Rec 1.16.1.3.** It would be helpful to clarify why NICE no longer recommends girls/ women should only undergo oocyte/ egg cryopreservation if they are well enough, it	Thank you for this comment.

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			in table	will not worsen their condition, and enough time is available before the start of their treatment.	The committee thought this is part of basic good clinical judgments and care. However, the committee did agree to reinstate the 2013 recommendation around factors to take into account when deciding on cryopreservation, including diagnosis, prognosis etc. (see recommendation 1.53.2).
NHS Sussex ICB	Guideline	094	4th row in table	**2026 Rec 1.7.1.** We feel that the 2013 recommendations have been misinterpreted in the text in the right hand column. The 2013 recommendations 1.9.1.1 and 1.9.1.2 are not suggesting these groups of patients have access to 12 cycles of NHS funded artificial insemination (AI). If this were the case, up to 12 cycles of AI would be recommended for same sex couples, as they are included within the scope of recommendations 1.9.1.1 and 1.9.1.2, and it is clear that this is not the case. We suggest this change is reviewed in light of the above as it is a significant change to the current recommendations which have widely been interpreted as 6 cycles of self-funded AI followed by 6 NHS funded IUI for all groups of patients within the scope of the recommendation.	Thank you for your comment. We recognise that the 2013 recommendations may have caused some confusion and in this update, we have tried to clarify these recommendations. The key issue to bear in mind is that the guideline only covers assessment and treatment for health-related fertility problems. People without known health-related fertility problems trying to conceive using artificial insemination are not within the scope of the guideline unless they have not conceived after 6 cycles. People who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychosexual problem are considered to have a health-related fertility problem and are therefore covered by this guideline.

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NHS Sussex ICB	Guideline	094	4th row in table	**2026 Rec 1.7.1.** Offering 12 cycles of IUI to people unable to have intercourse because they have a disability/psychosexual problem appears to be inequitable compared to the 6 cycles available to other people trying to conceive through AI. Same sex couples fall in the latter group and are also unable to have vaginal sexual intercourse. They are therefore essentially in the same position as the people with disability/ psychosexual problem, yet they are required to demonstrate their subfertility prior to NHS treatment. The reasons for this need to be explained, especially as both groups will fall under protected groups under the Equality Act 2010. Furthermore, patients undergoing donor insemination for medical reasons are only offered up to 6 cycles of IUI using donor sperm as per recommendations 1.12.1, 1.12.2 and 1.12.10. This appears inequitable compared to people with disability/ psychosexual problems who are offered 12 cycles of AI using partner or donor sperm.	Thank you for your comment. The scope of the guideline, consulted on and published in 2022, defined the guideline's population remit as: "Groups that will be covered in the update • People with health-related fertility problems • People who may require interventions to preserve fertility because of high risk of fertility problems due to clinical conditions or medical or surgical interventions In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination. The guideline will be applicable to all people seeking assessment and treatment of health-related fertility

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					problems who meet these criteria, irrespective of their sexual orientation, partnership status or gender reassignment. This includes single people, people in heterosexual relationships, people in same sex relationships, people who are non-binary, undergoing or have undergone gender transition and people using a surrogate." The key issue to bear in mind is that the guideline only covers assessment and treatment for health-related fertility problems and as such does not exclude people based on their sexual orientation or relationship status and the guideline's recommendations do not determine treatments based on the person's sexual orientation or relationship status. Please also see the equalities and health inequalities impact assessments (found in the History tab of the guideline website) which explored this issue further.
North East and North Cumbria ICB	Guideline			1. Would it be challenging to implement of any of the draft recommendations? Please say why and for whom. Please include any suggestions that could help users overcome these challenges (for example, existing practical resources or national initiatives.'	Thank you for this comment. The use of 'consider' recommendations is discussed in the NICE Guidelines Manual (https://www.nice.org.uk/process/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869) – see section 9.3

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				Implementing increased IUI pre IVF and potential increased expectations re this and increasing the total number of IVF cycles will increase public expectation regards access and funding. Wording re IUI cycles pre IVF for same sex single trans patients will also raise expectations. It will not increase the ability of ICB's to fund these services. There should be a clear statement regards definitions of 'consider' and obligations of providers to fund the guidelines to try and create a more realistic interpretation of the guidelines. They are an excellent reflection of current evidence including cost benefit as ever,, but perhaps don't inform the public clearly that they are that and divorced from the reality of funding it on the ground that the NHS must try and navigate. The result will be predictable publicity regards the NHS not meeting the high expectations given here in places and we will get a multitude of complaints and queries regards not delivering. It could be avoided with appropriate wording and publicity. The public will interpret the guidelines as a delivery document.	***Reflect the strength of the recommendation*** *In 'strong' recommendations (see the section on strength of recommendations) for actions that should (or should not) be offered, use directive language such as 'offer' (or 'do not offer'), 'advise', or 'ask about'. In keeping with the principles of shared decision making, people may choose whether or not to accept what they are offered or advised.* *If there is a closer balance between benefits and harms (activities or interventions that could be used), use 'consider' to reflect that the recommendation is 'weak'* Strong recommendations have not been made with respect to IVF cycles relative to existing NICE guidance.
North East and North Cumbria ICB	Guideline			1. Would implementation of any of the draft recommendations have significant cost implications? Any increased IVF cycles would increase cost above current baseline. Impact of IUI pre IVF not totally clear given potential reduction of numbers going on to IVF.	Thank you for this comment. We accept that were IVF cycles provided in line with either previous or new NICE guidance, this would represent a cost above current baseline. We note that the updated guideline only makes a weaker

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					recommendation to consider 3 additional cycles compared to previous NICE guidance. The economic analysis suggested that IUI provided as a treatment option prior to IVF would be unlikely to reduce costs. This was because the reduction in IVF treatment would not fully offset the costs of an additional treatment. However, the economic modelling suggested there was some uncertainty with respect to the magnitude of the net cost impact if IUI was provided prior to IVF.
North East and North Cumbria ICB	Guideline	009	011	Smoking is referred to rather than nicotine ingestion, which can be via a variety of routes (vaped, gums, mucosal 'pads'). As these become more common and often as part of smoking cessation or smoking alternatives can more specific advice be given as Nicotine itself is an active substance, with arterial/arteriolar vasoconstriction effects which may or may not have a deleterious fertility effect. Guidance would be really helpful.	Thank you for your comment. The impact of nicotine-containing products, e-cigarettes, gums, mucosal 'pads' and vaping on fertility was not within the scope of this guideline update and no evidence has been reviewed on this, so the committee are unable to make recommendations on this topic. Several stakeholders made a similar comment, and we have noted this as a potential topic for future updates.
North East and North Cumbria ICB	Guideline	021	018	Not specific about primary or secondary hypogonadism, which may effect response to treatment and eligibility criteria and no specifics about how long it is reasonable to treat for before cessation.	Thank you for your comment. Recommendation 1.24.1 covers both primary and secondary hypogonadism, and decisions about how long treatment should continue are best guided by

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					clinical judgment. Therefore, no specific details about these have been added to the recommendation.
North East and North Cumbria ICB	Guideline	030	016	In same sex couples would 6 cycles of IUI by HFEA approved provider be expected to prove infertility and THEN a further 4 cycles of IUI WITH stimulation prior to or as an alternative to IVF be recommended on evidence- that is how I read it. Could this be made more specific and clearer re this cohort of patients please. Could the evidence based recommendation be proposed as such and there be explicit wording regards elements NHS funding of the pathway may vary across the country. Not raising expectations, cause for challenge and working with ICB providers on this would be much appreciated although perhaps outwith the remit.	Thank you for this comment. The recommendation you're referring to is about people with unexplained fertility problems who have tried to conceive for 2 years through regular unprotected vaginal sexual intercourse and does not apply to same sex couples using IUI to conceive. People using IUI to conceive are covered by the previous section and would be offered a further 6 cycles of unstimulated IUI (after an initial 6 cycles) before IVF treatment, given there are no contraindications or known causes of infertility.
North East and North Cumbria ICB	Guideline	031	028	I am fully aware and respect the evidence based and necessary independent nature of this guideline review and proposed revisions.I am aware that only 30% of ICB's offer > 1 cycle of ivf to begin with and that 'consider' in the guidance is just that but the Guidelines team must be aware of the public take on this proposed change, and potential headlines, and the increasing financial pressures on the NHS and ICB's. This proposed inclusion is setting the NHS up for multitudes of written complaints, challenges to policy documents and paperwork in an already stretched and overworkedt system. Wholly predictable fallout from this should be considered	Thank you for this comment. The guideline committee were aware that the implementation of recommendations had to be considered as part of their deliberations. Whilst 3 cycles of IVF are still recommended to be offered as in previous NICE guidance, a weaker recommendation is made for an additional 3 cycles. These are based on the best available cost effectiveness evidence. The committee did not think that many patients would want more than 3 cycles if previous attempts were unsuccessful but noted that expectations are already

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				carefully and perhaps reworded or formulated in a tempered way reflecting anticipated restraints on implementation on organisations. The aim should be to lower expectations from the start re access to more than three cycles.Please!	unmet in many areas of the NHS where NICE recommendations are not adhered to.
North East and North Cumbria ICB	Guideline	40	27	Guideline suggests offering this cohort of patients 6 cycles of donor insemination which should be IUI as per 1.12.9 recommendation- currently many ICB's do not fund this and it is expected this cohort of patients including single people self fund HFEA approved cycles prior to referral for IVF or further infertility services. After 3 cycles as per1.12.8 tubal assessment may be appropriate also. From reading this the public is led to believe all of this should be expected from the NHS. As mentioned this is often not the case. Can the wording be changed to reflect the evidence orientated pathway suggestion requiring these steps without the implication of NHS provision- for example- 'the evidence suggests this pathway however funding models and funded NHS provision may vary across the country' or similar	Thank you for this comment. The recommendation you're referring to was removed after consultation because the committee agreed it was already covered by the recommendations about unstimulated IUI in section 1.37. Please note that this guideline only covers health-related fertility problems, thus, people without known health-related fertility problems using artificial insemination to conceive are not covered in the guideline, unless they do not conceive in the first 6 cycles. At this stage, as defined in the 2022 scope of the guideline, they are considered to have a health-related fertility problem (see recommendation 1.16.5) and should be offered further assessment and investigation and possibly further cycles of donor insemination (see recommendation 1.37.2).
North Middlesex University	Economic Model ART	005	020	The economic model omits cumulative costs of failed IVF cycles, which NICE acknowledges have a 70% failure rate (HFEA, 2020). It also excludes costs related to	Thank you for your comment.

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Hospitals; Trust				cryopreservation, ICSI, and FET. We request full publication of the model and recalculation of cost-effectiveness using symmetrical assumptions.	Cumulative costs of additional cycles of treatment are included in the calculation of strategy treatment costs as shown in Table 53, for example, in Evidence Review K. It is assumed that the estimates of cumulative live birth rates derived from the NMA are achieved over the maximum number of cycles listed in Table 41 of Evidence Review K. The unit cost for IVF is based on one fresh and one frozen embryo transfer. It includes the cost of drugs, scans and all components of the service including freezing of gametes and embryos for 2 years from the point the woman is seen by the consultant to when she ends her NHS care, or when she is no longer entitled to NHS care. The costs of ICSI were not deemed relevant as the IVF being evaluated did not include ICSI. The model was made available to registered stakeholders during consultation if they requested it. Furthermore, the model is described in detail in Appendix I of the Evidence Review K.
North Middlesex University	Economic Model ART	009	015	Economic Model for ART - The QALY framework used is inappropriate for fertility. It relies on fixed utility assumptions and ignores psychosocial dimensions	Thank you for your comment.

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Hospitals; Trust				(Boivin et al., 2022; Gameiro et al., 2012). Conclusions are fragile and sensitive to small changes in utility values. We recommend either removing QALY-based conclusions or qualifying their limitations.	The comments you make are reasonable, but we do acknowledge these limitations (see Evidence Review K and the discussion section in Appendix I of that report): *"The use of QALYs is problematic in the assessment of fertility treatments (Keller 2022) and considerable uncertainty exists with regard to how a live birth should be valued, not least because the negative impact of infertility may impact on broader measures of well-being than* *health-related quality of life."* However, notwithstanding these limitations, cost-effective allocation of finite NHS resources requires that a trade-off is made between the gains from expenditure on ART and its opportunity cost, in terms of the gains that would have accrued if this expenditure had been deployed elsewhere in the NHS. The use of QALYs facilitates such a trade-off whereas there is no established cost-effectiveness threshold (or "decision rule") to determine cost-effectiveness on a measure such as cost per live birth (or similar)
North Middlesex University	Evidence review A	057	032	The omission of Bahadur et al. (2020), which shows IUI babies are £40,000 cheaper than IVF, is a serious breach of academic integrity. This data must be integrated into model calibration.	Thank you for your comment. A literature search was conducted which yielded 4,314 articles. The articles that were found by the searches did

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Hospitals; Trust					not include this article. However, we did use this article as one of our sources to estimate the baseline multiples rate with IUI. Please note the following: • Cost saving is not a model input variable. The "saving" is calculated from other model inputs. Model unit costs which could be varied in a sensitivity analysis are given in Table 48 and Table 50 of Evidence Review K. • Bahadur 2020 uses HFEA 2012-16 data for multiples. The economic model is based on more recent 2021 HFEA data for multiples in IVF which shows a much lower rate for IVF multiples (5.1% v 13.9%). • Our model used a more recent and sophisticated cost analysis to estimate the cost of multiple birth (Jacklin and Marceniuk (2018) than the COMBS (Ledger 2006) used in this Bahadur 2020. • No explicit cost per live birth for IVF or IUI is given separately in Bahadur 2020. • The costing in Bahadur too opaque and therefore it is not clear how the figures underpinning the claim that "IUI babies are £40,000 cheaper than IVF" is derived. So, for example, assuming a

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					formula for cost per live birth for each intervention of: Cost ÷ LBR Then it is difficult to determine how the "baseline tariffs and success rates" have generated such a large cost saving. E.g. <u>Average analysis</u> IVF 4699 ÷ 0.273 Av cost = £17,212 IUI 800 ÷ 0.120 Av cost = £6,677 <u>Incremental</u> Δ cost = 3899 Δ LBR = 0.152 ICER = £25,651 • Nor does the Bahadur paper justify the assertion that "IUI is more cost-effective than IVF in delivering 1 LB against current tariffs". This suggests at best only a partial understanding of

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					how ICERs are used to assess cost-effectiveness. The paper includes no discussion of the threshold at which society would be willing to pay for an additional LB.
North Middlesex University Hospitals; Trust	Evidence review A	063	012	The continued reliance on Bhattacharya 2008, which used outdated Clomid-IUI protocols, skews cost-effectiveness against IUI. NICE should use modern Gn+IUI data and meta-analyses.	Thank you for your comment. Within Evidence Review K, Bhattacharya 2008 is referenced on several occasions and it is not clear what this comment relates to given the page and line numbers provided. Bhattacharya 2008 was included in the NMA because it met the inclusion criteria specified in the review protocol. The live birth NMA included 17 studies in total and the results of the NMA (and it's use within the economic model) underpinned committee recommendations, rather than any single study. The NMA included recent Gn+IUI data (e.g. Thyagaraju 2022) and one of the advantages of NMA over pairwise meta-analysis is that it facilitates decisions between multiple comparators where head-to-head RCT evidence may not always exist. Bhattacharya 2008 was also used to estimate baseline

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					expectant management conception in sensitivity analyses. This sensitivity analysis led to an improvement in the cost-effectiveness of Gn+IUI relative to the base case analysis and was used to support a consider recommendation for Gn+IUI.
North Middlesex University Hospitals; Trust	Evidence review B	034	010	The model ignores long-term NHS costs associated with higher complication rates in IVF-conceived children. These downstream liabilities must be included.	Thank you for this comment. The model accounts for additional costs associated with multiple births, primarily due to increased prematurity. Higher complication rates for singleton IVF/ART births relative to births from spontaneous conception is debated. Sanders (2022) – found no difference in singletons IVF, IUI, ovulation drugs when compared with no treatment in sub fertile women. Whereas Wu (2022) found that pregnancies conceived by ART have higher risks of adverse obstetric outcomes and vascular complications compared with spontaneous conception. The issue is further complicated by some confounding with age and that some of the difference is likely explained by sub-fertility/underlying infertility. Sensitivity analysis was undertaken using a higher cost for IVF and this could be viewed as a proxy for any such

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					long-term complication costs not taken into account in the base case analysis. Modelling always involves some simplification, and therefore we consider our approach is defensible and in line with other published analysis (van Eekelen 2020).
North Middlesex University Hospitals; Trust	Evidence Review E	012	045	Section 1.3.4 – The draft guideline disproportionately focuses on Clomiphene-IUI (ClomC+IUI), which is widely acknowledged as ineffective (Weiss et al., 2018). This creates a misleading narrative against IUI overall. Effective Gn-IUI protocols (Erdem et al., 2015; Farhi & Orvieto, 2009) are relegated to sensitivity analyses. We recommend reassessing IUI using Gn-IUI protocols and integrating contemporary registry data.	Thank you for your comment. It is not entirely clear what specifically this comment refers to given the section cited, page and line numbers provided. We think the comment relates to Evidence Review K but there is no section 1.3.4. In line with NICE methods on assessing the best available clinical evidence, an NMA was undertaken to pool direct and indirect evidence on ART. https://www.nice.org.uk/process/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869 *"When multiple competing options are being appraised, network meta-analysis is the preferred approach to use"*

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					A review protocol developed in advance of the search (see Appendix A) was used to identify studies for the NMA. The NMA and the economic model (which utilised results from the live birth NMA) were then used by the guideline committee to make recommendations based on the best available clinical and cost-effectiveness evidence. Therefore, we do not agree that the guideline disproportionately focuses on ClomC+IUI. NICE would ordinarily only use registry data when undertaking analysis based on Real World Evidence, which might be undertaken in the absence of randomised evidence.
North Middlesex University Hospitals; Trust	Evidence Review J 1a – Artificial Bundling of Treatments	002	021-030	IUI unfairly bundled with IVF, inflating costs. Model IUI-only vs IVF-only pathways using real-world data	Thank you for this comment. It is not clear what this comment relates to especially as Evidence Review J does not consider IUI, whether "bundled" with IVF or not. However, we assume the comment actually relates to the strategies assessed in

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					the economic analysis reported in Appendix I of Evidence Review K. We do not think that the pathway approach is artificial. The 2013 guideline did not recommend IUI as a first line alternative to IVF. In this guideline update we aimed to assess whether this position was still supported based on the best available clinical and cost-effectiveness evidence. The pathway approach was considered to align with international guidance and practice (NICE 2013, ASRM 2020 and ESHRE 2023) and IUI has the potential to avert some of the costs of IVF as a cheaper first line alternative. The approach has also been used in the published literature (e.g. van Eekelen 2020). Therefore, the evaluated strategies (or pathways) were considered by the guideline committee to reflect the options that could be reasonably recommended if there was supporting clinical and cost-effectiveness evidence.
North Middlesex University Hospitals; Trust	Evidence Review J 1a – Bhattacharya 2008	002	039-045	Reliance on obsolete Clomid-IUI trial. Replace with modern Gn+IUI data and meta-analyses	Thank you for your comment. Bhattacharya 2008 was included in the NMA because it met the inclusion criteria specified in the review protocol. The live birth NMA included 17 studies in total and the results of the NMA (and its use within the economic model) underpinned committee recommendations,

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					rather than any single study. The NMA included recent Gn+IUI data (e.g. Thyagaraju 2022) and one of the advantages of NMA over pairwise meta-analysis is that it facilitates decisions between multiple comparators where head-to-head RCT evidence may not always exist. Bhattacharya 2008 was also used to estimate baseline expectant management conception leading to live birth in sensitivity analyses. This sensitivity analysis led to an improvement in the cost-effectiveness of Gn+IUI relative to the base case analysis. It was considered as the best source of an alternative estimate of baseline births for a NICE guideline as the only included expectant management study in the NMA undertaken in a UK setting.
North Middlesex University Hospitals; Trust	Evidence Review J 1a – Omission of Bahadur 2020	002	031-028	Exclusion of cost-saving IUI data. Include Bahadur 2020 in scenario modelling	Thank you for this comment. Having looked at that paper we considered there was insufficient detail in the cost analysis undertaken to include this as a model scenario. A more detailed response is provided in response to a similar comment.
North Middlesex University	Evidence Review J 1a – Opaque	002	005-020	Lack of published model code, assumptions, and replicability. Publish full model code, parameter distributions, and WinBUGS/CODA draws	Thank you for this comment. An executable version of the model was made available at consultation to all stakeholders on request.

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Hospitals; Trust	Model Construction				A full write-up of the original health economic analyses developed for this guideline are provided in Appendix I of Evidence Reviews J and K.
North Middlesex University Hospitals; Trust	Evidence Review J 1b – Complications	003	016-020	Ignored NHS liabilities for IVF-conceived children. Include lifetime health costs in economic model	Thank you for this comment. The NHS has "liabilities" for all conceived children whether conceived through IVF/ART or spontaneous conception. Therefore, the approach in the model was to only consider the additional costs resulting from an IVF/ART conceived child relative to a child conceived from spontaneous conception. Therefore, the model does account for additional costs associated with multiple births, primarily due to increased prematurity. The committee considered that these were likely to be the most important long term cost difference between IVF/ART conceived children relative to children conceived from spontaneous conception. Higher complication rates for singleton IVF/ART births relative to births from spontaneous conception is debated. Sanders (2022) – found no difference in singletons IVF, IUI, ovulation drugs when compared with no treatment in sub fertile women. Whereas Wu (2022) found that pregnancies conceived by ART have higher

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					risks of adverse obstetric outcomes and vascular complications compared with spontaneous conception. The issue is further complicated by some confounding with age and that some of the difference is likely explained by sub-fertility/underlying infertility. Sensitivity analysis was undertaken using a higher cost for IVF and this could be viewed as a proxy for any such long-term complication costs not taken into account in the base case analysis. Modelling always involves some simplification, and therefore we consider our approach is defensible and in line with other published analysis (van Eekelen 2020).
North Middlesex University Hospitals; Trust	Evidence Review J 1b – Cryopreservation & FET	003	001-010	Missing costs for FET cycles and cryopreservation. Include full IVF costs including multiple FETs	Thank you for this comment. The unit cost for IVF is based on one fresh and one frozen embryo transfer. It includes the cost of drugs, scans and all components of the service including freezing of gametes and embryos for 2 years from the point the woman is seen by the consultant to when she ends her NHS care, or when she is no longer entitled to NHS care.
North Middlesex	Evidence Review J	003	021-025	Use of undisclosed HFEA data. Publicly disclose HFEA data and assumptions	Thank you for this comment.

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University Hospitals; Trust	1b – HFEA Cost Data				We presume this is referring to "2018-19 data from a personal communication with the HFEA was used to estimate the proportion of treatment cycles to attribute lower costs arising from cancellation". This data is 'disclosed' along with accompanying explanatory notes in Appendix I Evidence Review J, Table 12 and again in Table 51 in Appendix I Evidence Review K.
North Middlesex University Hospitals; Trust	Evidence Review J 1b – No Disaggregation	003	011-015	IVF and ICSI treated as one cost. Separate cost and effectiveness data for IVF and ICSI	Thank you for this comment. We think this comment relates to Evidence Review K. The costs of ICSI were not deemed relevant as the IVF being evaluated did not include ICSI.
North Middlesex University Hospitals; Trust	Evidence Review J 1c – Conceptual Invalidity	003	026-040	QALYs inappropriate for fertility outcomes. Replace QALYs with cost per live birth and healthy child	Thank you for this comment. The limitations of QALYs in the context of fertility treatment is discussed in Appendix I of Evidence Review K (p157). *"The use of QALYs is problematic in the assessment of fertility treatments (Keller 2022) and considerable uncertainty exists with regard to how a live birth should be valued, not least because the negative impact of infertility may impact on broader measures of well-being than*

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					health-related quality of life." However, notwithstanding these limitations, cost-effective allocation of finite NHS resources requires that a trade-off is made between the gains from expenditure on ART and its opportunity cost, in terms of the gains that would have accrued if this expenditure had been deployed elsewhere in the NHS. The use of QALYs facilitates such a trade-off whereas there is no established cost-effectiveness threshold (or "decision rule") to determine cost-effectiveness on a measure such as cost per live birth (or similar). For this reason the QALY is used in the NICE reference case to value health effects (see the NICE Guidelines Manual, https://www.nice.org.uk/process/pmg20/chapter/incorporating-economic-evaluation#the-reference-case).
North Middlesex University Hospitals; Trust	Evidence Review J 1d – Sampling Bias	004	001-010	Selective use of van Eekelen model. Present multiple plausible baselines and show impact	Thank you for this comment. Whilst we do not accept our use of the van Eekelen data biases results, we do acknowledge there is uncertainty with respect to this model input. Bhattacharya is used as an alternative source of baseline spontaneous conception leading to live birth

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					data in several sensitivity analyses. This is described in Appendix I of Evidence Review K (see for example p121 and p128).
North Middlesex University Hospitals; Trust	Evidence Review J 1e – Mild Male Factor	004	011-015	Undefined clinical terms. Define sperm parameters and treatment thresholds	Thank you for your comment. We assume this comment is about defining mild male factor fertility problems. For the purpose of the evidence reviews, studies that included people with a single abnormal semen parameter (a single variable usually assessed in at least 2 analyses) would be eligible for inclusion (abnormal defined as a value below the 5th centile defined by the World Health Organization, 2021: semen volume 1.4ml; sperm concentration 16 × 106/mL; total sperm number 39 × 106 per ejaculate; total motility 42%; progressive motility 30%). However, there was variability in the inclusion criteria across the relatively small number of studies where 'mild male factor fertility problems' were considered. The committee agreed there is no established definition for 'mild male factor' fertility problem and did not want to define it. Based on consultation feedback, the recommendations no longer refer to 'mild male factor fertility problems' because the committee did not think it is a helpful category to use since it is not well-defined.

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North Middlesex University Hospitals; Trust	Evidence Review J 1f – Cumulative Rates	004	016-020	Misleading cumulative success rates. Present per-cycle success rates and dropout impact	Thank you for this comment but unfortunately, we could not determine what content this comment relates to. If the stakeholder is referring to estimates of cumulative live birth rates, it would have been helpful if they could have explained why they are misleading and why their alternative is better. In regard to 'dropout impact', patients have the right to cease treatment (IVF/IUI) at any point, but it is not clear why that would affect cost-effectiveness as if they do not get a live birth because they have dropped out, then the NHS has not paid for it either. So a hypothetical cohort who do not drop out is reasonable as costs/QALYs are presented per patient anyway.
North Middlesex University Hospitals; Trust	Evidence Review J 1g – Strategy Exclusion	004	021-030	Exclusion of valid clinical pathways. Include full range of clinical strategies in modelling	Thank you for this comment. We presume that this comment relates to Evidence Review K, where the economic evaluation explicitly considers pathways based on strategies of 1st line and 2nd line treatment. We consider that the included strategies are reasonable for the purposed of decision making. The 2013 guideline did not recommend IUI as a first line alternative to IVF. In this guideline update we aimed to assess whether this position was still supported based on the best available clinical and cost-effectiveness evidence. The pathway

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					approach was considered to align with international guidance and practice (NICE 2013, ASRM 2020 and ESHRE 2023) and IUI has the potential to avert some of the costs of IVF as a cheaper first line alternative. The approach has also been used in the published literature (e.g. van Eekelen 2020). Therefore, the evaluated strategies (or pathways) were considered by the guideline committee to reflect the options that could be reasonably recommended if there was supporting clinical and cost-effectiveness evidence.
North Middlesex University Hospitals; Trust	Evidence Review J 2 – Internal Uncertainty	005	001-010	Downgrade IVF to "consider" and present IUI as valid	Thank you for this comment. The comment appears to suggest that IUI is not supported by the guideline. The updated NICE guideline recommends IUI treatment in multiple places, including considering IUI as a first-line treatment option for those with unexplained fertility problems.
North Middlesex University Hospitals; Trust	Evidence Review J 3 – Socio-Economic Costs	005	011-020	IVF imposes hidden burdens on patients. Model patient time, recovery, and socio-economic costs	Thank you for this comment. Costing for the economic analysis was undertaken in line with the NICE Reference Case as described in Developing NICE guidelines: the manual (https://www.nice.org.uk/process/pmg20). As per the NICE Reference Case the analysis took an NHS and PSS (Personal Social Services) perspective.

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					This is also explained in Appendix I of Evidence Review K. We presume that the stakeholder means societal costs rather than socio-economic costs as the latter has little meaning in a HTA context. However, societal costs are not usually incorporated into health economic analysis undertaken by NICE.
North Middlesex University Hospitals; Trust	Evidence Review J 4 – Global Outlier Status	005	036-040	NICE diverges from ESHRE and ASRM. Align with international best practices supporting IUI	Thank you for your comment. NICE recommendations are based on the evidence reviewed by NICE's independent advisory committees and may not always align with other guidelines. The comment appears to suggest that IUI is not supported by the guideline. The updated NICE guideline recommends IUI treatment in multiple places, including considering IUI as a first-line treatment option for those with unexplained fertility problems.
North Middlesex University Hospitals; Trust	Evidence Review J 4 – HFEA & Committee Ties	005	021-035	Potential regulatory capture and bias. Disclose committee interests and manage conflicts	Thank you for your comment. The committee members' interests are declared in the Register of interests. The involvement (or previous involvement) of some of committee members in HFEA's advisory committee was not considered to be in conflict with their work on the NICE guideline.

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North Middlesex University Hospitals; Trust	Evidence Review K	018		The grouping of heterogeneous interventions (e.g., combining fresh and frozen IVF cycles, or lumping all gonadotropins) risks masking clinically important differences. This reduces the granularity and clinical utility of the findings.	Thank you for this comment. In line with NICE methods on assessing the best available clinical evidence, a network meta-analysis (NMA) was undertaken for this review as it facilitates decisions between multiple comparators where head-to-head RCT evidence may not always exist. This allowed both direct and indirect evidence on ART to be pooled. https://www.nice.org.uk/process/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869 "When multiple competing options are being appraised, network meta-analysis is the preferred approach to use" In an NMA it is common practice to group similar interventions. This can be necessary to achieve network connectivity and to make meaningful comparisons. When individual interventions are too granular or sparsely studied, the network may become disconnected, limiting the ability to estimate relative effects across all treatments. Combining similar interventions improves statistical power, reduces inconsistency, and allows for more robust and interpretable results. All grouping was agreed by the committee, in the context of an NMA, and therefore we believe the findings have clinical relevance.

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North Middlesex University Hospitals; Trust	Evidence Review K	022		Only 16 RCTs (n=4,755) reported live birth outcomes, compared to 36 RCTs (n=7,406) reporting clinical pregnancy. This over-reliance on surrogate outcomes weakens the validity of treatment rankings. The guideline should downgrade the strength of recommendations based on clinical pregnancy alone.	Thank you for your comment. As stated in 'The committee's discussion and interpretation of the evidence' section in this evidence review, whilst the committee were reassured that the results of the clinical pregnancy network meta-analysis (NMA) were broadly consistent with that of the live birth NMA, they were not important in making recommendations in the context of the live birth treatment effects that were obtained. The clinical pregnancy NMA did not inform decision-making and so there were no recommendations made based on clinical pregnancy outcomes alone.
North Middlesex University Hospitals; Trust	Evidence Review K	022	033	The draft misrepresents safety outcomes. IVF-associated risks such as OHSS (Nelson, 2017), congenital anomalies (Hansen et al., 2013; Davies et al., 2012), and neonatal complications are underreported or unreferenced. We recommend including comparative safety data across ART modalities.	Thank you for your comment. OHSS was included as an outcome in this review, and it is noted in 'The outcomes that matter most' section of this evidence review that the committee prioritised the rate of OHSS as an important outcome as it is necessary when discussing and deciding on whether to undertake ovarian stimulation that risks are considered and weighed up against potential benefits. This outcome was chosen as the one most likely to be reported in relevant studies and therefore the best outcome to represent the safety of the interventions.

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North Middlesex University Hospitals; Trust	Evidence Review K	028		Table 4 - The Odds Ratio for IVF vs expectant management (OR 3.54, 95% CrI: 1.52–9.25) overlaps substantially with Gonadotropin + IUI (OR 2.02, 95% CrI: 0.93–4.39). This wide and overlapping credible interval undermines the conclusion that IVF is unequivocally superior. The statistical uncertainty should be explicitly acknowledged in the recommendation rationale.	Thank you for your comment. The 95% CrIs for gonadotrophin plus IUI versus expectant management cross the line of no effect, showing substantial imprecision in the effect estimate and introducing uncertainty to the intervention's effectiveness, as the 95% CrIs show the true effect of the intervention could be inferior to expectant management. On the other hand, while the 95% CrIs for IVF are wide, they do not cross the line of no effect and therefore consistently show a benefit of IVF over expectant management. The above is explicitly acknowledged in 'The committee's discussion and interpretation of the evidence' section of this evidence review (K): "The committee noted the very wide credible intervals for the odds ratios for assisted reproduction techniques relative to expectant management for all 3 NMAs undertaken for the live birth outcome which meant that conclusions about the relative treatment effect are very uncertain, reflecting the limitations and variation in the studies included in the NMA. Nevertheless, for the full population and mixed prognosis NMAs, the committee noted that IVF and gonadotropin or clomifene citrate plus IUI, had the highest odds ratios and were the only interventions

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					which had credible intervals that did not cross the line of no effect."
North Middlesex University Hospitals; Trust	Evidence Review K	030		Tabel 6 - Gonadotropin + IUI shows a statistically significant benefit for live birth (OR 2.27, 95% CrI: 1.09–4.79), yet is dismissed in favour of IVF. This dismissal is not supported by the evidence and should be reconsidered.	Thank you for your comment. Table 6 shows the results for participants with a mixed prognosis only. These data informed the relative treatment effects used in the health economic analysis. This analysis suggested that IVF was the most cost-effective treatment but there was also some evidence for the cost-effectiveness of Gn + IUI, which was included in the recommendations. The committee's use of the evidence to inform recommendations is detailed in 'The committee's discussion and interpretation of the evidence' section of this evidence review.
North Middlesex University Hospitals; Trust	Evidence Review K	033		The "mixed prognosis" group is highly heterogeneous, yet strong conclusions are drawn from it while the "poor prognosis" group is dismissed. A more nuanced stratification would improve clinical relevance.	Thank you for your comment. The recommendations were based on the best available evidence of clinical and cost-effectiveness. Of particular importance was an economic evaluation undertaken using the clinical evidence of relative treatment effect estimated from an NMA of live birth from the "mixed prognosis" subgroup.

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					The NMA of this sub-group was used to inform the economic analysis because studies without prognostic restriction best matched the population of interest for guideline recommendations (a separate economic analysis was used to inform access criteria for IVF). Heterogeneity in this sub-group was addressed by excluding those studies that selected on poor or intermediate prognosis. **As noted in Appendix M of Evidence Review K:** ***"The NMA for the live birth outcome in the mixed prognosis population included nine studies of seven treatments (Figure 66). There was no evidence of heterogeneity and so the results from the fixed effect NMA model are shown in Figure 67".***
North Middlesex University Hospitals; Trust	Evidence Review K	035		The committee places undue weight on ranking probabilities (e.g., IVF 46–80%) despite highly uncertain effect sizes. Ranking probabilities are unreliable when CrIs are wide, and should not drive strong recommendations.	Thank you for your comment. Recommendations were made after significant discussion and consideration of the evidence, including the limitations and uncertainties in the studies included in the network meta-analysis (NMA). Odds ratios and credible intervals were considered as well as ranking probabilities from both the full population and mixed prognosis NMAs, and the committee agreed the NMAs provided good evidence on the clinical effectiveness of

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					IVF and gonadotropin plus IUI even if the precise effect size was highly uncertain. The full rationale for recommendations made is provided in the committee's discussion and interpretation of the evidence' section of the review.
North Middlesex University Hospitals; Trust	Evidence Review K	047		Table 16 - The OR for multiple gestation with Gonadotropin + clomiphene citrate + IUI is 171.60 (95% CrI: 0.25–6,093,000), which is implausible and suggests model failure. This safety analysis should not inform recommendations. The guideline should clearly state that the NMA for multiple gestation is unreliable.	Thank you for your comment. Originally, it had been intended to use a network meta-analysis to estimate the baseline risk of multiple birth, however the data was particularly sparse and the limited trial data for multiples with expectant management were much higher than observed in practice and this led to unreliable estimates of relative treatment effect. The limitations of the multiple gestation NMA were noted and meant that it was not incorporated within the health economics model, and these results did not inform decision-making. This is explicitly stated in 'The committee's discussion and interpretation of the evidence' section of this evidence review: "Therefore, the committee did not think they could reasonably use the effectiveness data from the multiple birth pregnancy NMAs to inform recommendations."
North Middlesex University	Evidence Review K	052		The economic model's conclusion that IVF is cost-effective is highly sensitive to assumptions about baseline birth rate and utility gain. This fragility should be reflected	Thank you for this comment.

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Hospitals; Trust				in the recommendation wording, with IVF downgraded to a "consider" option.	NICE produces recommendations on the best available clinical and cost-effectiveness evidence. This suggested that IVF would be cost-effective as a first line treatment. Much of the literature considers that a QALY approach underestimates the benefits of live birth (e.g. Keller 2022, Skedgel 2023).
North Middlesex University Hospitals; Trust	Evidence Review K	052		The use of HUI-2 instead of NICE's preferred EQ-5D-3L for QALY estimation lacks justification. This deviation may distort cost-effectiveness conclusions and should be addressed in the methods section.	Thank you for this comment. We are not aware of any studies that have estimated QALYs from a live birth in a sub-fertile population using EQ-5D-3L. Our approach is described in Appendix I in the section titled "Health State Utilities and QALYs". Whilst that section refers to the previous guideline (CG156) to justify the use of HUI-12, we agree that this should be explained explicitly in the current guideline and have amended the text to that effect.
North Middlesex University Hospitals; Trust	Evidence Review K	052–056		The economic model omits long-term costs and burdens including emotional toll, time off work, cryopreservation logistics, and increased abnormalities in IVF/ICSI singleton babies. These should be factored into cost-effectiveness conclusions.	Thank you for this comment. Costing for the economic analysis was undertaken in line with the NICE Reference Case as described in Developing NICE guidelines: the manual (https://www.nice.org.uk/process/pmg20). As per the NICE Reference Case the analysis took an NHS and

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					PSS (Personal Social Services) perspective. This is also explained in Appendix I of Evidence Review K. The unit cost for IVF is based on one fresh and one frozen embryo transfer. It includes the cost of drugs, scans and all components of the service including freezing of gametes and embryos for 2 years from the point the woman is seen by the consultant to when she ends her NHS care, or when she is no longer entitled to NHS care. The model accounts for additional costs associated with multiple births, primarily due to increased prematurity. Higher complication rates for singleton IVF/ART births relative to births from spontaneous conception is debated. Sanders (2022) found no difference in singletons IVF, IUI, ovulation drugs when compared with no treatment in sub fertile women. Whereas Wu (2022) found that pregnancies conceived by ART have higher risks of adverse obstetric outcomes and vascular complications compared with spontaneous conception.

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					The issue is further complicated by some confounding with age and that some of the difference is likely explained by sub-fertility/underlying infertility. Sensitivity analysis was undertaken using a higher cost for IVF and this could be viewed as a proxy for any such long-term complication costs not taken into account in the base case analysis.
North Middlesex University Hospitals; Trust	Evidence Review L Intracytoplasmic sperm injection for non-male factor fertility problems Answer to Question 1			The main challenge will be changing entrenched practice in some clinics. Clear, unambiguous wording in the final recommendation will be key.	Thank you for this comment. As outlined in the section on 'Cost effectiveness and resource use' in the evidence review, the guideline committee agreed that the recommendations based on the evidence in this review are consistent with current NHS practice.
North Middlesex University Hospitals; Trust	Evidence Review L Intracytoplasmic sperm injection			Implementation will have significant POSITIVE cost implications. It will prevent use of a more expensive procedure (ICSI) where a cheaper, equally effective one (IVF) is available.	Thank you for this comment. That is correct. As outlined in the section 'Cost effectiveness and resource use' in the evidence review, recommendations will have no significant resource impact on the NHS.

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	for non-male factor fertility problems Answer to Question 2				
North Middlesex University Hospitals; Trust	Evidence Review L Intracytoplasmic sperm injection for non-male factor fertility problems Extended Recommendation			Where IVF itself is not clinically indicated—particularly in cases of unexplained infertility or mild ovulatory disorders—IUI should be considered as a first-line treatment. This aligns with the same principles: less invasive, lower cost, and comparable effectiveness in selected populations.	Thank you for this comment. Evidence review L focused on determining the clinical and cost effectiveness of ICSI compared to standard IVF in non-male factor fertility problems. The comparison of interest was ICSI versus standard IVF and not IUI.
North Middlesex University Hospitals; Trust	Evidence Review L Intracytoplasmic sperm injection	008	006–008	We strongly support the conclusion that there is "no clinically important difference between ICSI and c-IVF for any of the primary outcomes." This should form the bedrock of the final recommendation.	Thank you for this comment. The guideline committee did not make a specific recommendation about no important difference between ICSI and standard IVF, however in the 'Benefits and

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	for non-male factor fertility problems Summary of the Evidence				harms' section of the evidence review, they stressed that in most cases where infertility was not a result of male factor problems, people should not usually receive ICSI in addition to standard IVF. It is explicitly recommended that for non-male factor fertility problems ICSI should not be used if the semen parameters are normal.
North Middlesex University Hospitals; Trust	Evidence Review L Intracytoplasmic sperm injection for non-male factor fertility problems Outcomes that Matter Most	010	001–012	Live birth is the critical outcome. The highest-quality evidence shows no difference between ICSI and IVF, making routine use of ICSI unjustifiable.	Thank you for this comment. The guideline committee do not recommend routine use of ICSI in people with non-male factor fertility problems. It is explicitly recommended that for non-male factor fertility problems ICSI should not be used if the semen parameters are normal.
North Middlesex University	Evidence Review L Intracytoplasmic	010	031–038	The low-to-moderate evidence quality does not imply hidden benefit. The burden of proof lies with proponents of the more invasive and costly intervention.	Thank you for this comment. Based on the available evidence the guideline committee agreed that in cases where infertility was not

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Hospitals; Trust	sperm injection for non-male factor fertility problems Quality of the Evidence				a result of male factor problems, ICSI should not be given as an additional treatment to standard IVF.
North Middlesex University Hospitals; Trust	Evidence Review L Intracytoplasmic sperm injection for non-male factor fertility problems Benefits and Harms	011	009–015	Exceptions (e.g. failed fertilisation, PGT-M) are clinically justified. The recommendation should be framed as "Do not offer ICSI routinely," allowing for specific, evidence-based exceptions.	Thank you for this comment. The guideline committee explicitly recommended that for non-male factor fertility problems ICSI should not be used if the semen parameters are normal. They also recommended considering ICSI in some circumstances, e.g. if the partner with male reproductive organs has abnormal semen parameters or if a previous IVF treatment cycle has resulted in failed fertilisation/very low fertilisation rate. In the Benefits and harms section of the evidence report L, the committee explained in more detail 'some circumstances where ICSI might be indicated such as when a previous IVF treatment cycle has resulted in failed fertilisation or very low fertilisation rate as there

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					could be an undiagnosed sperm factor dysfunction; or when pre-implantation genetic testing is indicated for a monogenic disorder in order to prevent contamination from paternal genes'.
North Middlesex University Hospitals; Trust	Evidence Review L Intracytoplasmic sperm injection for non-male factor fertility problems Cost Effectiveness and Resource Use	011	017–024	With a unit cost ~£500 higher per cycle and no improvement in outcomes, routine ICSI represents unjustifiable NHS resource use.	Thank you for this comment. ICSI is not recommended for routine use, but a recommendation was made that allows ICSI to be considered in those with abnormal semen parameters or where previous IVF treatment has resulted in failed or very poor fertilisation. An explicit 'do not use ICSI' recommendation was made for people with normal semen parameters. In the Cost-effectiveness and Resource use section a single economic study is discussed. Although the study was only partially applicable to an NHS setting the committee agreed with the authors' conclusion that ICSI did not appear cost-effective.
North Middlesex University Hospitals; Trust	Evidence Review L Intracytoplasmic sperm injection	011	025–026	Aligning with this recommendation will likely free up resources by curbing unnecessary use of a more costly technology.	Thank you for this comment.

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	for non-male factor fertility problems Cost Effectiveness and Resource Use				
North Middlesex University Hospitals; Trust	Evidence Review L Intracytoplasmic sperm injection for non-male factor fertility problems Methods and Process	006–007	016–012	The committee's exclusion of sibling oocyte studies is methodologically sound. It prioritises robust patient-centred outcomes over intermediate lab metrics.	Thank you for this comment.
North Middlesex University	Evidence Review L Intracytoplasmic	010–011	039–8	Routine ICSI in non-male factor infertility increases cost and exposes oocytes to unnecessary intervention. This violates the principle of least invasive effective treatment.	Thank you for this comment. The guideline does not recommend routine ICSI in non-male factor infertility. Indeed, it is explicitly

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Hospitals; Trust	sperm injection for non-male factor fertility problems Benefits and Harms				recommended that it should not be used for people with normal semen parameters.
North Middlesex University Hospitals; Trust	Evidence Review S Sperm DNA fragmentation	017	030	Section 2 – The review dismisses antioxidants, sperm selection, and surgical retrieval due to "no consistent benefit." However, many RCTs were underpowered, heterogeneous, and used different assays (TUNEL, SCSA, SCD, Comet), making pooling inappropriate. Several trials showed signals of benefit (e.g., RR 2.45 for antioxidants). These should be considered hypothesis-generating, not ineffective.	Thank you for your comment. The evidence showed no clear benefit of treating sperm DNA fragmentation using antioxidants, sperm selection, or surgical sperm retrieval, with most studies reporting no benefit for the majority of outcomes. Therefore, the committee agreed that there was insufficient evidence to justify recommending antioxidants, sperm selection, or surgical sperm retrieval. The committee acknowledged the need for further research to identify and validate the best assay, define a threshold for high DNA fragmentation, clarify its association with subfertility and develop a standardised antioxidant and vitamin treatment and dose (particularly given the potential for unexpected adverse effects, as in Ménézo 2007). However, given all these unknowns, the committee agreed it would be premature to draft a fully

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					specified and implementable research recommendation that would be able to deliver conclusive results.
North Middlesex University Hospitals; Trust	Evidence Review S Sperm DNA fragmentation	020	018	Section 3 – The report equates "no clinically important difference" with "no effect." With small samples and wide confidence intervals, null findings may reflect type II error. NICE should revise its interpretation to "uncertain benefit" rather than "no benefit," especially in emerging fields.	Thank you for your comment. Our standard approach is to use the minimally important difference (MID) or minimal clinically important difference (MCID), where available, to assess the clinical importance of findings. Therefore, when there is no effect, we use terms such as 'no clinically important difference' or 'no evidence of clinically important difference'.
North Middlesex University Hospitals; Trust	Evidence Review S Sperm DNA fragmentation	027	006	Section 7 – The review notes lack of economic data and suggests SDF testing adds cost and delay. However, targeted use could reduce repeated failed IVF cycles, saving cost and emotional burden. NICE should not use absence of cost-effectiveness data as justification for dismissal.	Thank you for this comment. The committee were not persuaded that the link between SDF and subfertility is sufficiently well established for the targeted use proposed in the comment. Given the cost of the tests and absence of evidence of a clinical benefit, the committee recommended that SDF not be undertaken. The lack of cost-effectiveness data was secondary to the clinical evidence in informing the committee's recommendations.
North Middlesex University	Evidence Review U	007	012	The draft undermines male fertility diagnostics and stepwise care, contradicting HFEA guidance (2018, 2020,	Thank you for this comment.

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Hospitals; Trust				2025). We recommend aligning with HFEA to support less invasive pathways and male factor investigations.	It is not clear what specifically this comment relates to given the page and line numbers provided, and it is also not clear which specific HFEA guidance it refers to. The rationale behind the recommendations is outlined in detail in the Benefits and harms section of the evidence review.
North Middlesex University Hospitals; Trust	Guideline			The guideline should acknowledge the profound uncertainty in the evidence base, especially regarding comparative safety (e.g., OHSS, neonatal outcomes). This uncertainty should be made clear to clinicians and patients.	Thank you for your comment. The uncertainty in the evidence is documented in the evidence reviews and reflected in the strength of the recommendations.
North Middlesex University Hospitals; Trust	Guideline			The draft's language includes subjective phrases such as "the committee thought," which reflect opinion rather than evidence. We recommend removing subjective language and basing conclusions strictly on cited evidence.	Thank you for your comment. The recommendations are based on evidence (where such exists) but because clinical and cost-effectiveness evidence is rarely straight forward, the interpretation of the evidence is done by the committee. It is important we document the committee's deliberations and interpretations of the evidence underpinning the recommendations.
North Middlesex University Hospitals; Trust	Guideline			Historical context suggests IVF/ICSI dominance was driven by commercial interests rather than evidence (Bahadur et al., 2020). NICE should avoid restrictive policies in areas where evidence was suppressed.	Thank you for your comment. The new recommendations are based on the analysis and interpretation of the best available evidence.

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North Middlesex University Hospitals; Trust	Guideline			Question 1: Implementation of IVF-first recommendations will be challenging for underfunded regions and Integrated Care Boards (ICBs), with significant cost implications. IUI offers a more cost-effective and less invasive alternative. National alignment with ESHRE and HFEA would support equitable implementation.	Thank you for this comment. We recognise the difficult decisions ICBs must make on the allocation of scare resources, and the committee did discuss implementation. However, the committee considered that the recommendations they made were in line with the best available clinical and cost-effectiveness evidence. Our analysis did not suggest that IUI was a more cost-effective alternative.
North Middlesex University Hospitals; Trust	Guideline			NICE should consider a parallel recommendation: "Do not routinely offer IVF where IUI is clinically appropriate." This would reinforce a tiered approach to fertility care, reserving IVF for cases where simpler interventions have failed or are unsuitable.	Thank you for this comment. NICE produces recommendations on the best available clinical and cost-effectiveness evidence. This suggested that IVF would be cost-effective as a first line treatment.
North Middlesex University Hospitals; Trust	Guideline			Just as ICSI should not be used without clear indication, IVF should not be escalated prematurely. Offering IUI first respects patient autonomy, reduces physical and emotional burden, and optimises resource allocation.	Thank you for this comment. NICE produces recommendations on the best available clinical and cost-effectiveness evidence. Gn-IUI can be considered as a first-line treatment in the updated guideline.
North Middlesex University Hospitals; Trust	Guideline	005	012	Section 1 – The committee's rejection of SDF testing overlooks historical precedent. IVF, ICSI, and FER were introduced without RCT evidence due to clinical need and biological plausibility. Applying a higher evidentiary threshold to SDF is inconsistent with NICE's past	Thank you for your comment. Evidence Review S is a systematic review of randomised controlled trials and examines the effectiveness of treating DNA fragmentation, and

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				approach to innovation. NICE should acknowledge this precedent and adopt a proportionate stance.	subsequently whether testing is worthwhile. The guideline committee agreed that based on the evidence showing no clear benefits of treating sperm DNA fragmentation, there was no justification for routine testing of sperm DNA fragmentation. In other words, since treatment does not improve clinical outcomes, the DNA fragmentation test does not lead to any actionable steps. In addition, the committee were concerned that sperm DNA assays are expensive tests which can take weeks to get results for. Based on the potential advantages of saving lost time in time-sensitive fertility pathways, and without effective treatments to rationalise testing from a potential cost-saving perspective, the committee agreed that testing for sperm DNA integrity (fragmentation) should not be carried out.
North Middlesex University Hospitals; Trust	Guideline	011	008	Section 4 – The review prioritises live birth as the sole outcome, downplaying intermediate markers like reduced SDF%, improved blastocyst formation, and embryo quality. These outcomes are clinically relevant and consistently associated with miscarriage risk. NICE should acknowledge their value in informing treatment decisions.	Thank you for your comment. We are unclear what this comment is referring to but based on the page and line number, we think this is a comment on recommendation 1.13.1(Complementary therapy, page 11, line 8). Complementary therapy, such as herbal medicine and acupuncture, was not within the scope of this update. Evidence Review S examined the effect of antioxidants and lifestyle advice, which are sometimes regarded as

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					complementary therapy. The review considered the following outcomes, in addition to live birth: clinical pregnancy, miscarriage, pregnancy loss, embryo quality/grading and percentage of DNA fragmentation. The evidence showed no clear benefit of antioxidants, with most studies reporting no benefit for the majority of outcomes. No evidence was found for lifestyle advice. Therefore, the committee agreed that there was insufficient evidence to justify recommending antioxidants and lifestyle advice for these outcomes.
North Middlesex University Hospitals; Trust	Guideline	016	045	Section 1.3.4 – The economic model lacks transparency. Full model code, parameter distributions, and WinBUGS/CODA draws must be published to allow independent replication and scrutiny.	Thank you for this comment. Executable versions of the economic models were made available at consultation to all stakeholders on request. A full write-up of the original health economic analyses developed for this guideline are provided in Appendix I of Evidence Reviews J and K.
North Middlesex University Hospitals; Trust	Guideline	017	023	Section 1.3.5 – The model artificially bundles IUI with IVF, inflating IUI pathway costs. NICE must compare IUI-only vs IVF-only strategies using real-world data.	Thank you for this comment. It is not clear what this comment relates to, but we assume it is the strategies assessed in the economic analysis reported in Appendix I of Evidence Review K.

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					We do not think that the pathway approach is artificial. The 2013 guideline did not recommend IUI as a first line alternative to IVF. In this guideline update we aimed to assess whether this position was still supported based on the best available clinical and cost-effectiveness evidence. The pathway approach was considered to align with international guidance and practice (NICE 2013, ASRM 2020 and ESHRE 2023) and IUI has the potential to avert some of the costs of IVF as a cheaper first line alternative. The approach has also been used in the published literature (e.g. van Eekelen 2020). Therefore, the evaluated strategies (or pathways) were considered by the guideline committee to reflect the options that could be reasonably recommended if there was supporting clinical and cost-effectiveness evidence. In line with NICE methods on assessing the best available clinical evidence, an NMA was undertaken to pool direct and indirect evidence on ART. https://www.nice.org.uk/process/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869 "When multiple competing options are being appraised, network meta-analysis is the preferred approach to use"

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North Middlesex University Hospitals; Trust	Guideline	018	010	Rec 1.2.1 – The IVF-first recommendation contradicts ESHRE guidance (2020), which supports Gn-IUI as first-line for unexplained infertility. This risks making UK practice an outlier and undermines patient-centred care.	Thank you for this comment. NICE produces recommendations on the best available clinical and cost-effectiveness evidence. Gn-IUI can be considered as a first-line treatment in the updated guideline.
North Middlesex University Hospitals; Trust	Guideline	018	030	IVF cost modelling excludes cryopreservation, storage, and multiple FET cycles. These omissions understate the true cost of IVF and must be corrected using real-world data.	Thank you for this comment. The unit cost for IVF is based on one fresh and one frozen embryo transfer. It includes the cost of drugs, scans and all components of the service including freezing of gametes and embryos for 2 years from the point the woman is seen by the consultant to when she ends her NHS care, or when she is no longer entitled to NHS care. For costing purposes, we assume that all IVF cycles include one fresh and one frozen embryo transfer. This will over-estimate IVF costs where conception is achieved using a fresh embryo and underestimate costs where cycles involve more than one frozen embryo transfer. We believe it is a reasonable simplifying assumption that the underestimation and overestimation will broadly balance out. Sensitivity analysis assesses the impact of assuming lower/higher costs for IVF treatment.

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North Middlesex University Hospitals; Trust	Guideline	019	010	The model fails to distinguish between IVF and ICSI, despite their cost and clinical differences. NICE must disaggregate these procedures in both cost and effectiveness modelling.	Thank you for this comment. NICE does not recommend ICSI for most of the population covered by the economic analysis reported in Evidence Review K. Recommendation 1.50.3: Do not use ICSI for non-male factor fertility problems if the semen parameters are normal. [2026] The model population in Evidence Review K is described: *"The model setting was for the NHS and the population was people with unexplained health related fertility problems, mild endometriosis, and people with a single abnormal semen parameter"* (p117). Therefore, ICSI was not included as a treatment comparator in this analysis. For the model developed to determine cost-effective access criteria for NHS funded IVF treatment, IVF with ICSI was included as an alternative to IVF, but only in the case of male factor cause of sub-fertility. A different cost was used for IVF with ICSI compared to IVF alone (see Table 11). The IVF prediction models

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					included IVF with ICSI and therefore difference in cumulative live birth rates were estimated within the economic model.
North Middlesex University Hospitals; Trust	Guideline	020	005	The recommendation to bypass IUI risks worsening health inequalities, especially in underfunded regions. It reduces patient autonomy by removing the option of a graduated, less invasive pathway. We recommend retaining Gn-IUI as a first-line treatment to ensure equity.	Thank you for this comment. Gn-IUI was not recommended in the previous guideline, but it can now be considered as a first-line treatment in the updated guideline.
North Middlesex University Hospitals; Trust	Guideline	020	005	Cost data sourced via "personal communication with HFEA" lacks transparency and independence. NICE must publicly disclose this data and its assumptions.	Thank you for this comment. Cost data was not sourced from the HFEA, but we presume you are referring to *"2018-19 data from a personal communication with the HFEA was used to estimate the proportion of treatment cycles to attribute lower costs to arising from cancellation"* This data is 'disclosed' in Table 12 along with accompanying explanatory notes in Appendix I Evidence Review J, Table 12 and also in Table 49 in Appendix I Evidence Review K.
North Middlesex University Hospitals; Trust	Guideline	021	015	The use of QALYs to evaluate fertility treatments is conceptually invalid. NICE should report cost per live birth and cost per healthy child as co-primary outcomes.	Thank you for this comment. The limitations of QALYs in the context of fertility treatment is discussed in Appendix I of Evidence Review K.

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					"The use of QALYs is problematic in the assessment of fertility treatments (Keller 2022) and considerable uncertainty exists with regard to how a live birth should be valued, not least because the negative impact of infertility may impact on broader measures of well-being than health-related quality of life." However, notwithstanding these limitations, cost-effective allocation of finite NHS resources requires that a trade-off is made between the gains from expenditure on ART and its opportunity cost, in terms of the gains that would have accrued if this expenditure had been deployed elsewhere in the NHS. The use of QALYs facilitates such a trade-off whereas there is no established cost-effectiveness threshold (or "decision rule") to determine cost-effectiveness on a measure such as cost per live birth (or similar). For this reason the QALY is used in the NICE reference case to value health effects (see the NICE Guidelines Manual, https://www.nice.org.uk/process/pmg20/chapter/incorporating-economic-evaluation#the-reference-case)
North Middlesex	Guideline	022	020	The model's baseline spontaneous conception rate (van Eekelen) biases results. Alternate baselines (e.g.,	Thank you for this comment.

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University Hospitals; Trust				Bhattacharya) must be presented to show policy sensitivity.	Whilst we do not accept our use of the van Eekelen data biases results, we do acknowledge there is uncertainty with respect to this model input. Bhattacharya is used as an alternative source of baseline spontaneous conception leading to live birth data in several sensitivity analyses. This is described in Appendix I of Evidence Review (see for example p121 and p128).
North Middlesex University Hospitals; Trust	Guideline	023	010	The term "mild male factor" is undefined and clinically ambiguous. Recommendations must specify sperm parameters to ensure clarity and appropriate treatment pathways.	Thank you for this comment. The guideline committee discussed that there was no established definition for mild male factor. They agreed to remove the term mild male factor from the guideline recommendations as this is a poorly defined and unhelpful category.
North Middlesex University Hospitals; Trust	Guideline	024	005	The use of cumulative live birth rates across multiple cycles is misleading. Per-cycle success rates and dropout rates must be presented to reflect real patient experience.	Thank you for this comment. The stakeholder has not correctly referenced their comment in terms of guideline documentation, page and line number so it's not clear what they are referring to. We think they may be referring to Figure 2 in the main guideline document. This simply updates a figure from the previous guideline that was used to support a recommendation that us not being updated as part of

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					this update. However, since consultation, this figure has been further updated with more recent data from the HFEA dashboard.
North Middlesex University Hospitals; Trust	Guideline	025	015	The exclusion of valid clinical strategies (e.g., IUI→EM, EM→IUI→IVF) from the model due to committee preference limits patient choice and injects bias. NICE must broaden the decision space.	Thank you for this comment. This is discussed in Appendix I of Evidence Review K. The included strategies reflect international practice and guidance (ASRM 2020, NICE 2013, ESHRE 2023). Therefore, they were considered by the guideline committee to reflect the options that could be reasonably recommended if there was supporting clinical and cost-effectiveness evidence. For those with unexplained infertility, eligibility for NHS funded IVF requires that they have not conceived after 2 years of regular unprotected vaginal intercourse, with or without IUI. Therefore, expectant management can be deemed an entry criterion into the model for many of the people covered by the recommendations. The recommendations do not preclude a longer period of expectant management should that reflect patient choice.
North Middlesex	Guideline	026	020	The committee acknowledges uncertainty in the model but still makes strong recommendations for IVF. This	Thank you for this comment.

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University Hospitals; Trust				contradiction undermines the credibility of the guidance and calls for a downgrade to "consider."	We think this relates to Appendix K, although the stakeholder's signposting is unclear. Many similar comments have been made by this stakeholder but we note that recommendations are based on the best available clinical and cost-effectiveness evidence and that original health economic analysis undertaken for this guideline found IVF to be the most cost-effective intervention.
North Middlesex University Hospitals; Trust	Guideline	027	030	The socio-economic burden of IVF on patients (e.g., time off work, recovery, psychological toll) is ignored. These hidden costs must be modelled and acknowledged.	Thank you for this comment. Costing was undertaken in accordance with NICE methods as described in the NICE Guidelines Manual (https://www.nice.org.uk/process/pmg20/chapter/incorporating-economic-evaluation). This was also noted in the "Cost and resource use" section of the write-up of the economic analyses in Appendix I of Evidence Reviews J and K. Costing was undertaking using an NHS and personal social services perspective as per the NICE reference case.
North Middlesex University	Guideline	028	010	NICE's reliance on undisclosed HFEA cost data and the HFEA's dual role as regulator and fee recipient raises	Thank you for this comment.

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Hospitals; Trust				serious conflict of interest concerns. Full disclosure and mitigation strategies are required.	Cost data was not sourced from the HFEA but we presume this is referring to *"2018-19 data from a personal communication with the HFEA was used to estimate the proportion of treatment cycles to attribute lower costs to arising from cancellation".* This data is 'disclosed' in Table 12 along with accompanying explanatory notes in Appendix I Evidence Review J, Table 12 and again in Table 49 in Appendix I Evidence Review K.
North Middlesex University Hospitals; Trust	Guideline	029	005	NICE must disclose all financial and institutional interests of committee members involved in drafting the guideline and explain how conflicts were managed.	Thank you for your comment. The committee members' declared interests are documented in the Interests register, which has been available and updated throughout the development of the guideline. It is available on the published guideline's website under "History".
North Middlesex University Hospitals; Trust	Guideline	030	015	NICE's stance against IUI contradicts international best practices from ESHRE and ASRM. Recommendations must be realigned to reflect global consensus supporting IUI as a valid first-line treatment.	Thank you for this comment. Unlike previous NICE guidance, the updated guideline now recommends that up to 4 cycles of IUI with ovarian stimulation using gonadotrophins can be considered prior to IVF.
North Middlesex University	Guideline	031	020	The model's sensitivity to baseline spontaneous conception rates (e.g., van Eekelen vs Bhattacharya)	Thank you for this comment.

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Hospitals; Trust				materially affects policy conclusions. NICE must present a range of plausible baselines.	Van Eekelen was used to estimate the baseline spontaneous conception rate in the base case analysis based on expert committee opinion. This prediction model was developed in a cohort of 4,999 couples. Appendix I of Evidence Review J, presents several sensitivity analyses using data from the Bhattacharya study to estimate the baseline spontaneous conception rate. That was chosen as the only UK study with an expectant management arm in the NMA. Given the uncertainty around baseline spontaneous conception the committee thought there was sufficient cost-effectiveness evidence to support a weaker recommendation to offer gonadotropin plus IUI as a 1st line treatment followed by IVF if unsuccessful.
North Middlesex University Hospitals; Trust	Guideline	032	014	Section 6 – SDF is linked not only to fertility but also to miscarriage, adverse pregnancy outcomes, and possibly congenital abnormalities. NICE's stance risks missing opportunities to improve pregnancy safety. A more cautious, enabling approach is warranted.	Thank you for your comment. The guideline committee agreed that based on the evidence showing no clear benefits of treating sperm DNA fragmentation, there was no justification for routine testing of sperm DNA fragmentation and for treating sperm DNA fragmentation (Evidence Review S). In other words, since treatment does not improve clinical outcomes, the DNA fragmentation test does not lead to any actionable steps. In addition, the committee were

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					concerned that sperm DNA assays are expensive tests which can take weeks to get results for. Based on the potential advantages of saving lost time in time-sensitive fertility pathways, and without effective treatments to rationalise testing from a potential cost-saving perspective, the committee agreed that testing for sperm DNA integrity (fragmentation) should not be carried out. This recommendation reflects HFEA's position on unproven treatment add-ons. HFEA patient information states: *The results of a sperm DNA damage test are unlikely to impact on the management of your treatment.*
North Middlesex University Hospitals; Trust	Guideline	032	025	NICE must formally acknowledge the profound uncertainty in its own model and present both IVF and Gn+IUI as equally valid first-line options, allowing for patient-centred decision-making.	Thank you for this comment. NICE produces recommendations on the best available clinical and cost-effectiveness. The full economic analysis, reported in Appendix I of Evidence Review K, found that in most scenarios a strategy of IVF first-line was cost-effective relative to a strategy of Gn+IUI. (see Table 74). In the base case analysis, the IVF strategy had a 55% probability of being cost-effective compared to Gn+IUI with an 18% probability of being cost-effective.

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					However, as you note, there was some uncertainty within the model with Gn+IUI having improved cost-effectiveness under certain scenarios and assumptions. Therefore, the committee agreed that IUI using ovarian stimulation with gonadotropin could be considered as a treatment alternative to IVF, unlike previous NICE guidance.
North Middlesex University Hospitals; Trust	Guideline	036	002	Section 5 – The recommendation against all SDF testing contradicts NICE's own acknowledgement of observational data showing testicular sperm has lower fragmentation and positive antioxidant findings. A blanket rejection is inappropriate. NICE should allow selective use in recurrent implantation failure, unexplained infertility, or recurrent pregnancy loss.	Thank you for your comment. Please note that recurrent pregnancy loss is outside the scope of the guideline. The guideline committee agreed that based on the evidence showing no clear benefits of treating sperm DNA fragmentation, there was no justification for routine testing of sperm DNA fragmentation and for treating sperm DNA fragmentation (Evidence Review S). In other words, since treatment does not improve clinical outcomes, the DNA fragmentation test does not lead to any actionable steps. In addition, the committee were concerned that sperm DNA assays are expensive tests which can take weeks to get results for. Based on the potential advantages of saving lost time in time-sensitive fertility pathways, and without effective treatments to rationalise testing from a potential cost-saving perspective, the committee agreed that testing for sperm

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					DNA integrity (fragmentation) should not be carried out. The recommendation reflects HFEA's position on unproven treatment add-ons. HFEA patient information states: *'The results of a sperm DNA damage test are unlikely to impact on the management of your treatment.'*
North Middlesex University Hospitals; Trust	Guideline	041	003	Section 8 – NICE acknowledges the need for further research but fails to issue specific recommendations. This undermines progress. NICE should provide targeted guidance on standardising assays, thresholds, and trial design to resolve current uncertainties and avoid historical delays.	Thank you for this comment. It is not clear what specifically this comment relates to given the page and line number provided.
North Middlesex University Hospitals; Trust	Guideline	055		The guideline mentions declarations of interest but does not explain how conflicts were managed during development. Given the commercial stakes in ART, full transparency is essential to maintain trust.	Thank you for your comment. The committee members' declared interests are documented in the Interests register, which has been available and updated throughout the development of the guideline. It is available on the published guideline's website under "History".
North Middlesex University Hospitals; Trust	Guideline	059		The guideline's strong recommendation for IVF as first-line treatment may strain NHS capacity and reduce access to fertility care, worsening health inequalities. A more balanced approach is needed to preserve equitable access.	Thank you for this comment. NICE produces recommendations on the best available clinical and cost-effectiveness evidence. As per the previous NICE guideline it is recommended that 3 cycles of IVF are offered. The committee recognised that more

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					widespread implementation of this recommendation would have a resource impact. In addition, the revised guideline also recommends that 4 cycles of IUI with ovarian stimulation using gonadotropin can be considered.
North Middlesex University Hospitals; Trust	Guideline	060		The draft leans toward a one-size-fits-all approach, underemphasizing shared decision-making. Many patients may prefer less invasive options like IUI. The guideline should explicitly support shared decision-making and patient choice.	Thank you for this comment. The guideline recommends that treatment options are discussed, including the benefits, risks and their individual preferences. Following those discussions, up to 4 cycles of IUI with ovarian stimulation using gonadotrophins can be considered prior to IVF. In the rationale for their recommendation; "The committee acknowledged that some people may prefer the less invasive treatment of IUI to IVF."
North Middlesex University Hospitals; Trust	Guideline	090		Appendix M - Threshold analysis shows that small changes in individual study estimates can alter the ranking of treatments. This model instability should be explicitly acknowledged in the guideline and used to temper the strength of recommendations.	Thank you for this comment. It is correct that the threshold analysis shows that treatment effectiveness would be sensitive to small changes in the Goverde study, this reflects that this study contributed a large proportion of IVF participants within the study.

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					However, the threshold analysis showed that for 11 of the 12 studies that contributed to the mixed prognosis live birth network meta-analysis (the NMA utilised within the economic model), the confidence intervals lied comfortably within the invariant threshold. This implies that the finding that IVF was the most cost-effective treatment was not sensitive to changes in these 11 studies. Whilst we recognise that estimates of clinical and cost-effectiveness are characterised by some uncertainty, but we do not accept that the model had instability. Furthermore, the uncertainty within the trial data is addressed by undertaking probabilistic sensitivity analysis. As a result of this uncertainty the committee agreed that IUI using ovarian stimulation with gonadotropin could be considered as a treatment alternative to IVF, unlike previous NICE guidance.
North Middlesex University Hospitals; Trust	Guideline Implementation Challenge			Clinics may be incentivised to escalate to IVF prematurely. NICE should support implementation through audit tools, commissioning guidance, and patient education materials that reinforce the value of IUI in appropriate cases.	Thank you for this comment. NICE does produce tools to support implementation of its guidance (https://www.nice.org.uk/implementing-nice-guidance), but the main role of the guideline developers

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					is to produce recommendations on the best available evidence of clinical and cost-effectiveness. The updated guideline now allows IUI to be considered as a first line alternative to IVF and therefore we think that, if anything, any incentive to escalate IVF is reduced.
NUH Life Fertility Services, part of Nottingham University Hospitals NHS Trust	Guideline	012	013	1.2.29 We are supportive of this amendment and strongly feel it is in the best interests of patients. In our experience patients and GPs are unsure what to do when patients who have experienced miscarriage or ectopic pregnancy in their period of trying to conceive, and having to "restart the clock" is extremely difficult for patients to bear.	Thank you for this comment. Please note that based on stakeholder feedback, the committee agreed to include ectopic pregnancy in this recommendation, in addition to miscarriage.
NUH Life Fertility Services, part of Nottingham University Hospitals NHS Trust	Guideline	021	005	1.4 It is excellent to see the section on male factor fertility has been expanded and updated for this version, and we support the recommendations made.	Thank you for this comment.
NUH Life Fertility Services, part of Nottingham University	Guideline	030	012	1.8.3 We are pleased to see the return of stimulated IUI as a treatment option for couples with unexplained fertility problems, mild endometriosis or mild male factor. Our unpublished data from NUH Life patients supports the use of stimulated IUI as a cost-effective first line fertility	Thank you for your comment in support of this guideline recommendation.

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Hospitals NHS Trust				treatment in this group of patients (aged 39 and under), as well as offering patient choice, and exploring less invasive and lower risk treatment options before moving on to IVF. We have previously submitted our cost-effectiveness data to the East Midlands ICBs to help inform their funding policy review.	
NUH Life Fertility Services, part of Nottingham University Hospitals NHS Trust	Guideline	038	003	1.11 We strongly support these additional guidelines around the use of ICSI	Thank you for this comment.
NUH Life Fertility Services, part of Nottingham University Hospitals NHS Trust	Guideline	039	008	1.12.1 Is there a typo in this line? Should it say "severe reduction in semen quality"?	Thank you for your comment. This has been corrected to "severe deficits".
NUH Life Fertility Services, part of Nottingham University	Guideline	042	023	1.14.7 We support the recommendation of continued storage for people who remain at risk of infertility.	Thank you for your comment.

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Progress Educational Trust	Guideline	005	025	**Rec 1.1.5** Please can the wording 'peer group or other relevant organisation for support' be amended to 'relevant support group'. A growing number of individuals and organisations now offer peer support for a fee, and are liable to exploit the proposed wording for promotional purposes.	Thank you for this comment. Based on stakeholder feedback, the committee agreed to remove 'peer group' from the recommendation, only referring to 'relevant organisation for support'.
Progress Educational Trust	Guideline	008	004	**Rec 1.2.4** We note that data from the HFEA is from 2015-2019, and that 2019 data is described as preliminary. Is there more recent and more robust data that you could use?	Thank you for your comment. Table 2, which your comment refers to, has been updated in terms of cumulative probability of clinical pregnancy through 6/12 cycles of IUI based on more up to date data from HFEA dashboard (data from 1991 to 2023, however, data from 2020 to 2023 is preliminary).
Progress Educational Trust	Guideline	010	016	**Rec 1.2.17** When a specific BMI is presented as a threshold beneath which patients should be advised to increase their body weight, if menstruation is irregular or absent, this is	Thank you for your comment. Recommendation 1.9.4 was not within the scope of this guideline update to review new evidence for. We don't disagree with your comment, but this would be outside of the remit of this guideline to address. However, we expect health care professionals to use their clinical and professional

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				appropriate only in the context of additional consideration and support. Specifically, it should be considered that there may be another underlying cause for the irregular or absent menstruation (and that this may warrant investigation), and that the patient may need specialist support in order to help them gain weight.	judgment in their practice to consider potentially underlying causes or other considerations relevant to the clinical scenario.
Progress Educational Trust	Guideline	012	009	**Rec 1.2.28** This section is predicated on the assumption that people will self-fund treatment in a licensed clinic. However, many people do not take this course of action, but use sperm donors they meet online. These donors will not have been screened for sexually transmitted infections, and will not have had their family history taken by a medical professional. Sometimes, people who choose this route find that the donor demands sexual intercourse. This recommendation encourages patients to use donors outside clinics which poses a risk to their health and safety.	Thank you for your comment. The committee acknowledged that due to the costs of donor insemination and people needing to self-fund, people may end up using unregulated donor insemination which can be unsafe. Therefore, they made a recommendation to advise people who are thinking about using donor sperm to conceive to have treatment in a licensed fertility clinic to ensure clinical safety and legal parenthood. See recommendation 1.1.4 and associated short explanation of why the committee made the 2026 recommendation and how it might affect practice.

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				If women have to self-fund intrauterine insemination, they should nonetheless receive NHS-funded care – for example tests, drugs and advice – which will optimise their chances of success. They should also be given advice about how to stay safe when seeking intrauterine insemination.	
Progress Educational Trust	Guideline	012	013	**Rec 1.2.29** The addition of this recommendation is welcome, as some commissioners have been restarting the clock each time there is a miscarriage, which then delays investigation of possible infertility. We hope that this change will prevent that bad practice.	Thank you for this comment.
Progress Educational Trust	Guideline	014	027	**Rec 1.3.10** For clarity, please include a definition of what constitutes 'a very low sperm count'.	Thank you for this comment. The committee agreed to amend the recommendation and now it refers to people who have a persistent sperm concentration of less than 5 million per ml.
Progress Educational Trust	Guideline	029	018	**Rec 1.7.2**	Thank you for this comment.

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				It is not necessarily good medical practice to offer six cycles of intrauterine insemination when six rounds of donor insemination have failed. It may not be what a medical professional would advise, particularly when the patient's age is taken into consideration. There is a cost attached to the use of donor sperm, and donor sperm is not in plentiful supply. In light of these facts, it may not make sense to continue to use donor sperm without an investigation.	This recommendation has been clarified that further 6 cycles of unstimulated donor IUI should be offered (after the initial 6 cycles) if there are no contraindications and no suspected or known clinical cause of infertility.
Progress Educational Trust	Guideline	031	028	**Rec 1.9.5** The wording of the recommendation 'consider up to 3 further full cycles of IVF treatment' is bitterly disappointing. Our charity, the Progress Educational Trust, has campaigned for many years to improve access to NHS-funded fertility treatment. We were looking forward to a long overdue increase in the number of full cycles of NHS-funded treatment recommended by NICE. Asking ICBs to 'consider' offering a further three cycles is risible. Since NICE published the first version of its	Thank you for this comment. NICE produces recommendations on the best available clinical and cost-effectiveness evidence. As per the previous NICE guideline it is recommended that 3 cycles are offered. The committee considered that the evidence for this recommendation was even better supported this time. However, a weaker recommendation was made to consider an additional 3 cycles of IVF in those who have not achieved a live birth in previous attempts. This reflected that the evidence for cost-effectiveness evidence supporting these additional cycles was subject to greater uncertainty.

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				Guideline in 2004, the majority of commissioning bodies have not implemented the recommendation to fund three full cycles of IVF. Since the majority of ICBs are already flaunting the NICE Guideline, there is zero reason to believe that they would be moved by something framed as a matter for mere consideration. Furthermore, other than specifying that the patient should be under 40 years of age, there is no guidance as to circumstances in which ICBs should 'consider up to 3 further full cycles of IVF treatment'.	This is explained in the guideline *"The analysis suggested that up to 6 cycles could be cost effective using a threshold of £20,000 per QALY; however, there were some uncertainties in the evidence, particularly for cycles 4 to 6. These uncertainties related to concerns about increasing selection bias in the datasets informing the prediction models and the very small numbers of women in these datasets having 4 or more cycles, resulting in considerable sampling uncertainty around the point estimates for predicted live birth rates for these higher order IVF cycles. The committee agreed that the evidence was not sufficiently robust to justify increasing the number of cycles initially being offered, because of its potentially significant resource impact, but agreed that further cycles, beyond the initial 3, could be considered"* We additionally refer you to the wording of recommendations in the NICE Guidelines Manual (https://www.nice.org.uk/process/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869) – see section 9.3 **Reflect the strength of the recommendation:**

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					In 'strong' recommendations (see the section on strength or recommendations) for actions that should (or should not) be offered, use directive language such as 'offer' (or 'do not offer'), 'advise', or 'ask about'. In keeping with the principles of shared decision making, people may choose whether or not to accept what they are offered or advised. *If there is a closer balance between benefits and harms (activities or interventions that could be used), use 'consider' reflecting that the recommendation is 'weak'* The guideline developers did not want to provide prescriptive criteria for what is a weaker "consider" recommendation. However, the recommendation to consider a further 3 full cycles of IVF, also states that any consideration of further cycles should include a discussion of the probability of success and the implications of further treatment.
Progress Educational Trust	Guideline	032	002	**Rec 1.9.6** The wording of this recommendation is very unclear.	Thank you for this comment. The wording of this recommendation has been revised to make it clearer although your interpretation in the comment is correct.

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				Is it intended to mean that if a patient has previously received a self- or NHS-funded cycle of IVF, then that cycle would be deducted from the amount of NHS-funded IVF that an ICB would provide? If so, then given that most ICBs only offer one cycle of NHS-funded IVF, this would preclude most people from accessing NHS treatment. Furthermore, how is this recommendation to be interpreted where an ICB funds (or has previously funded) only a partial cycle (for example, one round of stimulation and one fresh and one frozen transfer)?	Based on the best available clinical and cost-effectiveness evidence NICE recommends that 3 cycles of IVF of offered. We recognise that ICBs have to make difficult decisions and NICE cannot enforce implementation of its guidance or ensure that recommendations are interpreted as intended.
Progress Educational Trust	Guideline	032	003	**Rec 1.9.6** Previously self-funded cycles of IVF should not be counted when a patient is being considered for NHS-funded treatment. This is wrong on general principle, and also because it could result in a perverse incentive for patients to lie about treatment they have received in the private sector. This in turn could obscure parts of their medical history that might be relevant to their current treatment. People often resort to self-funded treatment either because they cannot access NHS-funded treatment at all,	Thank you for this comment. In this guideline, previous cycles, irrespective of how they are funded, are counted as they are a prognostic marker. The prediction model used to inform the economic analysis suggested that previous unsuccessful IVF cycles were associated with a lower probability of success (even after allowing for the possibility of selection bias). Such a "depletion of susceptibles" effect would be expected unless a successful IVF outcome was completely random. So, for example, the ovarian reserve in a population who had not had successful live birth from previous IVF cycles

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				or because they cannot access NHS-funded treatment in a timely way. If their local ICB were to changes its policy, thereby enabling them to access NHS-funded treatment, why should they be penalised for having previously had to resort to self-funded treatment?	would on average be lower than a treatment naive population. Therefore, clinical and cost-effectiveness depend on previous cycles of IVF.
Progress Educational Trust	Guideline	032	005	**Rec 1.9.7** This is a lamentable reduction in NHS-funded provision. It is disappointing that the use of donor eggs has not been recommended, or seemingly even considered, for these patients. If egg donation were to be recommended, then the age limit would not need to be lowered. Egg donation is a safe and cost-effective way to treat many women aged 40 or older.	Thank you for your comment. NICE produces recommendations on the best available clinical and cost-effectiveness. The economic analysis reported in full in Appendix I of Evidence Review J did not find good evidence that IVF was cost-effective in those aged 42 years. Recommendations for IVF provision for those aged 40-41 years is unchanged from the previous guideline. Evidence on IVF using donor eggs was not reviewed for this guideline update and has not been commented on. Please note, NICE welcomes topic suggestions from stakeholders which will be considered for NICE topic prioritisation process: Topic suggestion | NICE.
Progress Educational Trust	Guideline	036	008	**Rec 1.10.24** This blanket statement relating to PGT-A is not aligned with information on add-ons from the statutory regulator of	Thank you for your comment. While the HFEA gave PGT-A a green rating for reducing the chances of miscarriage for most fertility patients, they also stated that reducing the chance of miscarriage

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				fertility treatment, the Human Fertilisation and Embryology Authority (HFEA). At https://www.hfea.gov.uk/treatments/treatment-add-ons/pre-implantation-genetic-testing-for-aneuploidy-pgt-a/ the HFEA says that PGT-A is 'Rated green for reducing the chances of miscarriage for most fertility patients', and says that 'findings from high quality evidence shows this add-on is effective at reducing the chances of miscarriage for most fertility patients'. Given the contrast between this statement from the regulator and the wording employed here by NICE, how are commissioners and patients supposed to understand whether or not this is a treatment they should pay for?	still might not translate to an increased chance of having a baby due to the evidence showing no benefit of PGT-A for live birth rates as well as the potential risks associated with PGT-A, as noted in evidence review N and on the HFEA's website. An additional risk of PGT-A is that it often reduces the number of embryos with the potential to result in a healthy live birth available for transfer, therefore lowering the likelihood of a fertility patient undergoing embryo transfer at all, as well as their chances of having a baby. Additionally, although the point estimate reported in the studies considered by the HFEA favoured PGT-A in terms of reducing miscarriage, the 95% confidence intervals all crossed the line of no effect, which would usually (according to standard NICE methodology) be interpreted as showing no important difference between interventions for the outcome miscarriage rates. The Cochrane review also concluded that it is uncertain whether PGT-A with blastocyst-stage biopsy improves miscarriage rate. The committee agreed that the available evidence showed uncertainty regarding PGT-A's effect on miscarriage rates, but were aware of emerging evidence that was published too recently to be included in either of the considered reviews which could show a benefit of PGT-A in terms of reducing

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					miscarriage rates. The recommendation on PGT-A has therefore been amended to the following: "Do not offer pre-implantation genetic testing for aneuploidy (PGT-A) as part of fertility treatment to improve live birth rates." This reflects the fact that the evidence does not show effectiveness of PGT-A in terms of improving live birth rates, while leaving room for other clinical reasons PGT-A might be considered.

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Progress Educational Trust	Guideline	General	General	Although reference is made in the draft guideline to 'trans men' and to 'non-binary people with female reproductive organs', and although certain parts of the draft guideline are potentially relevant to same-sex female couples and to single people, there is no reference in the draft guideline to same-sex male couples or to surrogacy. A decision was clearly made at the outset to exclude certain patient groups and treatment scenarios from the scope of the guideline, and this decision was wrong. Are same-sex male couples not as worthy of being served by the fertility guideline as everyone else? This failure makes the guideline out of date before it has even been published.	Thank you for your comment. The scope of the guideline, consulted on and published in 2022, defined the guideline's population remit as: "**Groups that will be covered in the update** • People with health-related fertility problems • People who may require interventions to preserve fertility because of high risk of fertility problems due to clinical conditions or medical or surgical interventions In this guideline, people with health-related fertility problems are those who have a known health-related impediment to fertility, or those who do not achieve a pregnancy: • after 12 months of regular unprotected sexual intercourse or • after 6 cycles of artificial insemination. The guideline will be applicable to all people seeking assessment and treatment of health-related fertility problems who meet these criteria, irrespective of their sexual orientation, partnership status or gender reassignment. This includes single people, people in heterosexual relationships, people in same sex

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					relationships, people who are non-binary, undergoing or have undergone gender transition and people using a surrogate." The scope also defined the topic areas to be updated and you're correct that not all treatment scenarios were included. The key issue to bear in mind is that the guideline only covers assessment and treatment for health-related fertility problems and as such does not exclude people based on their sexual orientation or relationship status and the guideline's recommendations do not determine treatments based on the person's sexual orientation or relationship status.
Progress Educational Trust	Guideline	General	General	Why was so much time and attention focused on IVF add-ons, in communications and publicity concerning the draft guideline and the accompanying consultation? Out understanding is that IVF add-ons are very seldom used in the NHS, and so the opinion of NICE on these add-ons was of limited relevance to this guideline and its usefulness.	Thank you for your comment. NICE is aware of growing usage of IVF add-on treatments whereby patients are increasingly self-funding these interventions that do not have explicit NICE guidance on their use. When the scope of the guideline update was developed and consulted on in 2022, it was agreed that it was important to review the evidence for their effectiveness in order to make evidence-based recommendations, so patient users of

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					this guideline as well as clinicians can make informed decisions.
Progress Educational Trust	Guideline	General	General	The term 'spontaneous' and variations thereof are used 24 times in the draft guideline, usually in relation to 'spontaneous conception'. We question the appropriateness of this, and think that it may cause confusion and be lead to misinterpretation. In some instances, the term 'natural conception' would be more appropriate – for example, where the draft guideline states 'However, the chances of a live birth both by spontaneous conception and by using assisted reproductive technology decline with advancing age because of decreasing ovarian reserve' (p47, line 12). In other instances – such as where the guideline states 'they have not spontaneously conceived after 12 cycles of artificial insemination' (p31, line 18) – the word 'spontaneously' can simply be removed altogether.	Thank you for this comment. The guideline committee discussed the terms 'spontaneous' and 'natural' and other options but agreed that spontaneous conception or pregnancy was their preferred term for this guideline. The committee did not want to use the term 'natural' because it would imply other ways of conceiving would be 'unnatural'. We have removed the word 'spontaneous' from the recommendation where it was referring to artificial insemination, this was an error. The term 'spontaneous conception' has been added to the Terms used in this guideline.
Progress Educational Trust	Guideline	General	General	The press release which was issued by NICE to launch this consultation – see https://www.nice.org.uk/news/articles/fertility-clinics-must-end-unproven-treatments-that-don-t-help-couples-have-	Thank you for your comment. While NICE makes recommendations based on the best available evidence on cost-effectiveness, we acknowledge that decisions about commissioning and

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				babies – undermined the guidance in advance in the most appalling way. Professor Jonathan Benger, Chief Medical Officer and Interim Director of the Centre for Guidelines at NICE, was quoted in the press release saying: 'We recognise the NHS faces significant financial challenges, and integrated care boards must weigh up local priorities when determining how many IVF cycles to fund.' This provides commissioners with the perfect excuse to ignore the Guideline once it has been finalised and published by NICE. It has been more than 20 years since NICE published the first version of its fertility guideline, during which time the guideline has never been implemented in full in England. In the past, NICE has issued robust statements to try to ameliorate this situation. By contrast, Professor Benger's statement actually has the potential to make the access to NHS-funded fertility worse for patients, rather than improving it. When you publish the final version of your guideline, please take this point into consideration. Be more positive and assertive in your general communications, and in your dealings with ICBs. This is the least that fertility	funding are made at the local level. The recommendation about offering initial 3 cycles is based on evidence that showed it to be cost-effective. In fact, we state in the guideline that the evidence for this recommendation is now stronger than before. However, the evidence on any further cycles is more uncertain and this is reflected in the recommendation to 'consider' these.

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				patients should be able to expect of an organisation with the phrase 'Health and Care Excellence' in its name.	
Queen Mary University of London (QMUL),	Guideline	036	007-009	**Comment on Embryo Selection Strategies in IVF** We are concerned that the absence of a clear recommendation on the use of time-lapse imaging may inadvertently contribute to potentially misleading representations of its benefits to patients. Evidence from Perrotta et al. (2024) indicates that time-lapse is frequently advertised as a tool to improve clinical outcomes, despite the lack of supporting evidence. We would therefore welcome a recommendation that explicitly clarifies the position outlined on page 67 of the guideline document. While time-lapse imaging should not be offered to improve ongoing pregnancy, clinical pregnancy, or live birth rates, it may have value in supporting undisturbed embryo incubation and in research contexts. Perrotta, M., Zampino, L., Geampana, A., & Bhide, P. (2024). Analysing adherence to guidelines for time-lapse imaging information on UK fertility clinic websites. *Human Fertility*, *27*(1). https://doi.org/10.1080/14647273.2024.2346595	Thank you for your comment. The decision not to make a recommendation on the use of time-lapse imaging reflected the committee's consideration of the lack of evidence of their effectiveness in terms of ART outcomes, balanced against the potential for future health technology developments using these systems, the possible benefits of an undisturbed incubation environment (such as the reduced likelihood of human error), and the low financial risk to patients because most institutions no longer usually charge for the use of time-lapse incubation in current practice, compared to the potential cost and resource implication of recommending against their use.

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Queen Mary University of London (QMUL),	Guideline	066	025	The document states that "Evidence on the effect of PGT-A on miscarriage is also uncertain." This statement contradicts the current assessment of the Human Fertilisation and Embryology Authority (HFEA) rating system, which rates PGT-A *green* for reducing the chances of miscarriage for most fertility patients. Such inconsistency risks creating confusion for patients, who may encounter conflicting information across sources. It would be crucial for this discrepancy to be addressed to ensure consistency between NICE guidelines and the HFEA's public information.	Thank you for your comment. The text you're referring to has been amended to "Emerging evidence shows a potential benefit of PGT-A in terms of reducing miscarriage; however, this did not translate to improved pregnancy and live birth rates." The recommendation on PGT-A has been amended to the following: "Do not offer pre-implantation genetic testing for aneuploidy (PGT-A) as part of fertility treatment to improve live birth rates." This reflects the fact that the evidence does not show effectiveness of PGT-A in terms of improving live birth rates, while leaving room for other clinical reasons PGT-A might be considered.
RCN	Guideline	General	General	The Royal College of Nursing invited members who care for people with fertility issues. The comments below reflect the views of our reviewers.	Thank you for the comments.
RCN	Guideline	General	General	The updates are comprehensive and there is not much to be added overall.	Thank you for your comment.
RCN	Guideline	General	General	The following comments are suggested to enhance the guidelines: • Possibly including a note about weight loss medication, particularly the importance of stopping at least three months prior to conception.	Thank you for this comment. Advice on weight loss medication, Vitamin D and or lifestyle advice was not within the scope of this guideline update so no evidence on this was reviewed. However, the guideline committee agreed to amend the recommendation on prescribed, over-the-counter and

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				• We are surprised that there is nothing in the guidelines about Vitamin D – it might be useful to consider this. • A mention that lifestyle information should ideally be given at the earliest opportunity as it could also strengthen the guidance, though we know that is one of the aims of the pre-conception document.	recreational drug use by including drugs such as GLP-1 agonists.
RCN	Guideline	General	General	We have a few comments about the numbers of cycles of donor insemination and when to test tubal patency which we are aware are done differently in Scotland. As NICE guidelines can be adapted / adopted by Scottish Intercollegiate Guidelines Network (SIGN) guidance for use in Scotland, we would support the points made above	Thank you for this comment. New evidence on the number of cycles for donor insemination was not reviewed by the committee for this update as it was not in the scope but recommendations on IUI have been amended for clarity.
RCN	Guideline	General	General	We are glad to see ovarian reserve being considered. Overall, it is a great document, and it has been good to revisit the current guidelines.	Thank you for your comment.
Royal College of General Practitioners	Guideline	General		We note an absence of guidance for fertility services on managing fertility in trans men and trans women who are taking gender-affirming hormone therapy. We would like to see clear, evidence-based guidance addressing fertility preservation, assessment, and treatment options for transgender patients - or, if robust evidence is lacking, an explicit recommendation that research be commissioned to fill this	Thank you for your comment. The guideline section on fertility preservation now includes fertility preservation for medical indications, including people preparing for treatments that may impair their fertility. This could include people preparing for gender-reaffirming treatments, such as hormone therapies. The evidence review found some evidence

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				gap.	among trans people, this is documented in evidence review R.
Royal College of General Practitioners	Guideline	006		1.2.2 - We do not recommend including exact percentage figures in this case. These figures will not apply universally and are likely to vary significantly over time. They will also differ considerably depending on individual factors such as age - for example, outcomes for a woman aged 22 will differ greatly from those for a woman aged 39. Presenting fixed percentages risks oversimplifying complex, variable data and may become outdated quickly.	Thank you for your comment. This recommendation is in a section that was not part of the current update and we have kept it as it was, apart from updating the percentage figures with more recent figures from HFEA. These figures give a population-level idea of what the chance of pregnancy is. The updated table 2 in the guideline gives further detail by age and we have added a reference to the table from the recommendation.
Royal College of General Practitioners	Guideline	010		1.2.19 - We suggest amending the guidance to clarify the source of occupational health advice. The current wording - "and if necessary, direct them to appropriate advice" - could be misinterpreted as implying an NHS or GP referral route. We recommend revising this to: "and if necessary, direct them to their employer's occupational health scheme for appropriate advice." This would make it clear that occupational health support is the responsibility of the employer, not the NHS	Thank you for this comment. This recommendation has been amended by adding an example of 'workplace occupational health team'.
Royal College of General Practitioners	Guideline	012		1.2.29 - We were pleased to see the inclusion of clear guidance for GPs regarding the timing of referral	Thank you for your comment.

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				following miscarriage. This clarity will support more consistent and timely management of patients experiencing fertility problems.	
Royal College of General Practitioners	Guideline	012		1.2.30 - We agree that earlier referral is appropriate for individuals aged 36 years or over, or where there is a known or suspected cause of infertility. However, the guidance would benefit from greater clarity around what is meant by "earlier" referral. Specifying a timeframe (for example, referral after a defined period of trying to conceive) would support consistency in GP decision-making and prevent unnecessary variation or premature referrals.	Thank you for this comment. The committee considered your and other stakeholders' comments on this issue and agreed to amend the recommendation by replacing 'an earlier referral' with 'referral at presentation'.
Royal College of General Practitioners	Guideline	020		1.3.39 - We agree that assessment of rubella immunity is an important component of fertility care. In our experience, fertility clinics routinely require rubella serology before accepting referrals, which is appropriate given that many individuals are uncertain of their vaccination history and some may not have developed immunity despite vaccination. Ensuring universal screening would minimise the risk of congenital rubella, which remains an entirely preventable cause of harm.	Thank you for this comment.
Royal College of General Practitioners	Guideline	031		1.9.3/4 We note an inconsistency in the proposed guidance regarding age criteria for IVF access. As written, a	Thank you for this comment.

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				first cycle may be offered to individuals up to age 42, but those who begin treatment before 40 are not eligible for further cycles once they reach their 40th birthday. This appears inequitable and may disadvantage individuals whose treatment spans their 40th birthday. We suggest that the guidance be reviewed to ensure consistency and fairness in access to IVF funding and treatment across the full eligible age range.	Age cut-offs in the guideline recommendations are based on the best available clinical and cost-effectiveness evidence. We do not agree that there is an inconsistency with the guidance as written. Up to 3 cycles are offered providing the age at starting a given cycle is less than 40 years. A 2nd or 3rd cycle of IVF is not offered if the age at starting the treatment cycle would be 40 or 41 years. This reflects that both age and previous IVF attempts without a live birth are both predictors of treatment effectiveness (and cost-effectiveness). It is intentional not to offer further cycles after an individual reaches age 40 (and they will have had the same 1 cycle as people eligible for 1 cycle at age 40 and 41 years).
Scottish Government	Guideline	General	General	Scottish Government would like to register our disappointment that the following information has been removed from the guideline: *1.10.4.1* *Women should be informed that female BMI should ideally be in the range 19 to 30 before commencing assisted reproduction, and that a female BMI outside this*	Thank you for this comment. This recommendation was based on an old evidence review which was not updated and the committee thought it was not particularly useful and has been used to deny treatment even though BMI has not been an access criterion for IVF treatment in the guideline. The committee agreed that BMI advice should focus on health optimisation rather than being used as a strict

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				range is likely to reduce the success of assisted reproduction procedures. and that there is now no information contained in the guideline in regard to how BMI can affect fertility treatment or how BMI can affect the safety of treatment for the patient. We feel that this is a gap in the information being provided and would like something around this to be considered for addition to the guideline before it is finalised and published.	eligibility criterion. General advice around BMI and fertility covered in the section on 'Initial advice' was thought to be sufficient.
The Fertility Alliance	Guideline - IVF Access	046	020	We support NICE's recognition that up to six IVF cycles may be clinically and economically justified, and that self-funded treatment should not exclude people from NHS-funded care. These are positive developments that better reflect real patient experience and align with current cost-effectiveness evidence. NICE Guidelines are evidenced based, therefore leaving the decision to "consider up to three further cycles" allows local Integrated Care Boards (ICBs) to interpret the guidance differently. **Suggested amendment:**	Thank you for this comment. We are glad that you support changes to the NICE guidelines on access to IVF on the NHS, which are based on the best available evidence on clinical and cost-effectiveness. However, the recommendation to "consider" an additional 3 cycles of IVF reflects that the evidence in support of this recommendation is weaker. See Appendix I in Evidence Review J: *"This increased uncertainty at higher order IVF cycles is of greater importance as there is a lack of randomised*

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				Replace "consider up to three further cycles" with wording that makes clear the NICE recommendations is six IVF cycles where clinically appropriate. **Rationale:** Patients frequently report that inconsistent local policies cause significant distress and inequity. A stronger national direction would reduce regional variation and promote continuity of care. Clearer language would help ensure fair and compassionate access to NHS-funded fertility care across the UK.	*trials with which to compare the output of the prediction models."* *"There are legitimate concerns about potential selection bias in the prediction models as well as uncertainty relating to small samples especially at 4 cycles of IVF and above."* *"Therefore, while the committee believed that the cost-effectiveness evidence now supported the provision of 6 cycles to women aged 39 years and below, they recognised that the evidence was not sufficiently robust to make a strong recommendation for more than 3 cycles, although they did recommend that up to 6 cycles could be considered."*
The Fertility Alliance	Male Fertility (Medical and Surgical Management)	024	1.3.5 – 1.4.13	The more inclusive approach to male fertility in the 2026 draft is a much-needed improvement. The use of inclusive language, evidence-based testing, and removal of unproven interventions all strengthen the quality of care. Despite this, the psychological aspects of male infertility remain under-recognised. Men and partners frequently report feeling excluded from fertility care discussions and unsupported after diagnosis or treatment failure. **Suggested addition:** "Emotional and counselling services should be offered equally to all individuals affected by fertility problems,	Thank you for your comment. We agree that psychological support for men and partners is important. Recommendation 1.1.1 already states that couples who experience problems in conceiving should be seen together because both partners are affected by decisions surrounding investigation and treatment. This includes men and partners, ensuring an inclusive approach.

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				including men and partners, recognising the specific psychological impact of male infertility." **Rationale:** Fertility care should be inclusive of all genders and partners, not just the person undergoing treatment. This change would encourage a more holistic, family-centred approach and help reduce stigma surrounding male infertility - a key barrier to early help-seeking and open discussion.	We recognise psychological effects of fertility problems and the value of emotional and counselling services. Recommendations 1.2.1 to 1.2.5 cover these aspects for both partners/all genders and partners. Therefore, we believe this is already addressed within the guidance.
University College London Hospitals	Guideline	016	021	Rec 1.3.16 *Do not use follicle-stimulating hormone (FSH) measurement as a predictor of ovarian response or outcome of assisted conception.* This recommendation is too sweeping; if FSH is very elevated (>15 iu/L), it is indeed a predictor of poor ovarian response, and moreover FSH >30 iu/L is identified in the NICE guideline on menopause as diagnostic of POI. Perhaps the committee intended this recommendation to avoid the cut-off FSH imposed by funding bodies for NHS treatment? All the ICBs that we deal with adopted cut-offs to restrict treatment, based on the previous guideline criteria for prediction of poor response. However, stating that FSH is not to be used at all may also have unintended consequences.	Thank you for your comment. FSH can be used to aid in diagnosing premature ovarian insufficiency, the diagnosis of which can determine access to fertility treatments and ART; a separate NICE Clinical Knowledge Summary recommends a specific FSH threshold of >30 IU/L for this purpose: https://cks.nice.org.uk/topics/menopause/diagnosis/diagnosis-of-premature-ovarian-insufficiency/. The committee also acknowledged that FSH can be used to aid in predicting ovulation dysfunction, however the evidence review only intended to address the ability of ovarian reserve markers to predict outcomes related to assisted and spontaneous conception, and the evidence showed FSH did not have prognostic ability in this context. The recommendation made based on this

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					evidence therefore only addresses its predictive ability in this regard. This does not preclude the use of FSH testing in other contexts.
University College London Hospitals	Guideline	031	021	Rec 1.8.3 This is a major change from the previous guideline, and to be welcomed. Having contributed to the last guideline, we recall that there was inadequate evidence to support IUI treatment, but clinical experience indicated that it was effective in selected cases. Survey of the British Fertility Society shortly after 2013 guideline publication showed that there was widespread disagreement with the NICE 2013 recommendation and most centres intended to continue to offer IUI to these groups of patients. Over the intervening years, IUI has not been commissioned and has therefore almost fallen out of use in NHS centres. Implementation of this new recommendation may therefore be difficult, as current clinical experience is limited and clinical opinion has shifted.	Thank you for this comment. Based on the committee's knowledge and experience, IUI is used and clinical expertise for IUI still exists, so we do not think this is a problem.
University College London Hospitals	Guideline	031	028	Rec 1.9.5 *consider up to 3 further full cycles of IVF treatment.* This is going to be impossible to implement in NHS services. At present, very few funding bodies support the current recommendation of 3 full cycles. There is great inequity and geographical variation in NHS IVF provision, and this may exacerbate it further. In our opinion, it would be better to support implementation of the current 3-cycle recommendation across the NHS	Thank you for this comment. The guideline committee were aware that the implementation of recommendations had to be considered as part of their deliberations. Whilst 3 cycles of IVF are still offered as per previous NICE guidance, a weaker recommendation was made for an additional 3 cycles. The committee did not think that many patients

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				rather than ask for more. Even if the ICBs had the finances to fund 6 cycles, this would need expansion of services and resources are not adequate. We foresee many difficult conversations with couples whose expectations are raised by reading this recommendation.	would want more than 3 cycles if previous attempts were unsuccessful but noted that expectations are already unmet in many areas of the NHS where NICE recommendations are not currently adhered to. Furthermore, it is recommended that a discussion of the probability of success and the implication of more treatment accompanies the consideration of any further 3 cycles if the person has not conceived after the first 3 full cycles.
University College London Hospitals	Guideline	042	002	Rec 1.14.1 Thank you for broadening the indications for fertility preservation [FP]. We already see an increasing number of patients who receive gonadotoxic therapies for non-malignant conditions. They are referred in the expectation of FP. Currently our ICBs vary in their approach, some fund FP for benign conditions and others restrict it to oncology. We waste a lot of time on IFRs (Individual funding requests). This inclusion is very welcome.	Thank you for this comment. According to the committee's knowledge and experience, there is indeed some variation in how different areas offer cryopreservation for non-cancer treatment related medical indications, although they thought that for the most part ICBs already offer this. We hope the recommendations will improve equitable access to fertility preservation across the country.
University College London Hospitals	Guideline	042	023	Rec 1.14.7 This is a sensible recommendation to review at least every 5 years following fertility preservation. Currently, nearly all ICBs fund for 10 years in oncology patients and there is no incentive to review or discard earlier. This change will improve efficiency of our storage facilities and reduce the number of 'unclaimed' gametes and embryos in storage.	Thank you for this comment. The recommendations include continuing NHS-funded storage as needed and we agree that in the case of younger people, the need to store materials may be considerably longer than with older individuals. However, the committee thought that a follow-up at least

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				However, special provision will need to be made for teenagers and young adults who will require extended storage. They are often difficult to follow up as they move. Implementation of this recommendation may need to be phased in, as it will increase the workload of our staff initially, by contacting all patients who have stored between 5 and 10 years.	every 5 years would allow the situation to be reviewed and would minimise risk of losing contact with people.
University College London Hospitals	Guideline	044	019	The definition of *full cycles of IVF treatment* is crucial to implementation of NICE's recommendations. It affects recommendations 1.9.4-1.9.8. At present, very few funding bodies support the current recommendation of 3 full cycles. ICBs vary in their interpretation, some ICBs specify a maximum number of transfers and others do not, leading to inequity in treatment. Moreover, some couples achieve a large number of embryos and could potentially have multiple frozen-thaw replacement cycles, affecting access to services for other couples. As mentioned above, this may lead to very difficult conversations in clinic when expectations have been raised.	Thank you for your comment. We agree that this is an important part of the IVF recommendations and the guideline makes it clear what is meant by a full cycle. We are aware that some ICBs are not following the guideline recommendations. Restricting the maximum number of embryo transfers would not be evidence-based and could perversely encourage double embryo transfer. Regarding the scenario you describe about some couples having multiple frozen embryos from one cycle and this impacting access to services for other people: we are not aware of this being a problem. Couples with a larger number of embryos have a better prognosis and are less likely to need multiple transfers.
University College London Hospitals	Guideline	051	013	This conclusion is too sweeping. FSH has inter-cycle and intra-cycle variation, and FSH within range does not predict response; however if FSH is very elevated it is associated with poor response, and indeed >30 iu/L is	Thank you for your comment. FSH can be used to aid in diagnosing premature ovarian insufficiency, the diagnosis of which can determine

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				identified in the NICE guideline on menopause as diagnostic of POI.	access to fertility treatments and ART; as you have noted, a separate NICE Clinical Knowledge Summary recommends a specific FSH threshold of >30 IU/L for this purpose: https://cks.nice.org.uk/topics/menopause/diagnosis/diagnosis-of-premature-ovarian-insufficiency/. The committee also acknowledged that FSH can be used to aid in predicting ovulation dysfunction, however the evidence review only intended to address the ability of ovarian reserve markers to predict outcomes related to assisted and spontaneous conception, and the evidence showed FSH did not have prognostic ability in this context. The recommendations made based on this evidence therefore only address their predictive ability in this regard. This does not preclude the use of FSH testing in other contexts.
University College London Hospitals	Guideline	051	019	It would be more helpful to enable measurement of AMH in the community; until this is available to GPs, FSH measurements will continue to be done. AMH tests are not much more expensive than FSH/LH and much more useful, because AMH is a marker for PCOS and POI as well as a predictor of IVF response. We have been using AMH for 15 years in specialist care and it is hard to understand why it is not available in many secondary care centres and not at all in primary care. It could be cost-effective if introduced with appropriate	Thank you for your comment. The evidence showed AMH had greater ability than FSH for predicting outcomes related to assisted and spontaneous conception, and the committee agreed FSH should not be used in this context. The recommendation not to use FSH to predict these outcomes was therefore made with the intention to reduce this practice. However, FSH can be used in other contexts, for example, to aid in diagnosing premature

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				protocols, because reduction in FSH measurement (often poorly timed and repeated) along with other unnecessary tests in primary care (such as prolactin in regularly cycling women, and full biochemistry in healthy subfertile women) would fund AMH.	ovarian insufficiency. The recommendations therefore do not preclude the use of FSH testing in other contexts.
University College London Hospitals	Guideline	062	017	*uncertainties in the evidence, particularly for cycles 4 to 6. These uncertainties related to concerns about increasing selection bias in the datasets informing the prediction models and the very small numbers of women in these datasets having 4 or more cycles…* In view of the limitations of the evidence, it is hard to see how the committee can justify doubling the number of cycles? This would have a very large impact on services, and the economic the modelling is weak even to support a qualified 'consider' recommendation.	Thank you for this comment. NICE produces recommendations on the best available clinical and cost-effectiveness evidence. As per the previous NICE guideline it is recommended that 3 cycles are offered. The committee considered that the evidence for this recommendation was even better supported this time. Reflecting weaker evidence, a 'consider' recommendation is also made for a further 3 cycles. The committee did not think that a large number of patients would want more than 3 cycles if previous attempts were unsuccessful. However, they did recognise a large impact on services if existing NICE recommendations to offer up to 3 full cycles of IVF were adhered to.
University College	Guideline	063	024	This appears to be a typographical error	Thank you for this comment.

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London Hospitals					It is not clear what typographical error the comment refers to.
University College London Hospitals	Guideline	083		Table - *Take into account the outcome of previous IVF treatment when assessing the likely effectiveness and safety of any further IVF treatment. [new 2013] (1.11.1.7)* This recommendation has been removed, but it was actually a useful and sensible recommendation which supports clinicians when discussing failed cycles. We are fortunate to work with ICBs that commission 3 cycles of IVF, and many couples request this as a right, making it difficult for the clinician to decline. Having this NICE recommendation to refer to can be helpful when stopping treatment.	Thank you for this comment. The recommendation referred to in the comment has been replaced with recommendation 1.39.7 which states that if a person is under 40 years of age and has not conceived after 3 full IVF cycles, the probability of success and the implications of more treatment should be discussed and 3 further IVF cycles should be considered.
University College London Hospitals	Guideline	086		Table - *When deciding to offer fertility preservation to people diagnosed with cancer, take into account the following factors: • diagnosis • treatment plan • expected outcome of subsequent fertility treatment • prognosis of the cancer treatment • viability of stored or post-thawed material. [new 2013] (1.16.1.3) This recommendation was deleted because it is more relevant for cancer guidelines rather than fertility problems guideline. Part of good standard practice.* This recommendation has been removed, but it is a key recommendation for the safety and effectiveness of fertility preservation. It is indeed essential for cancer guidelines as well, and bears repetition.	Thank you for this comment. The guideline committee acknowledged the comment and agreed to update this section of the guideline by reinstating the 2013 recommendation with some minor edits on the factors to be considered when offering fertility preservation such as diagnosis, treatment plan, expected outcome of subsequent fertility treatment etc.

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				In clinical practice (and two decades of experience in providing a large fertility preservation service) many referrals are received from oncology without sufficient information, and the onus is put on the fertility practitioner to counsel the patient. The message has got through to oncology that patients should be referred, which is of course to be welcomed. The referring teams cannot be expected to know details of FP procedures so they often do not appreciate the potential risks. On the receiving end, fertility specialists cannot be expected to know details of all the oncology conditions, and the ethos of fertility clinics is to put the patient through treatment. This would rarely be an issue for male patients storing sperm, but for females this has sometimes resulted in patients being put through challenging and potentially risky procedures that will not be of benefit. This recommendation is therefore a useful and important reminder to communicate and obtain all relevant information to guide the FP decision. We have several examples where further information obtained on treatment plan, prognosis etc led to changed decision-making. For example, referral for rectal cancer that did not mention pelvic radiation; egg freezing was offered (which carries higher risks when undertaken shortly after major pelvic surgery); additional information on treatment plan	

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				revealed that uterine function would be affected and surrogacy would be needed for subsequent use; counselling on surrogacy influenced the patient's decision not to proceed.	
University College London Hospitals	Guideline	097		Table - *In women aged under 40 years, any previous full IVF cycle, whether self- or NHS-funded, should count towards the total of 3 full cycles that should be offered by the NHS. [2013] (1.11.1.6)* It seems unnecessary to replace this recommendation, since it covers the new recommendation, and the wording is shorter and clearer.	Thank you for this comment. The committee were aware that in some areas people were not offered NHS-funded IVF cycles if they have had any self-funded IVF treatment, therefore they wanted to make it clearer that previous self-funded IVF treatment should not preclude anyone receiving NHS-funded IVF treatment. The recommendation has been amended to make it explicit and now it states that if people are under 40 years of age and have had self-funded IVF treatment, access to NHS-funded IVF treatment should not be ruled out and any previous IVF cycles (whether self-funded or NHS-funded) should be counted towards the total number of full cycles offered by the NHS.
Univfy Inc	Evidence review J			We commend NICE, its fertility assessment committee and the authors of this "Evidence review J" Draft for Consultation ("DRAFT", hereafter) for recognizing the importance of data- and model-driven IVF prognostics counselling in improving patient-centric care and transparency.	Thank you for this comment.

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Univfy Inc	Evidence review J	General	General	Patient-Centred Care Implications - The review should emphasise that validated MLCS models address NICE's patient-centred care goals by: (1) Providing transparent, individualised IVF outcomes risk assessments based on patient-specific characteristics, (2) Enabling shared decision-making through accurate prognostic information, (3) Supporting diverse healthcare providers with consistent, validated counselling tools, and (4) Improving patient engagement and treatment completion rates through realistic expectation setting.	Thank you for this comment. While NICE guidelines do emphasise the importance of patient-centred care—including shared decision-making, transparent communication, and individualised treatment planning—recommendations must be based on independently evaluated evidence that meets NICE's methodological standards. This includes robust data on clinical effectiveness, cost-effectiveness, and applicability across NHS settings. At present, the guideline does not comment on specific proprietary tools or models unless they have been included in the evidence review and assessed accordingly. If MLCS models have undergone such evaluation and demonstrate clear benefits aligned with NICE's criteria, they may be considered in future updates or relevant technology appraisals. We appreciate your input and encourage submission of peer-reviewed evidence or independent evaluations that support the claims made.
Univfy Inc	Evidence review J	General	General	Recommendation for Updated Guidelines - The evidence strongly supports acknowledging that validated MLCS models represent a significant advancement over non-centre-specific approaches. The updated fertility guideline should explicitly recognise the superior clinical accuracy,	Thank you for this comment. The committee could only make recommendations based on included studies identified using a pre-specified review protocol. Based on the reviewed

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				patient counselling utility, and healthcare delivery optimisation demonstrated by validated individual prediction models, particularly for NHS implementation where scaled and distributed centre-specific optimisation could better serve diverse patient populations while optimising resource allocation.	evidence, the committee agreed not to recommend the use of a clinical prediction model in routine clinical practice. We acknowledge the potential value of MLCS models to address the needs of diverse populations, however we did not look at the evidence.
Univfy Inc	Evidence review J	General	General	We wish to respond to the following questions: 1. Would it be challenging to implement of any of the draft recommendations? Please say why and for whom. Please include any suggestions that could help users overcome these challenges (for example, existing practical resources or national initiatives. 2. Would implementation of any of the draft recommendations have significant cost implications? The cost and feasibility of end-to-end model development for real-world usage, including EMR integration, quality assurance and ongoing evaluation, are important issues to consider. In fact, highly scalable implementation of validated MLCS models as reported by Yao et al, Nature Communications 2025, have been in clinical usage in fertility centres in the UK, EU, Switzerland, Canada and the US. The cost of implementation and usage is made	Thank you for this comment. These comments do not seem to relate directly to draft recommendations.

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				feasible and affordable based on local IVF pricing and currency considerations. Therefore, instead of assuming MLCS is infeasible and opting for "free" online, non-validated models of poorer quality, this question should be raised to allow each stakeholder, including patients, fertility centres and the NHS to evaluate for themselves. A "free" tool is limited if the benefits -- IVF access, affordability, utilization and ultimately, family-building -- are not realized. More importantly, there is great cost-efficiency (i.e. significant cost savings) for a public-private partnership that leverages public organization's pre-existing infrastructure and Univfy's platform for efficient training, validation and deployment of MLCS models for interested fertility centers to use on a voluntary, "opt-in" basis. There are cost-efficient ways to support and establish a UK-Univfy initiative to implement nation-wide MLCS models for UK fertility centres and/or patients. Univfy is open to these and other formats of collaboration and mutual cost-savings to help more people in the UK to have a family.	
Univfy Inc	Evidence review J	006-034		Missing Evidence: This DRAFT has not fully addressed recent developments in validated scientific model design or provided sufficient detail regarding the practical	Thank you for this comment.

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				application of these models in patient-centric IVF prognostics counselling, clinical decision-making and the real-world impact on both live birth and safety outcomes. In particular, the DRAFT would benefit from a more comprehensive appraisal of how these models can inform economic considerations within both NHS-funded and self-funded care pathways, including supporting financial discussions for patients pursuing private care. An in-depth, peer-reviewed, internationally co-authored review covered many of this DRAFT's "included" IVF prognostic models and some of the "excluded" models with discussion of additional important scientific and clinical considerations: Yao MWM, Jenkins J, Nguyen ET, Swanson T, Menabrito M. Patient-Centric In Vitro Fertilization Prognostic Counselling Using Machine Learning for the Pragmatist. Semin Reprod Med. 2024 Jun;42(2):112-129. doi: 10.1055/s-0044-1791536. Epub 2024 Oct 8. PMID: 39379046; PMCID: PMC11581823. https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0044-1791536	The article referred to in the comment does not meet our inclusion criteria and it was also published after the date of our literature search 11/10/2023. In addition, studies were included based on the criteria specified in the review protocol.

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				Specifically, Yao et al. discussed many of the models referenced in the DRAFT with respect to: 1) their strengths and limitations; 2) gap in model validation best practice; 3) limitations of multi-site or multi-centre models without centre-specific validation; 4) the potentially detrimental risk of inflating model validation metrics if the training set includes a substantial portion of patients aged 42+ (meaning, the model can appear to perform better than it actually does for patients aged <40) -- this is an often overlooked issue that can affect clinical usage; 5) the importance of appropriate model design, down to the inclusion and exclusion of data and variables used, etc. based on the specific clinical application of the model. These considerations are essential when evaluating and implementing clinical outcomes models for the purpose of patient counselling and decision-making; or the testing of prognostics-driven clinical decision-making such as protocol selection and treatment recommendations; or healthcare economic resource allocation such as objectives of the economic models that are in the supplementary materials of this DRAFT.	

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Univfy Inc	Evidence review J	006-034	General	Omission: The DRAFT does not address requirements pertaining to appropriate and quality clinical application of IVF live birth prediction models. The choice of modelling approach dovetails directly with the technology required to train, validate, implement the model for clinical usage and apply ongoing evaluation of utilization impact. Addressing the following requirements is essential for successful, real-world, economical usage of clinical prediction models: 1) scalability (including centre-specific data usage and model validation to ensure local population relevance, reproducibility in model quality across centres, and if needed, multi-lingual capabilities); 2) UK GDPR compliance; 3) point-of-care usage enabled by integration with existing electronic medical records (EMR) systems; 4) quality assurance framework to ensure ongoing validation and utilization monitoring. Many of these points are discussed in: Yao MWM, Jenkins J, Nguyen ET, Swanson T, Menabrito M. Patient-Centric In Vitro Fertilization Prognostic Counselling Using Machine Learning for the Pragmatist. Semin Reprod Med. 2024 Jun;42(2):112-129. doi: 10.1055/s-0044-1791536. Epub 2024 Oct 8. PMID: 39379046; PMCID: PMC11581823. https://www.thieme-	Thank you for this comment. Our guideline was not primarily intended to produce recommendations on the use of IVF live birth prediction models within clinical practice in the NHS and therefore it was not part of our remit to address the points raised in this comment.

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				connect.com/products/ejournals/html/10.1055/s-0044-1791536	
Univfy Inc	Evidence review J	006-034	General	Missing Evidence: This DRAFT has not reviewed validated machine learning centre-specific (MLCS) models, an approach that has been reported in the peer-reviewed literature since 2010, with the most recent research published in 2025. MLCS models demonstrated superior performance to conventional age-based reporting and national registry-based modelling approaches using data from multiple centres without centre-specific validation. The items below provide more detailed discussion of specific issues, along with references.	Thank you for this comment. The guideline has reviewed models identified according to the criteria specified in the review protocol and MLCS models were not identified by our literature search. It is possible that such models may be considered in future updates or relevant technology appraisals.
Univfy Inc	Evidence review J	036-044	General	Recommendation for NHS Implementation Framework - Given the systemic failure of generalist models demonstrated in NICE's own review, the evidence strongly supports developing guidance for NHS Trusts to validate and implement MLCS models through: pilot programs assessing performance across diverse NHS populations, protocols for ongoing model performance monitoring and quality assurance, training frameworks for clinical staff, cost-effectiveness evaluation compared to failed current approaches, and patient	Thank you for this comment. It was not part of the guideline scope to produce recommendations on the validation and implementation of live birth prediction models (MLCS or otherwise). However, the committee discussed the model performance estimates for the clinical prediction models and noted that there was very little meta-analysable data, and no clinical prediction model met the pre-defined criteria for good discrimination and calibration.

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				consent/governance processes. Centre-specific optimisation could better serve diverse NHS patient populations while optimizing resource allocation compared to demonstrably inadequate generalist approaches.	The committee agreed not to recommend the use of clinical prediction models in routine clinical practice because there was no clear advantage of their use in counselling people about their chances of live birth.
Univfy Inc	Evidence review J	035-042	General	Missing Evidence: This DRAFT reviewed economic models for increasing IVF access and utilization, but omitted to discuss the crucial linkage between having an accurate IVF actuarial model for provisioning value-based IVF care. The importance of value-based IVF care as a method to align economic feasibility and quality (singleton live birth outcomes and maternal and newborn safety in fewer number of procedures and GBP) are discussed in-depth in the following peer-reviewed research publications: Yao MWM, Jenkins J, Nguyen ET, Swanson T, Menabrito M. Patient-Centric In Vitro Fertilization Prognostic Counselling Using Machine Learning for the Pragmatist. Semin Reprod Med. 2024 Jun;42(2):112-129. doi: 10.1055/s-0044-1791536. Epub 2024 Oct 8. PMID: 39379046; PMCID: PMC11581823. https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0044-1791536	Thank you for this comment. The article by Jenkins (2020) is a commentary and therefore it would not meet our inclusion criteria. Two other articles were published after the date of our literature search 11/10/2023.

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				Yao MWM, Nguyen ET, Retzloff MG, Gago LA, Nichols JE, Payne JF, Ripps BA, Opsahl M, Groll J, Beesley R, Neal G, Adams J, Nowak L, Swanson T, Chen X. Machine learning centre-specific models show improved IVF live birth predictions over US national registry-based model. Nat Commun. 2025 Apr 17;16(1):3661. doi: 10.1038/s41467-025-58744-z. PMID: 40246850; PMCID: PMC12006386. https://www.nature.com/articles/s41467-025-58744-z Jenkins J, van der Poel S, Krüssel J, Bosch E, Nelson SM, Pinborg A, Yao MMW. Empathetic application of machine learning may address appropriate utilization of ART. Reprod Biomed Online. 2020 Oct;41(4):573-577. doi: 10.1016/j.rbmo.2020.07.005. Epub 2020 Jul 15. PMID: 32819841. https://www.rbmojournal.com/article/S1472-6483(20)30376-X/fulltext	
Univfy Inc	Evidence review J	032-035	General	Missing Evidence and Missing Critique: This DRAFT appears to have expectations for IVF outcomes prediction to reach or exceed a C-statistics threshold of ≥0.75, which is typically possible/expected for diagnostic tests. However, the performance metrics for a prognostic model	Thank you for this comment. In line with NICE's processes and methods on assessing discrimination of prediction models, the minimally important difference of 0.75 (or 'good' discrimination) was based on Debray et al. 2017 (A

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				should not be dependent on or limited to a C-statistic threshold cut-off. The evaluation and meaning of the AUC ROC (or C-statistics) should be used very differently between prediction models (which are predicting whether an event, in this case live birth, will occur after IVF in the future) and diagnostic tests (which are detecting whether a condition, such as pregnancy or cancer or a certain illness, already exists in the patient's body). Those are completely different tasks. **This authoritative reference provides excellent discussion on the difference between prediction models and diagnostic tests and why they should be evaluated differently.** Cook NR. Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. Clin Chem. 2008 Jan;54(1):17-23. doi: 10.1373/clinchem.2007.096529. Epub 2007 Nov 16. PMID: 18024533. We provide a contrasting example of very high AUC ROC for context. The Alvarado Score has an AUC ROC of 0.985 for diagnosing acute appendicitis, which is possible and necessary to avoid misdiagnosed cases and fatality. For the diagnosis of acute appendicitis, clinical experts determined that AUC ≥ 0.9 is excellent discrimination;	guide to systematic review and meta-analysis of prediction model performance - PubMed).

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				AUC between 0.7 and 0.9 is moderate discrimination; and AUC between 0.5 to 0.7 is poor discrimination. That is for an acute surgical emergency that can be fatal or result in serious complications if surgery is not performed timely. There is also over 100 years history in the performance of surgical treatment for acute appendicitis. Arredondo Montero J, Martín-Calvo N. Diagnostic performance studies: interpretation of ROC analysis and cut-offs. Cir Esp (Engl Ed). 2023 Dec;101(12):865-867. doi: 10.1016/j.cireng.2022.11.011. Epub 2022 Nov 24. PMID: 36436801. https://www.elsevier.es/es-revista-cirugia-espanola-english-edition--436-articulo-diagnostic-performance-studies-interpretation-roc-S2173507722004203 Al-Wageeh S, Alyhari QA, Ahmed F, Altam A, Alshehari G, Badheeb M. Evaluating the Diagnostic Accuracy of the Alvarado Score and Abdominal Ultrasound for Acute Appendicitis: A Retrospective Single-Center Study. Open Access Emerg Med. 2024 Jul 6;16:159-166. doi: 10.2147/OAEM.S462013. PMID: 38994039; PMCID: PMC11236940. https://www.dovepress.com/evaluating-the-diagnostic-accuracy-of-the-alvarado-score-and-abdominal-peer-reviewed-fulltext-article-OAEM	

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Univfy Inc	Evidence review J	032-035	General	Missing Evidence and Missing Critique: There is a disproportionate emphasis on the use of C-statistics and calibration as methods for evaluating IVF live birth prediction models. C-statistics (aka area-under-the-curve receiver operating characteristic curve or AUC ROC) and calibration are performed routinely as a "base", but they are quite crude and do not necessarily discriminate models that enable clinically relevant benefits. In addition, C-statistics should not be judged as a number on its own (e.g. needing to be "0.75"), as there should be control models for comparison. We have reported in numerous research publications the importance of using an age-only control model that uses the same training and test data and subjected to the same MLCS methodology or the age-based IVF live birth rates being cited by physicians in current practice. We compare the AUC ROC (or C-statistics) of the multivariate MLCS model against the age-only control model and show the % of improvement in model metrics compared to age. As part of the analysis provided to clinicians, we show the percentage of patients who would receive a different prognosis from MLCS vs. age control model and the extent of that difference. A portion of patients may not have very different IVF prognoses between MLCS and age control models, but a substantial portion of patients	Thank you for this comment. In line with NICE's processes and methods on assessing discrimination of prediction models, the minimally important difference of 0.75 (or 'good' discrimination) was based on Debray et al. 2017 (A guide to systematic review and meta-analysis of prediction model performance - PubMed). The 2 articles cited were published after the date of our literature search 11/10/2023.

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				may have very different prognoses. It is not possible to know a priori which patients have different prognoses from the MLCS vs. age control models. Model performance metrics that have the same or greater impact on clinical usefulness are Posterior Log of Odds Ratio compared to Age (PLORA) -- i.e. colloquially, "how much better is the model compared to age", precision, recall, precision-recall AUC (PR AUC) and F1 score. These model metrics and the rationale for using them are explained in-depth in: Yao MWM, Jenkins J, Nguyen ET, Swanson T, Menabrito M. Patient-Centric In Vitro Fertilization Prognostic Counselling Using Machine Learning for the Pragmatist. Semin Reprod Med. 2024 Jun;42(2):112-129. doi: 10.1055/s-0044-1791536. Epub 2024 Oct 8. PMID: 39379046; PMCID: PMC11581823. https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0044-1791536 This research paper demonstrates how these model metrics are used and how they are useful with respect to IVF access and patient-centric counselling: Yao MWM, Nguyen ET, Retzloff MG, Gago LA, Nichols JE, Payne JF, Ripps BA, Opsahl M, Groll J, Beesley R,	

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				Neal G, Adams J, Nowak L, Swanson T, Chen X. Machine learning centre-specific models show improved IVF live birth predictions over US national registry-based model. Nat Commun. 2025 Apr 17;16(1):3661. doi: 10.1038/s41467-025-58744-z. PMID: 40246850; PMCID: PMC12006386. https://www.nature.com/articles/s41467-025-58744-z	
Univfy Inc	Evidence review J	031-034	General	NICE had set criteria for approving prediction model performance metrics to have C-statistic ≥ 0.75 and good calibration (O/E ratio 0.8-1.2). NICE's own analysis demonstrated that none of the "included prediction models" met these criteria. Specifically: Templeton model (C-statistic 0.62 - very poor), McLernon model (C-statistic 0.63-0.73 - below threshold), van Loendersloot model (C-statistic 0.64 - poor). Most models showed "very low quality" evidence. This systemic limitation of "included models" indicated two key points especially regarding IVF live birth prediction using information available prior to starting IVF (aka pre-IVF models): 1) We -- all of us including IVF experts, researchers, stakeholders of IVF globally -- do not understand enough about the molecular mechanisms of IVF failure and factors affecting IVF success (e.g. genomic, microbiome,	Thank you for this comment. It was not part of the guideline scope to produce recommendations to the NHS on the development, validation and implementation of prediction models (MLCS or otherwise).

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				environment, epigenetic factors, socioeconomic determinants of health, etc.). The standard of care (SOC) diagnostic tools that are used today are limited. Research is urgently needed to expand this knowledge. 2) The approaches used to train "included models" are limited in providing clinical benefits. Yao et al, Seminars in Reproduction 2024 discussed many limitations of those approaches. 3) The metrics used to validate these "included models" -- namely, C-statistic and calibration -- are also inadequate in evaluating IVF live birth models for clinical utility and economic modelling. Therefore, we urge this NICE committee to consider the following: 1) Instead of aiming to find a multicentre, one-size-fits-all model to recommend for clinical use for the UK, consider recommending an affordable, public-private collaboration to develop, validate and implement MLCS models for interested fertility centres in the UK. 2) Instead of seeking a model that meets certain threshold C-statistics (AUC ROC) values and calibration (which can themselves be very crude measures), consider adding model metrics that inform clinical utility. For example, in Yao et al, Nature Communications 2025, we reported that MLCS models showed PR-AUC 0.75	

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				(interquartile range, IQR 0.73, 0.77) vs. US registry model 0.69 (IQR 0.68, 0.71), p<0.05; F1 scores at live birth probability of 50% were 0.74 (IQR 0.72, 0.78) for MLCS models vs. 0.71 (IQR 0.68, 0.73) for US registry model, p<0.05. Clinical utility: ▪ Using the 50% live birth probability (LBP) threshold as an example: 23% of all patients would have been informed by the US registry model that their LBP was <50% when in fact it was ≥ 50%. ▪ Using the 75% live birth probability (LBP) threshold as an example: 11% of all patients would have been informed by the US registry model that their LBP was <75% when in fact it was ≥ 75%. The actual live birth rate of the group that received LBP of ≥ 75% from MLCS was 81%. ▪ MLCS2 models also appropriately placed 3.4% of patients in lower LBPs compared to the US registry model. Of course, we aim for higher model metrics including AUC ROC. However, it is important to let clinicians know that improved, validated prognoses are possible and let clinicians decide if they would like to learn more about this area of medical progress. Another reason it is important	

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				to learn about and consider using an improved technology is that not discussing or using an already significantly improved technology limits the human imagination of research advances that are possible. An ongoing desire to innovate and improve IVF success stems from advances on all fronts of IVF. If the pioneers of IVF have stopped using IVF to treat patients when the IVF live birth rate used to be <10%, then we wouldn't have the very efficacious IVF treatment for our patients today.	
Univfy Inc	Evidence review J	031-034	General	Poor External Validation Performance of Included Models - Critical evidence shows: McLernon model external validation demonstrated model over-estimation of live birth in multiple studies; Templeton model calibration plots showed systematic underestimation; van Loendersloot model external validation showed poor discrimination and calibration issues. Wide confidence intervals indicate high uncertainty (e.g., Hunault model O/E ratio: 0.001-417.28). In contrast, validated MLCS models eliminate these systematic biases through centre-specific validation on actual patient populations served, achieving model validation for each of local clinic's patient populations in UK, EU, Switzerland, Canada and US.	Thank you for this comment. The guideline has reviewed models identified according to the criteria specified in the review protocol and MLCS models were not identified by our literature search. It is possible that such models may be considered in future updates or relevant technology appraisals.

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Univfy Inc	Evidence review J	031-034	General	Inadequate Clinical Heterogeneity Handling - The DRAFT's "included models" demonstrate wide confidence intervals indicating high uncertainty, inconsistent performance across validation studies, failed centre-specific fitting attempts. Clinical heterogeneity across centres, protocols, and patient populations cannot be captured by generalist approaches. Validated MLCS models account for centre-specific protocols, patient populations, and clinical practices, achieving 100x improved data efficiency (MLCS models used a median data set size of 1,163 vs US registry used 121,561 cycles) while maintaining superior performance. Importantly, training and validating high performing IVF live birth prediction models are no longer limited to the largest fertility centres.	Thank you for this comment. Heterogeneity was addressed by downgrading the quality of the evidence for imprecision in those instances where 95% confidence intervals crossed decision making thresholds.
Univfy Inc	Evidence review J	031-034	General	Historical Data Mismatch with Current Practice - Many included studies used historical data (some from 1980s-1990s) that may not reflect current IVF practices and patient populations. The committee concluded "no clinical prediction model met pre-defined criteria" and agreed "not to recommend use of clinical prediction model in routine practice." This conclusion supports the need for better approaches like validated MLCS models that use current data, modern ML	Thank you for this comment. MLCS models were not identified by our literature search. It is possible that such models may be considered in future updates or relevant technology appraisals.

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				techniques, and centre-specific optimization to overcome fundamental limitations of generalist historical models.	
Univfy Inc	Evidence review J	045-047	General	Missing Evidence Led to Economic Models' Limitations: An economic model of IVF usage, especially with the use of public funds, should be based on the most direct measure -- probability of IVF live birth provided by a model with excellent model metrics that is validated for the local patient population (for local relevance). An economic model would perform much better if it were to use a multivariate approach that selects predictors based on the ability of each predictor's classifier functions as measured by objective measures. The references listed on pages 48-50 may not have the optimal attributes required to support an economic model for IVF funding. As discussed in the following references, expanding IVF access and utilization will require the use of value-based IVF care, which is a direct application of MLCS IVF live birth prediction models validated for local patient population. MLCS IVF live birth prediction models provide: 1) More accurate risk stratification enabling better treatment pathway selection, including decisions to use donor egg IVF;	Thank you for this comment. As we acknowledge "very important limitations exist for all prediction models incorporated into this economic analysis". Nevertheless, those prediction models were identified using a pre-specified review protocol. The models included a prediction model based on a large UK dataset, most relevant to our guideline population. The objective of the NICE economic model was not to expand IVF access and utilisation but rather to determine in which groups IVF would represent a cost-effective use of finite NHS resources. Prognostic counselling was not within the scope of the guideline update (see Guideline scope in the History tab of the guideline's website). Evidence on IVF using donor eggs was not reviewed for this guideline update and has not been commented on. The articles cited were published after the date of our literature search 11/10/2023.

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				2) 2-3x increased IVF utilisation rates through improved patient counselling (Yao et al. J Clin Med 2024 - see below); 3) Reduced inappropriate treatments through better identification of patients unlikely to benefit from IVF. Yao MWM, Jenkins J, Nguyen ET, Swanson T, Menabrito M. Patient-Centric In Vitro Fertilization Prognostic Counselling Using Machine Learning for the Pragmatist. Semin Reprod Med. 2024 Jun;42(2):112-129. doi: 10.1055/s-0044-1791536. Epub 2024 Oct 8. PMID: 39379046; PMCID: PMC11581823. https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0044-1791536 Yao MWM, Nguyen ET, Retzloff MG, Gago LA, Nichols JE, Payne JF, Ripps BA, Opsahl M, Groll J, Beesley R, Neal G, Adams J, Nowak L, Swanson T, Chen X. Machine learning centre-specific models show improved IVF live birth predictions over US national registry-based model. Nat Commun. 2025 Apr 17;16(1):3661. doi: 10.1038/s41467-025-58744-z. PMID: 40246850; PMCID: PMC12006386. https://www.nature.com/articles/s41467-025-58744-z	

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				Yao MWM, Nguyen ET, Retzloff MG, Gago LA, Copland S, Nichols JE, Payne JF, Opsahl M, Cadesky K, Meriano J, Donesky BW, Bird J 3rd, Peavey M, Beesley R, Neal G, Bird JS Jr, Swanson T, Chen X, Walmer DK. Improving IVF Utilization with Patient-Centric Artificial Intelligence-Machine Learning (AI/ML): A Retrospective Multicenter Experience. J Clin Med. 2024 Jun 18;13(12). doi: 10.3390/jcm13123560. PubMed PMID: 38930089; PubMed Central PMCID: PMC11204457.	
Univfy Inc	Evidence review J	006		Omission: The Introduction of this DRAFT has omitted important considerations regarding the role that validated IVF live birth outcomes prediction models can play in supporting equitable IVF access and affordability. While media coverage and some healthcare providers highlight the risk of "overpromising" IVF success, there is insufficient focus on the potential harm resulting from underestimating IVF live birth outcomes. Without recognising their appropriate, personalised potential for successful IVF outcomes, some patients may decide not to pursue treatment that may otherwise help them build a family. Validated machine learning, centre-specific (MLCS) prediction models show that IVF live birth rates are higher for larger groups of patients than	Thank you for this comment. We consider that the introduction is appropriate in the context of the review question and the guideline objective to identify those people in whom recommendations for cost-effective IVF treatment could be supported. NICE guidelines are developed for the NHS and patients considering private self-funded treatment are not part of their remit. The cited paper was published after the date of our literature search 11/10/2023.

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				previously believed. Making accurate and personalised IVF prognostic information available benefits both individuals and the wider health system. Public acknowledgement of these success rates can help inform resource allocation decisions and support the fair and effective use of existing or potential resources for equitable access through the NHS, while also providing valuable data for those considering private self-funded fertility treatment. Although private health insurance typically does not cover IVF treatment in the UK, some patients may seek partial support through select insurance policies or employer schemes. At the same time, using robust prediction models can enable healthcare professionals—whether in public or private settings—to identify those patients who are most likely to achieve a live birth, promoting cost-effective use of resources and maximising health outcomes for all. Efficacy of IVF has substantially improved since its initial development by Sir Robert Edwards and Dr. Patrick Steptoe, CBE. Conventional methods of providing IVF prognostics -- such as via age group-based IVF live birth rates or multicentre models without centre-specific validation -- do not reflect patients' personalised IVF prognostics in the context of local patient population relevance or local fertility centre's past outcomes.	

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				Yao MWM, Nguyen ET, Retzloff MG, Gago LA, Nichols JE, Payne JF, Ripps BA, Opsahl M, Groll J, Beesley R, Neal G, Adams J, Nowak L, Swanson T, Chen X. Machine learning centre-specific models show improved IVF live birth predictions over US national registry-based model. Nat Commun. 2025 Apr 17;16(1):3661. doi: 10.1038/s41467-025-58744-z. PMID: 40246850; PMCID: PMC12006386. https://www.nature.com/articles/s41467-025-58744-z A highly scaled artificial intelligence (AI)/machine learning (ML) platform has been available to enable the development, validation and provision of MLCS IVF live birth prediction models to support fertility centres in providing patients and healthcare professionals with accurate, validated, personalised IVF prognostic information for patients considering IVF for the first time; IVF after a previous failed (or successful) IVF treatment; donor egg IVF; egg freezing. The appropriate use of these models helps to ensure that neither overoptimistic nor unduly pessimistic expectations are communicated, supporting patient-centred shared decision making and efficient allocation of public or personal resources. Improved information may also enhance societal understanding of IVF outcomes, which can inform future decisions on service provision and funding.	

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				Note: Throughout this document, we use "IVF" to refer broadly to IVF, ICSI and assisted reproductive technologies (ART). With the appropriate inclusion and exclusion criteria and the use of relevant clinical data and outcomes, many of our comments can also be applied to IVF using donor eggs; IVF using gestational carrier; IVF for single women and same-sex women couples. In addition, the methods and comments may also apply to intrauterine insemination (IUI) treatments, natural cycle IVF, or mini-IVF, provided that the data set has sufficient representation or represents only the specified treatment. Therefore, we have not separately addressed prognostic models for these other types of fertility treatments.	
Univfy Inc	Evidence review J	044	General	Cost-effectiveness is not defined. The DRAFT does not show clear thresholds of the amount of funding (GBP per baby) that would be considered cost-effective. Although the use of chronological female age and clinical diagnosis are intuitive for clinicians, relying on these variables alone to develop economic models is problematic because: 1) chronological female age accounts for ~50% of the IVF live birth prediction prior to starting the 1st IVF cycle, so 50% of prediction is not accounted for;	Thank you for this comment. The cost-effectiveness of IVF is assessed using a cost-effectiveness threshold of £20,000 to £30,000 per QALY. In the context of NICE guidelines, the QALY is the preferred outcome to assess cost-effectiveness as it allows a comparison of value for money across different health care programmes. NICE aims to achieve an efficient allocation of finite resources across the NHS,

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				2) clinical diagnoses (aside from poor ovarian response - a negative predictor and severe male factor - a positive predictor in most cases assuming the appropriate treatment is used, e.g. ICSI, TESE, testicular biopsy, donor sperm as indicated) have much lower relative importance than other clinical factors such as female age in conjunction with AMH, BMI, duration of infertility, antral follicle count, etc., in most models that we have tested. Presumably the IVF treatment itself overrides and overcomes most diagnosable causes of infertility. Also, current clinical diagnoses such as PCOS and endometriosis likely lump conditions with different molecular mechanisms under more generic labels. Further, important molecular mechanisms or causes of IVF failure may not yet be conditions that can be diagnosed using available diagnostic tests. Another way to explain is that clinical diagnoses are far from the best classifiers for IVF success by any objective standards, so any clinical or economic models relying primarily on clinical diagnoses (even with female age together) do not discern patients needing different number of attempts or having different risks of recurrent IVF failure.	not just fertility services. It is for this reason that the cost/QALY approach is preferred to an alternative such as cost per baby. The predictors used for the economic analysis reflect those used in the prediction models to estimate relative treatment effectiveness. These in turn are based on data in the HFEA dataset, the most comprehensive registry of IVF treatment in a UK setting. The choice of prediction models is described in detail in Appendix I (starting on page 102). Diagnosis is important as any economic evaluation of IVF must also consider the treatment effectiveness relative to a comparator (such as expectant management).

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Univfy Inc	Evidence review J	045	029-036	Missing Evidence Led to Incorrect Conclusion: Based on the points provided in our comments and the fact that references demonstrating the validated, machine learning centre-specific IVF live birth prediction models were not considered in this DRAFT, we respectfully disagree with the committee's conclusion of not recommending the use of clinical prediction model in routine clinical practice. However, we understand that based on only the references that were evaluated, one would reach that conclusion because the models cited had many limitations and it is not clear how they would be implemented with quality assurance or evaluated for accountability moving forward. Notably, meta-analysis is not the appropriate approach. No meta-analysis will produce the actuarial and model metrics needed for an economic model for public funding for IVF. Instead, the appropriate method is to develop MLCS models validated for each clinic, and then use the objective prediction outcome variable (e.g. live birth) to show the GBP/IVF baby achievable given a certain budget. The policy makers can then see the GBP/IVF baby for patients in different validated prognostic tiers and together with IVF experts, determine reasonable thresholds for funding IVF. In addition, MLCS IVF	Thank you for this comment. Machine learning centre-specific live birth IVF prediction models were not identified that met the inclusion criteria of our review protocol and therefore the committee agreed not to recommend the use of a clinical prediction model in routine clinical practice. This evidence review was (primarily) undertaken to address predictive factors and models for the success of assisted reproduction techniques (ART) to inform recommendations on criteria for access to treatments. This is listed as a key area to be covered in the Guideline Scope (in the History tab of the guideline website).

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				prediction models designed for patients who have failed one or more IVF cycle can be used to determine funding thresholds for patients after failing an IVF cycle. Of course, there are additional considerations in the allocation of public funding such as whether to give each patient the same number of funded IVF treatments. MLCS models support policymakers by projecting the health (# of singleton babies, # families built), cost and services utilised (# of IVF cycles, # embryo transfers, etc.) for a range of policy scenarios being considered. MLCS models can also be used to support implementation of the chosen policy. In summary, based on directives of policy makers and IVF experts, the application of MLCS models as validated per clinic, enable public funding of IVF to result in predictable outcomes (e.g. number of patients helped, number of live births, etc.), predictable costs (for projection of public funds allocation), and predictable service utilization (so fertility centres can plan staffing and streamline operations) for a given population.	
Univfy Inc	Evidence review J	054, 186, 189	General	Criteria are unclear or inappropriate: It is not entirely clear what "Data Extraction" refers to, as a criterion for including or excluding studies for consideration. Our	Thank you for this comment.

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				interpretation from reading this page is that the research publication would need to provide the data set to enable committee reviewers to extract and audit the data. That criterion skewed the studies meeting inclusion criteria to be older (dating to times when it was easier to obtain permission to release data to the public domain). In the recent 10-15 years, many clinics and databases have policies in place that disallow sharing of clinical IVF data, even if anonymized or de-identified data, to the public due to various privacy concerns or concerns about reproductive health data being misused once in the public domain. That "Data Extraction" criteria excluded the following highly relevant research publications (that may lead the committee to different conclusions about the use of clinical IVF prediction models in routine practice). These research publications conveyed that the MLCS approach (building centre-specific IVF prediction models should be considered over aiming for a one-size-fits-all model that can apply to different clinics at different geographical locations for different patient populations. See Appendix J:	As outlined in the review protocol, the predictive performance of models was quantitatively synthesised in a meta-analysis and this required that the studies report a measure of variance which these studies do not do. This exclusion criterion does not require primary data to be available, but full and transparent reporting of summary statistics was required for a study to be included. The articles by Yao et al. 2025 and Yao et al. 2024 were published after the date of our literature search 11/10/2023. The article by Jenkins et al. 2020 is a commentary and therefore this would not meet our inclusion criteria.

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				Page 186, Reason for exclusion: "Data cannot be extracted". Note: This research paper reported IVF prediction models developed and validated for a single center using clinical data and outcomes of a first failed IVF cycle to predict the IVF outcomes of the second IVF cycle. This model is a "post-treatment model". Model metrics including AUC ROC and calibration were provided. Banerjee P, Choi B, Shahine LK, Jun SH, O'Leary K, Lathi RB, Westphal LM, Wong WH, Yao MW. Deep phenotyping to predict live birth outcomes in in vitro fertilization. Proc Natl Acad Sci U S A. 2010 Aug 3;107(31):13570-5. doi: 10.1073/pnas.1002296107. Epub 2010 Jul 19. PMID: 20643955; PMCID: PMC2922227. https://www.pnas.org/doi/10.1073/pnas.1002296107 Page 190, Reasons for exclusion: "Data cannot be extracted. No measure of variance reported for AUCs and no other extractable model performance data reported." Note: The above statement is not correct. This research paper reported a multicentre model that was validated for each of the 3 centres contributing data to the model training and validation. Model metrics including AUC ROC, calibration using Holsmer-Lemeshow goodness-of-fit test, prediction error for each prognostic tier, and improvement over age-control model and baseline (no	

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				model usage) measured in log likelihood. Detailed methods were provided on how each of these metrics were calculated. Choi B, Bosch E, Lannon BM, Leveille MC, Wong WH, Leader A, Pellicer A, Penzias AS, Yao MW. Personalized prediction of first-cycle in vitro fertilization success. Fertil Steril. 2013 Jun;99(7):1905-11. doi: 10.1016/j.fertnstert.2013.02.016. Epub 2013 Mar 21. PMID: 23522806. https://www.fertstert.org/article/S0015-0282(13)00273-2/fulltext Page 206-207, Reasons for exclusion: "Data cannot be extracted. No measure of variance reported for AUCs and no other extractable model performance data reported." Note: The above statement is not correct. This research paper reported validated MLCS PreIVF models that used multiple variables with the addition of AMH or AFC or both AMH and AFC to predicting IVF live birth outcome probabilities. Model metrics including AUC ROC, prediction error for each prognostic tier, PLORA, and improvement over age-control model measured in log likelihood, dynamic range and reclassification were reported. Detailed methods were provided on how each of these metrics were calculated. Nelson SM, Fleming R, Gaudoin M, Choi B, Santo-Domingo K, Yao M. Antimüllerian hormone levels and	

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				antral follicle count as prognostic indicators in a personalized prediction model of live birth. Fertil Steril. 2015 Aug;104(2):325-32. doi: 10.1016/j.fertnstert.2015.04.032. Epub 2015 May 21. PMID: 26003269. https://www.fertstert.org/article/S0015-0282(15)00306-4/fulltext The following research publication was not included. We urge the committee to review this research paper. Briefly, we compared 6 individual MLCS models (including updated versions) validated and were in clinical usage for 4-6 years against the US national registry-based, multicentre model. We reported the MLCS models were superior as measured by Precision-Recall AUC, F1 Score, and calibration. Further, we described the clinical utility of the superior models. The Discussion section is highly relevant to this "Evidence Review J" as we explained how these model metrics directly affect IVF access, IVF funding by public or private payer or the patients themselves, in addition to patients' decision-making. Yao MWM, Nguyen ET, Retzloff MG, Gago LA, Nichols JE, Payne JF, Ripps BA, Opsahl M, Groll J, Beesley R, Neal G, Adams J, Nowak L, Swanson T, Chen X. Machine learning centre-specific models show improved IVF live birth predictions over US national registry-based	

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				model. Nat Commun. 2025 Apr 17;16(1):3661. doi: 10.1038/s41467-025-58744-z. PMID: 40246850; PMCID: PMC12006386. https://www.nature.com/articles/s41467-025-58744-z The following review publications did not report original research on model training and validation, but they discussed model attributes based on the methods used for training and validation. We have mentioned various points in this document and urge the committee to review these papers because they give a very effective and different framework for thinking about prediction model attributes, clinical benefits and impact on IVF access and affordability: Yao MWM, Jenkins J, Nguyen ET, Swanson T, Menabrito M. Patient-Centric In Vitro Fertilization Prognostic Counselling Using Machine Learning for the Pragmatist. Semin Reprod Med. 2024 Jun;42(2):112-129. doi: 10.1055/s-0044-1791536. Epub 2024 Oct 8. PMID: 39379046; PMCID: PMC11581823. https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0044-1791536 Jenkins J, van der Poel S, Krüssel J, Bosch E, Nelson SM, Pinborg A, Yao MMW. Empathetic application of	

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				machine learning may address appropriate utilization of ART. Reprod Biomed Online. 2020 Oct;41(4):573-577. doi: 10.1016/j.rbmo.2020.07.005. Epub 2020 Jul 15. PMID: 32819841. https://www.rbmojournal.com/article/S1472-6483(20)30376-X/fulltext	
U-Ploid Biotechnologies Ltd	EHIA	006		Equality and Health Inequalities Assessment. U-Ploid welcomes the recognition of geographic inequity. Recommend the EHIA explicitly highlight (a) ICB-level variation in access/eligibility and (b) potential age-based and socioeconomic disparities (e.g., for women 35–41). Suggest monitoring and publishing ICB alignment progress and any differential impacts by deprivation and ethnicity.	Thank you for your comment. We have acknowledged your comment in the EHIA stage 5. Regarding monitoring ICB alignment progress, this is not within the remit of NICE. Department of Health and Social care lists current NHS funding for IVF treatment across England (see NHS-funded in vitro fertilisation (IVF) in England - GOV.UK) and HFEA monitors and collects data on IVF and ethnicity (see for example Fertility treatment 2023: trends and figures | HFEA).
U-Ploid Biotechnologies Ltd	Guideline			U-Ploid welcomes the staged update of CG156 and supports the emphasis on live birth outcomes, equity of access, and reducing ineffective add-ons across IVF pathways.	Thank you for your comment.
U-Ploid Biotechnologies Ltd	Guideline	016	017	Section 1.3.15 – Ovarian reserve testing. U-Ploid supports the use of anti-Müllerian hormone (AMH) and antral follicle count (AFC) for response prediction. Recommend clarifying that decisions on stimulation protocols, expected number of cycles, and counselling should prioritise live birth and cumulative live birth rate	Thank you for your comment. The recommendations in this section are intended to cover when to use ovarian reserve markers to predict outcomes related to assisted and spontaneous conception, and not how to provide ART. The sections

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				(CLBR) and time to live birth, rather than intermediate surrogate endpoints.	of the guideline titled Pituitary suppression and controlled ovarian stimulation now refers to the recently updated ESHRE guideline on Ovarian stimulation for IVF/ICSI, which provides guidance on decision-making for stimulation protocols.
U-Ploid Biotechnologies Ltd	Guideline	031	001	Section 1.9 – Access to IVF. U-Ploid supports clearer, cost-effective access rules and the definition of a full cycle. Implementation consideration: ask that integrated care boards (ICBs) align local eligibility and the definition of a full IVF cycle with the national standard within 12 months, and publish any justified local deviations with an accompanying Equality and Health Inequalities Assessment (EHIA), reviewed annually, to reduce unwarranted geographic variation.	Thank you for this comment. This request is beyond the remit of the NICE. We acknowledge the current geographic variation in the EHIA. Department of Health and Social care lists current NHS funding for IVF treatment across England (see NHS-funded in vitro fertilisation (IVF) in England - GOV.UK).
U-Ploid Biotechnologies Ltd	Guideline	036	007	Section 1.10.24 – Embryo selection. U-Ploid supports the "Do not offer PGT-A" stance on current evidence. We propose adding a surveillance/living-update trigger across add-ons for consistency: reconsider only if ≥2 adequately powered, multicentre RCTs in relevant IVF populations show a clinically meaningful improvement in live-birth (or a miscarriage reduction with net maternal–foetal benefit) with consistent external validity.	Thank you for your suggestion. While we may not apply exactly the suggested approach, NICE process for updating guidance will usually require there being substantial new evidence suggesting potential change to the current guidance.
U-Ploid Biotechnologies Ltd	Guideline	045	015	Research recommendations – new item. We propose adding: "Oocyte-quality therapeutic: Evaluate pre-IVF oocyte-quality therapeutics aimed at reducing meiotic errors in women aged >35 within IVF protocols. Can live	Thank you for this comment. In this update the guideline committee prioritised 5 other key research recommendations. All recommendations

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				birth rates be increased by reducing the rate of maternally inherited aneuploidies?"	for research are related to the evidence that has been reviewed and where a gap in evidence has been identified. Your suggested topics were not reviewed for this guideline update.

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