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Besins Healthcare	010	1.12 1.12.7	We request clarification on the point below from section 1.12: "The guideline may cross-refer to guidance from other developers, such as the European Society of Human Reproduction and Embryology (ESHRE) guideline on ovarian stimulation for IVF/ICSI (2019). No evidence reviews: the recommendations in the following sections will be stood down, as appropriate: 1.12.7 'Luteal phase support after IVF" Is the above point being removed from the NICE guidelines or being replaced by ESHRE (2019) guidelines?	Thank you for your comment. Sections 1.12.1 to 1.12.4 and 1.12.7 have not been prioritised for update as it is planned to refer to the comprehensive guidelines produced by the European Society of Human Reproduction and Embryology relating to ovarian stimulation. The decision on exactly which sections of the guideline to remove, and exactly what can be covered by the ESHRE guidelines will be discussed and agreed by the guideline committee.
Breast Cancer Now	General	General	The draft scope currently does not mention any guidance on ensuring patients with breast cancer (whether primary or metastatic) are provided with clear information about the potential impact of their treatment on their fertility, and an outline of the options available to them in order to preserve their fertility. A survey undertaken by Breast Cancer Now, in March 2018, found many women experienced significant variation in the information provided to them about fertility treatment and their options at the start of their cancer treatment. We would like to ensure that all women, regardless of where they live are given accurate and clear information about the potential impact of their cancer diagnosis on their fertility, and the options they are entitled to preserve their fertility, and how they access those options.	Thank you for your comment. The NICE guidance on early and locally advanced breast cancer: diagnosis and management (NG101) includes recommendations and information on fertility and family planning according to treatment options. The guideline update will have the opportunity to cross-refer to this guidance to facilitate the better management of people with breast cancer in relation to fertility, and the revised recommendations planned for section on preservation of fertility will also apply to people with all cancers, including breast cancer.
Breast Cancer Now	General	General	The draft scope does not currently mention national and regional variation in access to fertility, particularly within England, where ICSs are able to place their own restrictions	Thank you for your comment. The intention is that the updated guideline will provide clear advice to ICSs on the NICE-recommended investigations and treatments for health-

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			on access to fertility. We would like to ensure that Trust and ICS level restrictions will not be unilaterally placed within certain areas, which can lead to a postcode lottery for access.	related fertility problems. Thus it is hoped that implementation of the updated guideline will alleviate some of the geographical inequalities that currently exist in the treatment of health-related fertility problems.
Breast Cancer Now	General	General	Anecdotal evidence for women undergoing treatment for breast cancer further suggests that women do not always understand how they go on to access fertility treatment such as IVF or have further discussions around options for fertility once their cancer treatment is completed. We would like to see guidance supporting healthcare professionals to support and advise women undergoing fertility preservation about their options for accessing the fertility pathway once their cancer treatment is complete.	Thank you for your comment. The NICE guidance on early and locally advanced breast cancer: diagnosis and management (NG101) includes recommendations about discussion of fertility options and family planning. The guideline update will have the opportunity to include statements of good practice regarding liaison between services and to cross-refer to this guidance to facilitate the better management of people with breast cancer in relation to fertility. The revised recommendations planned for the section on preservation of fertility will also apply to people with all cancers, including breast cancer.
Breast Cancer Now	General	General	It would be helpful if the guidance could cover accessing pre-implantation genetic diagnosis for people with breast cancer with an inherited genetic fault.	Thank you for your comment. This is not a fertility treatment, therefore it is outside the scope of the guideline.
Breast Cancer Now	009	1.11	We appreciate the need to reassess access to IVF and to ensure that access is up to date with current evidence. However, in line with some of the points above, we would be concerned about greater restrictions being placed upon access to IVF, making it even harder for women to access treatment whilst undergoing cancer treatment to access and navigate the system.	Thank you for your comment. The evidence for 1.11 'Access criteria for IVF' will be reviewed and recommendations will be amended or added as appropriate. It is not possible to pre-suppose what the evidence may show but if there is evidence that offering treatments to certain groups is not a cost-effective use of NHS resources then this may be reflected in the access criteria. However, the access for women who have preserved their fertility while undergoing cancer

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				treatment is not likely to be restricted by the results of this review.
Breast Cancer Now	010	1.16	We understand the need to review guidelines for women with cancer who wish to preserve fertility and welcome evidence based recommendations. However, we would like to ensure that women undergoing cancer treatment who opt for cryopreservation are not having restrictions placed on their access to that. Given the nature of cancer treatment and its potential impact on egg viability, placing restrictions on this population would result in some patients being unable to access even private IVF post-treatment.	Thank you for your comment. For people who have stored gametes to preserve fertility due to medical conditions or treatment, the guideline already states that 'eligibility criteria used for conventional infertility treatment' do not apply and this is unlikely to change.
British Fertility Society	General	General	For specific mention of LBBTQ people in draft	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover LGBTQ people as long as the main criteria of health-related fertility problems are met, and this has been clarified in the scope.
British Fertility Society	General	General	Semenology: Reference to WHO 2010 should be updated to latest version as 2010 now out of date	Thank you for your comment. The link to the WHO manual in the section on semen characteristics links to the 2021 WHO laboratory manual for the examination and processing of human semen, which is the most up to date version available, so this link does not appear to be out of date.
British Fertility Society	007	1.3.2	Remove reference to post coital testing as not used anymore	Thank you for your comment. The current guideline recommends that post-coital testing of cervical mucus is not recommended because it has no predictive value. Therefore,

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				retaining this recommendation as planned will support your position that it is not used anymore.
British HIV Association	General	General	The draft scope makes no specific mention of HIV and how guidance needs to change to reflect evidence (although appreciate SaBTO are now reviewing this and any change from SaBTO may subsequently inform NICE guidance)	Thank you for your comment. NICE is aware that the British HIV association is currently updating its guidelines on sexual and reproductive health and that these may suitable for linking from the current guideline section 1.3 on 'Testing for viral status' and 'Viral transmission' in order to update this section. The handling of tissues as covered in the SaBTO guidelines is outside the remit of this NICE guideline and so will not be included.
British HIV Association	General	General	Three is no mention of needs of transgender individuals	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone as long as the main criteria of health-related fertility problems is met and the scope has been clarified to state this.
British HIV Association	General	General	There is no mention of fertility support for non-heterosexual couples or individuals other than for female-female couples, including guidance for surrogacy	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone, including the users of surrogates, as long as the main criteria of health-related fertility problems is met and the scope has been clarified to state this.

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British HIV Association	007	1.3.10.2	BHIVA does not think it is acceptable to recommend couples limit UPSI to the time of ovulation with an undetectable viral load.	Thank you for your comment. NICE is aware that the British HIV association is currently updating its guidelines on sexual and reproductive health and that these may suitable for linking from the current guideline section 1.3 on 'Testing for viral status' and 'Viral transmission' in order to update this section.
British HIV Association	007	1.3.10.4	If sperm washing is to be recommended, PrEP should probably be recommended here also, especially as PrEP is not recommended in 1.3.10.7.	Thank you for your comment. NICE is aware that the British HIV association is currently updating its guidelines on sexual and reproductive health and that these may suitable for linking from the current guideline section 1.3 on 'Testing for viral status' and 'Viral transmission' in order to update this section.
British Pregnancy Advisory Service	General	General	The draft scope currently limits focus to those with health-related fertility problems and those who may require interventions to preserve fertility. By limiting the scope in this way, an updated guideline risks furthering health inequalities experienced by groups such as same-sex couples and single women. Whilst the NICE equality impact assessment highlights the requirement of same-sex couples to demonstrate infertility by undergoing six round of IUI before they can access IVF, the proposed scope of the guidelines fails to proactively include specific guidance on best practice for case of same-sex couples, single women, trans individuals or other disadvantaged groups. Relying on commissioning bodies to	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone as long as the main criteria of health-related fertility problems is met and the scope has been clarified to state this. The updated guideline will clarify the criteria required to demonstrate health-related fertility problems. Where necessary, as described in the equality impact assessment linked from section 2 of the

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			interpret how best practice should be developed for these groups risks the perpetuation of wide variation in care experiences and access for same-sex couples and a deepening of inequality. FOI data has demonstrated the extent to which variation in commissioning practices have resulted in an unfair and unequal system. Recent figures found 73 CCGs (54%) did not routinely contribute any funding to patients who must undertake AI in order to verify their infertility (*https://www.bpas.org/media/3526/bpas-fertility-ivf-postcode-lottery-report-updated.pdf*). Whilst the scale of divergence can largely be attributed to funding issues, clear recommendations from NICE which guide provision and promote standardisation can help commissioners who are making difficult decisions about how to best serve disadvantaged groups in their communities – the current proposed scope does not seem to include space for recommendations of this nature. HFEA data shows that from 2010 to 2018 there was a 286.27% increase in the number of same-sex female couples undergoing fertility treatment cycles (https://www.hfea.gov.uk/about-us/publications/research-and-data/fertility-treatment-2019-trends-and-figures/). The experiences of these people must be explicitly within scope	scope, different recommendations may be made for different groups of people. Agreement of funding is outside the remit of NICE guidelines, but the implementation strategy for the guideline will outline the resource impact to support funding decisions.

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			of the NICE guideline and any updated guidance should reflect the growing trends within fertility care and offer clear information and best practice recommendations for clinicians who are providing care to patients that are not heterosexual couples. NICE guidelines may also be used by people accessing fertility care and their families. It is important that updated guidelines provide them with specific information on what they can expect from accessing treatment and the first stages of treatment, e.g. the six rounds of IUI needed to prove infertility and how this will be funded. It seems like the scope as outlined is seeking to avoid engagement in discussions around how fertility care should be provided for those not in a heterosexual couple. Whilst we understand these conversations can present challenges when considering how to develop best practice, there are thousands of people up and down the country for whom unequal access to care is a lived reality, NICE has a responsibility to reflect these lived realities and to improve care for these communities.	
British Pregnancy Advisory Service	001	019-023	Seems to suggest that because the government has made commitments around access for same-sex female couples NICE does not need to offer recommendations or best practice. There is currently no clarity on what powers the	Thank you for your comment. The Women's Health Strategy for England outlines that "there is no requirement for self-funding and the NHS treatment pathway for female same-sex couples will start with 6 cycles of artificial insemination, prior

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			government will be using to enforce their commitments and not including information within the NICE guideline is a missed opportunity to help deliver on a governmental commitment. Principle one of the NICE Charter states that NICE will prepare 'guidance and standards on topics that reflect national priorities for health and care.' Access for same-sex couple has been highlighted as a priority in the Women's Health Strategy and NICE guidelines should reflect this priority by including best practice guidance on recent government commitments.	to accessing IVF services if necessary". However, if conception does not occur after this period of time then one or both members of the same-sex couple (as appropriate) will be eligible for investigation and treatment of health-related fertility problems. The access criteria for health-related fertility problems will be included in the guideline, which will cover everyone as long as the main criteria of health-related fertility problems are met. The scope has been clarified to state this.
British Pregnancy Advisory Service	001	024-025	Currently the funding arrangements for the initial tests or procedures to demonstrate a health-related fertility problem are not within scope. However, cost effectiveness and acceptability is key part of NICE guidelines. Within the NICE charter it is stated that NICE aims to 'drive the uptake of effective and cost-effective new treatments and interventions to benefit the population as a whole and to improve and ensure equity of access to all members of society.' To remove a cost analysis for a specific group, who are already disadvantaged, is a failure. The guideline should make recommendations on funding arrangements for the initial tests or procedures to demonstrate a health-related fertility problem.	Thank you for your comment. The entry criteria for the guideline will be clearly defined as failure to conceive within a defined period of time or following a defined number of attempts at conception so tests or investigations will not be required to assess this. After these criteria have been met, any tests or investigations required for a health-related fertility problem included in the scope of the guideline will be recommended based on evidence of effectiveness and cost-effectiveness.
British Pregnancy	001	014	Currently states scope **may** include criteria on what constitutes sufficient evidence of health-related fertility problems to access further services, such as referral for	Thank you for your comment. The scope has been amended to state that access criteria for health-related fertility problems will be included in the guideline.

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Advisory Service			IVF. Scope **must** include address criteria on what constitutes sufficient evidence, particularly in relation to disadvantaged groups. As stated previously commissioners and health care professionals will be looking to this guideline to develop services and if recommendations for access criteria are not clearly defined there is a risk that access criteria will vary throughout the country for different groups. as is currently the case, creating further inequality.	
British Pregnancy Advisory Service	006		Should be withing scope to update the provision of information to include specific recommendations regarding information for same-sex female couples and single women.	Thank you for your comment. The recommendations on providing information (which are not included in the scope of this update) relate to all people, but where necessary, the committee may make editorial changes to the language to ensure it reflects the whole population to whom the guideline applies.
British Pregnancy Advisory Service	006	1.1.1	Principles of care, there should be scope to update the guideline to include information on the psychological effects of fertility problems in disadvantaged groups such as same-sex female couple.	Thank you for your comment. The recommendations on psychological effects of fertility problems (which are not included in the scope of this update) relate to all people, and the committee will be asked to consider editorial changes to this section to reflect that not all couples will be heterosexual.
Centre for Reproduction Research	General	General	The scope appears to adopt a fairly narrow definition when describing who might encounter health related fertility difficulties, specifically cis people within heterosexual couples (although we do note the acknowledgement of complexities in access to fertility treatment for female same-sex couples on page 1 and the fact this is outside of the scope of the guideline). For example, the text on why the	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone as long as the main criteria of health-related fertility problems are met. The scope has been clarified to state this. However, the language

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			guideline is needed (page 2, lines 11-18) appears to be based on heterosexual couples only and discounts the experiences of those in same sex couples as well as single persons experiencing fertility issues. Relatedly, the guideline makes no mention of Transgender people (as well as non-binary and other gender expansive people) and we wonder if a separate guideline is being developed regarding fertility for Transgender people and if so whether this might be noted and signposted to.	used in the guideline recommendations will be amended where necessary to make sure it is inclusive.
Centre for Reproduction Research	General	General	It was not clear from the scoping document whether age related fertility decline is to be included in the definition of 'health related' fertility problems (it is not specifically mentioned as a cause, but then neither is it explicitly excluded). This definition has implications for the reviews to be completed and treatments recommended. For example, oocyte donation would be considered a treatment option in the context of age related fertility decline.	Thank you for your comment. Health-related fertility problems (where conception does not occur following a defined period of time) are more likely to occur in older women and this is reflected in the equality assessment which is linked from section 2 of the scope. This assessment will be used during development to ensure that recommendations meet the needs of the groups listed within it, including whether different treatments are required based on age.
Centre for Reproduction Research	001	013	The document refers to "mental health problems that reduce or limit the ability to have children." We were unclear what this means and wondered if further explanation would help to clarify. We are not aware of there being any evidence that having a mental health problem can reduce or limit an ability to have children. Rather this is a complex set of circumstances that have yet to be teased out in the literature. It is the case that some studies suggest people with depression are more likely to also have infertility issues	Thank you for your comment. We have removed the reference to mental health problems in this introductory section of the scope.

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			but it is not clear whether there is causation here - it is too early in the literature to make these causal assumptions that mental health problems cause infertility. There is enough literature to show that people with mental health problems are more likely to contract sexually transmitted infections and this could be the cause of infertility (not the mental health problem itself). The concern is that if not worded delicately this may cause concern amongst readers experiencing mental health difficulties, and may cause stigmatising and other unanticipated effects. We would encourage NICE include a Psychiatrist as a stakeholder or advisor to avoid making incorrect casual assumptions.	
Centre for Reproduction Research	002	011-018	If this text is to be used in the guideline we would encourage that it be updated to a) make reference to fertility difficulties beyond heterosexual couples, b) use more up to date evidence: is there evidence to suggest 1 in 6 heterosexual couples still accurate or has this changed (the data is from the 80s/90s)?, c) be more consistent e.g. specifying the main cases of male (not only female) fertility problems, being clearer about how many cases of fertility problems in heterosexual couples are due to male factor, female factor, both and how many unexplained, etc. and d) include references (some points here are without references). A more comprehensive and transparent summary using newer data would be of benefit and would	Thank you for your comment. Your points have been addressed in turn: a) This section of the scope has been updated to include information from the HFEA on the proportion of fertility treatments for same sex couples and single people (data was not available on transgender and non-binary people). b) HFEA data suggests that between 1 in 6 and 1 in 7 heterosexual couples need help to conceive so this figure has not been amended. c) The details on causes of male infertility have been expanded to be more in line with the level of detail given on female causes.

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			help future-proof the guidance further as it presently reads as dated and will be further so once released.	d) Hyperlinked references have been added to this section of the scope.
Centre for Reproduction Research	006	Lines not provided	The scope states that 'no evidence reviews' will be undertaken with regard to 'Initial advice to people concerned about delays in conception' and that recommendations from the 2014 guideline will be retained as appropriate. These recommendations relate to, amongst other things, age and lifestyle factors (e.g. smoking, alcohol, weight, tight underwear, etc.). We would encourage you to undertake reviews of the evidence and provide an updated discussion of the evidence and recommendations based on the most up to date evidence. For example, with regard to male age, the 2014 guideline notes only one piece of evidence that male fertility declines with age, but several recent reviews suggest there is now a large body of evidence regarding this (e.g. (Johnson et al. 2015, Mazur and Lipshultz 2018, Phillips et al. 2019, Sharma et al. 2015). Similarly, evidence about the impact of lifestyle and fertility can be complex and contradictory, and within media and public discourse certain messages may be perpetuated without evidence having been reviewed or being clear; the NICE guidelines provide an opportunity for this evidence to be reviewed and for a judgement to be made on the basis of a range of up-to-date evidence, and for recommendations to be based on this.	Thank you for your comment. The updated guideline will retain recommendations on initial advice as, although there may be more recent evidence, it is unlikely that the recommendations on lifestyle factors would change, and so other areas of the guideline were prioritised where an updated evidence review is likely to change the recommendations.

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Centre for Reproduction Research	006	Lines not provided	The section on 'psychological effects of fertility problems' in the 2014 guideline might be updated to not assume that all couples are heterosexual, and might better reflect the way the landscape of patient support has changed over the last eight years. For example we know that some patients value peer support via digital and social media settings that allow for anonymity (see Hanna and Gough, 2016, 2017, 2018). The 2014 recommendations make no reference to gender sensitive interventions for fertility issues, yet the existing evidence suggests that a one size fits all approach, e.g. formal counselling, is not always the most suitable way to support those experiencing fertility issues. Updating the guidance to reflect the landscape of support which exists for the various groups experiencing fertility issues would make for better patient signposting from clinicians.	Thank you for your comment. The updated guideline will retain recommendations on principles of care and may cross-refer to information resources from the HFEA to advise that people have access to up to date, evidence-based information and support. Where necessary, the committee may make editorial changes to the language to ensure it reflects the whole population to whom the guideline applies.
Centre for Reproduction Research	010	1.15 (no line numbers)	Suggest a review to consider evidence on the use of oocyte donation for age related fertility decline, as well as updating recommendations for support and counselling. NB we are aware there have been calls for updating the HFE Act, which may have an impact on advice about who should receive what kinds of counselling.	Thank you for your comment. A review of the effectiveness of donor eggs has not been prioritised for inclusion in the scope because the age of the recipient has only a minor effect on the success rate of donor egg treatment. Counselling has not been prioritised for inclusion in the scope of this guideline as we will retain recommendations on principles of care. In addition, the guideline may cross-refer to information resources from the HFEA to advise that people have access to up to date, evidence-based information and support.

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Centre for Reproduction Research	012	028	There is no mention of the use of posthumous gametes for use in fertility treatment and perhaps it is time to consider whether guidelines would be useful to clinicians, either within this document or separately. The related legal and ethical issues are covered by established case law and ethical guidance such as American Society of Reproductive Medicine, 2018. It has been practised albeit rarely for over 40 years and there is a body of literature on the medical issues associated with collection, storage and use of posthumously collected gametes (eg Gat et al, 2022; Jequier et al 2014, Omil-Lima et al, 2021). It would be useful to consider whether existing guidance on efficacy of treatment for the recipient also applies in this context, eg 1.2.13.5 which refers to eligibility of 'women of childbearing age' to be referred for IVF.	Thank you for your comment and the references provided. The use of posthumous gametes is governed by HFEA regulations. The guideline update will consider whether a cross-link to this resource is required.
Centre for Reproduction Research	015	021-024	Children are not covered in the existing ESHRE guidelines on fertility preservation which are for adolescents and adults only, and it's very good to see them included here. This is particularly the case since ovarian tissue cryopreservation/testicular tissue cryopreservation are the only options for prepubertal children. It would be informative to specify some of the conditions which it is anticipated would be included within this guideline. The research so far on ovarian tissue	Thank you for your comment and the references provided. The planned evidence review on preservation of fertility will include children and young people and will cover a range of conditions and treatments which are likely to adversely affect fertility. When developing the systematic review protocol (which will guide the evidence review process), the committee will agree on which conditions should be included. For people who have stored gametes to preserve fertility due to medical conditions or treatment, the guideline already states that 'eligibility criteria used for conventional infertility treatment' do not apply and this is unlikely to change, and the

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			cryopreservation has included sickle cell, Turner syndrome, galactosemia, Premature ovarian insufficiency and others. It would also be useful to consider what constitutes sufficient evidence in this area to be included in the guideline. The evidence that is available about successful transplantation and pregnancy rates is very scant for these conditions but is likely to vary due to the nature of each condition; for Turner syndrome for example, around 150 girls have taken part in research studies to successfully freeze their ovarian tissue, but none have had it reimplanted so far (Jeve et al, 2019), partly because the technology has not been available for long enough. An international panel of experts on Turner syndrome has recommended that ovarian tissue cryopreservation is made available to suitable girls with Turner syndrome (Shleedorn et al, 2020) so for this specific condition there is a consensus on its potential efficacy. However, patients generally express a very high satisfaction rate with ovarian tissue cryopreservation even if they have not had tissue reimplanted (Lotz et al, 2020; van der Coelen et al, 2022). Jeve et al argue that evidence of efficacy of reproductive preservation for cancer treatment was only provided by making the treatment available and tracking its success rates; this strategy may also be a useful way to produce evidence of efficacy in the case of rare diseases. Currently, outcome data alone does not give a full picture of efficacy.	intention of the guideline is to provide evidence-based recommendations for fertility preservation to reduce inequality in services.

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			It would also be useful to develop referral criteria and a pathway for access to treatment, which is likely to vary by health condition. Access to fertility preservation differs from region to region so opportunities to take up fertility preservation vary, and patients may wish to make private arrangements if time allows and if fertility preservation is not available through publicly funded treatment. Patients need timely information and should then be given the opportunity to consider fertility preservation prior to other treatment.	
Centre for Reproduction Research	015	031	It would be useful to amend the point on 'patient satisfaction', which would only capture a limited range of studies focussed on this specific measure, to 'patient *experience'*, which would be inclusive of research which considers, for example, the impact of treatment on work, day to day living, relationships etc.	Thank you for your comment. Another outcome of health-related quality of life is already included later in the list which may capture some of these facets of experience. However, these outcomes are only suggestions and the exact details of the outcomes to be included will be agreed by the committee when they develop the review protocol for each question, and patient experience will be considered as one of the possibilities.
Coeliac UK	008	General	We are pleased to see that the guideline is likely to cross refer to recommendations within the NICE guideline on coeliac disease, NG20. NG20 includes a recommendation that testing for coeliac disease should be considered in people experiencing unexplained subfertility or recurrent miscarriage and it is important that this guidance is reflected within NICE guidance on fertility problems. This is particularly important	Thank you for your comment and support of this planned cross-reference.

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			as of the estimated 1 in 100 people with coeliac disease in the UK, only 36% are diagnosed [1]. [1] Nartey Y, Crooks CJ, Card TR, West J, Tata LJ et al. (2021). Incidence and prevalence of coeliac disease across the United Kingdom (unpublished).	
Cooper Surgical	002		PICSI_NICE submission 2022_abbreviated. Documentary evidence in the support of the fertility add on "PICSI"	Thank you for your comment. This appears to relate to PICSI but may have been an attachment. It is not possible to attach documents to the consultation form so we have not received this. However, PICSI is included as an 'add-on' and will be considered as part of this update.
Cooper Surgical	002		Preimplantation genetic testing for aneuploidy – CooperSurgical. Documentary evidence in support of the fertility add-on PGTA.	Thank you for your comment. This appears to relate to PGT-A but may have been an attachment. It is not possible to attach documents to the consultation form so we have not received this. However, PGTA is included as an 'add-on' and will be considered as part of this update.
Department of Health and Social Care	General	General	We feel it would be helpful to set out the criteria and data sources used in identifying the clinical areas for review.	Thank you for your comment. The criteria and data sources used in identifying the clinical areas to be updated are contained in the surveillance review carried out by NICE and are available at https://www.nice.org.uk/guidance/cg156/evidence/surveillance-review-decision-june-2015-pdf-4357167517
Department of Health and Social Care	014-015	031-006	The list of fertility treatment add-ons is not exhaustive, so we feel there should be an explanation of why these particular add-ons have been included in the scope.	Thank you for your comment. It would not be possible to address all add-ons available, so the current list of add-ons

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				was determined by those which are most widely used, or for which there are concerns about efficacy, risks or cost.
Department of Health and Social Care	001	011-023	This paragraph would benefit from additional reference to the importance of equality issues.	Thank you for your comment. The section on 'purpose of the guideline' aims to summarise the context for the guideline. The equality considerations have been noted in section 2 with a link to the assessment that will be used during the development of the guideline to ensure recommendations meet the needs of the groups listed within it. In addition, in response to stakeholder feedback, the groups of people covered by the scope has been clarified in section 3.1
Department of Health and Social Care	001	012	The draft scope uses the term 'health-related fertility problems'. We feel this term will require reconsideration in order to take account of developing policy on care for female same sex couples, as well as transgender and non-binary people.	Thank you for your comment. The scope does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone as long as the main criteria of health-related fertility problems are met, and the scope has been clarified to state this.
Department of Health and Social Care	002	011-018	We feel this paragraph should acknowledge the effect of fertility problems on female same sex couples, and transgender and non-binary people. It would also benefit from a reference to the Women's Health Strategy's ambition to eliminate variation in access and outcomes of fertility treatments.	Thank you for your comment. This section of the scope has been updated to include information from the HFEA on the proportion of fertility treatments for same sex couples and single people (data was not available on transgender and non-binary people). The Women's Health Strategy for England is already referred to in the 'purpose of the guideline' section and so this reference has not been duplicated here.
Department of Health and Social Care	002	021	Reference to Clinical Commissioning Groups (CCGs) needs changing to Integrated Care Systems (ICSs)	Thank you for your comment. This reference to CCGs has been changed to Integrated Care Boards.

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Department of Health and Social Care	003	001-004	This paragraph on preserving fertility should explicitly include people with endometriosis, as well as those undergoing interventions when gender transitioning (in line with the equality impact assessment).	Thank you for your comment. Fertility preservation for people with confirmed moderate-severe endometriosis, as well as for people with other conditions or situations likely to impair their fertility will be covered by draft review question 4.1 What is the effectiveness and safety of fertility preservation for children and adults undergoing treatment for cancer and other conditions or situations which are likely to impair the fertility?
Department of Health and Social Care	003	026-027	We feel the term 'health-related fertility problems' will require reconsideration in order to take account of developing policy on care for female same sex couples, as well as transgender and non-binary people. These groups should be explicitly mentioned under the 'Groups that will be covered in the update' heading.	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone as long as the main criteria of health-related fertility problems are met and the scope has been clarified to state this.
Department of Health and Social Care	003	010	'Commissioners of NHS fertility services' should be first on the list under 'Who the guideline is for'.	Thank you for your comment. The order of this list has been amended as you suggest.
Department of Health and Social Care	004	001	This bullet point should widen the scope of consideration of fertility preservation by explicitly making reference to people with endometriosis and people undergoing transition.	Thank you for your comment. The section of the guideline on the preservation of fertility is being updated, and this will include people with any condition that impacts on their fertility, and this may include hormone treatment for transgender people, or with endometriosis. However, the specific details will be decided by the committee when they develop the detailed protocol for this review question.

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Department of Health and Social Care	005	007	The consideration of the effectiveness and safety of fertility preservation should be inclusive of people with endometriosis and people undergoing transition.	Thank you for your comment. The section of the guideline on the preservation of fertility is being updated, and this will include people with any condition that impacts on their fertility, and this may include people undergoing transitions or with endometriosis. However, the specific details will be decided by the committee when they develop the detailed protocol for this review question.
Department of Health and Social Care	010	1.16 Guideline area	The review of evidence on fertility preservation for populations beyond those with cancer should include people with endometriosis and people undergoing transition.	Thank you for your comment. The section of the guideline on the preservation of fertility is being updated, and this will include people with any condition that impacts on their fertility, and this may include people undergoing transition and people, or with endometriosis. However, the specific details will be decided by the committee when they develop the detailed protocol for this review question.
Ferring Pharmaceuticals	General	General	**OHSS Burden:** The scoping document does not mention one of the most important safety issues associated with ovarian stimulation, which is the risk of developing ovarian hyperstimulation syndrome (OHSS). We feel that relevant information concerning OHSS should be included in the updating guidelines. 30% of patients who undergo ovarian stimulation develop ovarian hyperstimulation syndrome (Howard 2018). https://pubmed.ncbi.nlm.nih.gov/29789345/ A daily mail article from 2017 published the inconsistencies in reporting of OHSS by clinics and by the NHS. In one year	Thank you for your comment. OHSS has not been prioritised for inclusion in this update as OHSS had been covered appropriately by the comprehensive guidelines produced by the European Society of Human Reproduction and Embryology (ESHRE) relating to ovarian stimulation for IVF/ICSI (2019), therefore the guideline may cross-refer to this document as appropriate. An audit covering admissions for one year carried out to assess if the discrepancy between the data on hospital admission and the number of cases of OHSS reported to the HFEA was due to errors in the admission code, or actual

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<table>
<tr><th>Stakeholder</th><th>Page no</th><th>Line no</th><th>Comments</th><th>Developer's response</th></tr>
<tr><td></td><td></td><td></td><td>(2010), clinics reported just 16 cases of severe OHSS, however, there had been almost 700 emergency hospital admissions for the condition – more than 43 times the number declared by IVF doctors (https://www.dailymail.co.uk/news/article-4471726/Fertility-clinics-accused-covering-IVF-effects.html).

<u>THE NUMBERS GAP</u>
CASES OF SEVERE OHSS REPORTED BY CLINICS
<table><tr><td>YEAR</td><td>NUMBER</td><td>YEAR</td><td>NU</td></tr><tr><td>2010</td><td>16</td><td>2013</td><td>46</td></tr><tr><td>2011</td><td>48</td><td>2014</td><td>42</td></tr><tr><td>2012</td><td>44</td><td>2015</td><td>60</td></tr></table>
NHS HOSPITAL EMERGENCY ADMISSIONS FOR OHSS
<table><tr><td>2010/11</td><td>691</td><td>2013/14</td><td>74</td></tr><tr><td>2011/12</td><td>841</td><td>2014/15</td><td>77</td></tr><tr><td>2012/13</td><td>701</td><td>2015/16</td><td>83</td></tr></table>
The number gaps can probably be explained by the fact that clinics are obliged to only report cases of patients having to be hospitalised because of severe or critical OHSS (HFEA 2018). But mild and moderate cases are not reported. NICE is requested to look into this issue and expand the reporting criteria for OHSS by clinics, more so as clinical focus has</td><td>under-reporting of cases did not find evidence of systemic under-reporting of OHSS. It concluded that the NHS coding system does not appear to be a reliable method of identifying cases of OHSS and the HFEA has since developed recommendations to improve reporting, including change to reporting requirement and form, information for patients and raising awareness of national guidelines.</td></tr>
</table>

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<tr><td></td><td></td><td></td><td>shifted to moderate or severe OHSS which affects 2-3% of patients; while milder forms may develop in 20-30% of all in-vitro fertilisation (IVF) cycles (Nelson, 2017). https://pubmed.ncbi.nlm.nih.gov/28262238/

The burden of treating private patients who have self-paid to undergo ART and are suspected to have ovarian hyperstimulation syndrome (OHSS), falls on the NHS, as all these patients are referred to the NHS for further diagnosis and management.

Reference prices for treatment of OHSS (Reference: 2017/18 and 2018/19 National Tariff: currencies and prices)
<table>
<tr><th></th><th>Mild</th><th>Moderate</th><th>Severe</th></tr>
<tr><td>Patient seen by consultant</td><td>£173/per appointment (outpatient)</td><td>£173/per appointment</td><td></td></tr>
<tr><td>Bed stay</td><td></td><td></td><td>£2,652 (7</td></tr>
<tr><td>Potentially intensive care</td><td></td><td></td><td>£5,581 (u</td></tr>
</table></td><td></td></tr>
</table>

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			Estimated cost £350 £350-£860 £18-£67k	
Ferring Pharmaceuticals	General	General	**Referring to NICE Guidance 1.1 Principles of care (1.1.2 'Psychological effects of fertility problems')** The scoping document states - "No evidence reviews: retain recommendations" We will request for NICE to review the new evidence available re: psychological aspects of infertility treatment. We recommend that appropriate heterogeneous support, tailored to the patient and/or their partner's needs, must be put in place for those wishing to receive it. This includes offering clear information on processes, understanding the patient and/or partner's expectations, and ensuring healthcare professionals are trained in delivering difficult news. The evidence indicating how infertility and its treatments can have a significant, detrimental impact on psychological health is well documented (Abdishahshahani et al., 2020; Hasanpoor-Azghdy et al., 2014; Masoumi et al., 2013). Patients often discontinue their treatment due to the psychological impact of fertility care (Brandes et al., 2009; Gameiro et al., 2012).	Thank you for your comment and the references provided. The psychological effects of fertility problems has not been prioritised for inclusion in the scope of this guideline update as the guideline may cross-refer to information resources from the HFEA to advise that people have access to up to date, evidence based information and support.

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			In a longitudinal study investigating a cohort of 1391 couples, findings indicated that approximately half of the couples stopped before any fertility treatment was started, and one-third stopped after at least one IVF cycle. The main reasons for withdrawal were emotional distress (22.3%) and poor prognosis (18.8%), (Brandes et al., 2009). This is further emphasized by a systematic review which indicated that the most frequent reasons for discontinuation of fertility treatment were postponement of treatment (39.18%, postponement of treatment or unknown 19.17%), physical and psychological burden (19.07%, psychological burden 14%, physical burden 6.32%), relational and personal problems (16.67%, personal reasons 9.27%, relational problems 8.83%), treatment rejection (13.23%) and organizational (11.68%) and clinic (7.71%) problems. Importantly, psychological burden was common across all stages (Gameiro et al., 2012). Quality of life for couples 4-5.5 years after unsuccessful IVF treatment, and for whom treatment did not result in childbirth, was investigated. Despite having undergone unsuccessful IVF within the public health system, more than 75% lived with children 4-5.5 years later. Of the study group, 26% (n=69) had undergone additional IVF treatment in private clinics and 44.9% of the 69 individuals undergoing additional IVF, reported pregnancies and childbirths. This	

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			subgroup of patients had a better quality of life, compared to those without children. Additional IVF treatment may result in increased quality of life (Johansson et al., 2009). A study examining the psychological outcomes associated with failed ART treatment outcomes in men and women found that both depression and anxiety increased after ART treatment failure with an overall pooled standardised mean difference (SMD) of 0.41 (95% CI: 0.27, 0.55) for depression and 0.21 (95% CI: 0.13, 0.29) for anxiety. In contrast, depression decreased after a successful treatment, SMD of -0.24 (95% CI: -0.37,-0.11). Both depression and anxiety decreased as time passed from ART procedure. Nonetheless, these remained higher than baseline measures in the group with the failed outcome even six months after the procedure. Studies included in the narrative synthesis also confirmed an association with negative psychological outcomes in relation to marital satisfaction and general well-being following treatment failure (Milazzo et al., 2016). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7034165/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4009564/ https://pubmed.ncbi.nlm.nih.gov/23802102/ https://pubmed.ncbi.nlm.nih.gov/19783833/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3461967/	

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			https://pubmed.ncbi.nlm.nih.gov/19172440/ Currently, a number of psychological interventions are offered across fertility clinics, with no standardized recommended approach. Recent research indicates that emotions can differ in nature and intensity from infertility diagnosis to treatment (Boivin et al., 2022). This is likely influenced by differences in treatment journey stages, and individual differences. Accordingly, psychological needs should be tailored and addressed specifically based on patients' individual needs meaning that a range of evidence-based patient support and psychological interventions should be accessible. Counselling is not always the right approach for all couples. There should be alternative patient support options to that, such as offering a Patient Support Program which is adaptable to the needs of individual patients and/or their partners. https://pubmed.ncbi.nlm.nih.gov/35351377/	
Ferring Pharmaceuticals	General	General	**Referring to NICE Guidance 1.1 Principles of care (1.1.2 'Psychological effects of fertility problems')** Principles of care: We suggest specific patient support programs are offered to IVF clinics targeted to patients and/or partners:	Thank you for your comment. The updated guideline will retain recommendations on principles of care and may cross-refer to information resources from the HFEA to advise that people have access to up to date, evidence-based information and support.

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			• To support patients so they should not feel they have to drop out of treatment due to concerns about its cost or the psychological impact of treatment. • For those couples who wish to receive counselling, different types of support should be offered, led by the patient and/or partner needs. • This should include offering clear information on the treatment process, understanding of the patient and/or partner expectations, and ensuring healthcare professionals are trained in delivering bad news.	
Ferring Pharmaceuticals	General	General	**In response to Question on comment form:** Are there any cost saving interventions or examples of innovative approaches that should be considered for inclusion in this guideline? • The impact of OHSS interventions on costs should be considered and publications addressing incidence of OHSS and impact on costs should be studied to enable better patient outcomes and potential cost savings and/or	Thank you for your comment. OHSS has not been prioritised for inclusion in this update as OHSS and dosing techniques to avoid it, have been covered appropriately by the comprehensive guidelines produced by the European Society of Human Reproduction and Embryology (ESHRE) relating to ovarian stimulation for IVF/ICSI (2019), therefore the guideline may cross-refer to this document as appropriate.

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			Algorithm-based dosing is an innovative approach to individualising treatment and should be evaluated by NICE in its review.	
Ferring Pharmaceuticals	General	General	The scoping document proposes that with the recommendations in sections 1.12.1, 1.12.2, 1.12.3, 1.12.4 and 1.12.7 in the current fertility guideline will be stood down, which means that it will not be carried forward, i.e. the recommendation will not appear in the new fertility guideline. NICE may link to other developers' guidance on these topics, such as to the ESHRE guidelines. Our understanding is that the new guideline will not cover these five topics except, possibly, through cross-referring to other developers' guidance. This is disappointing because these five topics are very important key issues in the fertility treatment process and we will request for NICE to reconsider their decision that these topics will be stood down, particularly section 1.12.3.	Thank you for your comment. OHSS has not been prioritised for inclusion in this update as OHSS had been covered appropriately by the comprehensive guidelines produced by the European Society of Human Reproduction and Embryology (ESHRE) relating to ovarian stimulation for IVF/ICSI (2019), therefore the guideline may cross-refer to it as appropriate. It has been agreed that it is not appropriate use of NICE resources to duplicate work that has already been carried out by other reputable guideline developers.
Ferring Pharmaceuticals	002	010	**Referring to NICE Guidance 1.9 Intrauterine insemination (1.9.1.2)** Ferring requests that the guidelines incorporate that 'health-related fertility problems' should include failure to achieve a pregnancy after 2-3 IUI cycles instead of 6 IUI cycles, if IUI is indicated.	Thank you for your comment and the references provided. The current '6 cycles' in recommendation 1.9.1.2 was decided based on evidence that 12 cycles was the equivalent to 12 months of regular unprotected sexual intercourse (in terms of success-rate). However, to minimise the amount of invasive procedures required, the number of cycles was reduced to 6 by committee consensus when the previous

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			In women with normogonadotropic anovulation and clomifene citrate failure, the addition of intrauterine insemination did not increase livebirth rates compared to sexual intercourse added to gonadotrophins or clomifene citrate therapy indicating that intrauterine insemination does not contribute to higher pregnancy chances in women with anovulatory subfertility (Weiss et al. 2018). https://pubmed.ncbi.nlm.nih.gov/29273245/ To evaluate the influence of female age and cause of infertility on the outcome of controlled ovarian hyperstimulation (COH) and intrauterine insemination (IUI): 2717 COH/IUI cycles were studied in 1035 subfertile couples. The cumulative clinical pregnancy rates were 39% and 58% after three and six COH/IUI cycles, respectively. The cumulative pregnancy rate significantly decreased with maternal age and differed by cause of infertility (Farhi & Orvieto, 2009). One study only looked at 2 IUI cycles. 199 women received rFSH and 110 received CC. Both cumulative clinical pregnancy and live birth rates per patient were significantly higher in gonadotropin group (43.1% and 37.6%) as compared to CC group (28.2% and 20%) ($p < 0.05$ and $p < 0.01$, respectively). Live birth rate per cycle were significantly higher in gonadotropin group (24.3%) in comparison with CC group (13.8%) ($p < 0.05$). However, clinical pregnancy rate per cycle was not different between groups (28.4% vs 20%) ($p > 0.05$) Erdem et al., (2015).	version of the guideline was developed. As part of this update, the evidence for section 1.9 (intrauterine insemination) will be reviewed, therefore the committee may reconsider the number of recommended cycles.

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			https://pubmed.ncbi.nlm.nih.gov/20540664/ https://pubmed.ncbi.nlm.nih.gov/25855325/ Moreover, the HFEA states that IUI is not a cheaper/less invasive alternative to IVF. **https://www.hfea.gov.uk/treatments/explore-all-treatments/intrauterine-insemination-iui/** Duran et al. (2002) conducted a comprehensive systematic review of IUI and concluded that although IUI is a successful contemporary treatment for appropriately selected cases of infertility, the clinical management of the infertile couple should be performed in an expedited manner, taking into consideration the age of the woman, the presence of multifactorial infertility and the cost-effectiveness of the available treatment alternatives. https://pubmed.ncbi.nlm.nih.gov/12206471/	
Ferring Pharmaceuticals	002	020	**Referring to NICE Guidance 1.11 Access criteria for IVF** We agree with NICE that there is considerable delay for patients to access treatment for infertility and would like to work with NICE to shorten the timelines for infertile couples to access treatment more quickly. Given the UK's low birth rates and the importance of valuing investment in fertility, the updated recommendations should seek greater differentiation between age groups in terms of the duration	Thank you for your comments and the references provided. We have addressed these in order: - The evidence on 'Access criteria for IVF' will be reviewed as part of the planned update and add new recommendations made as appropriate. This review plans to look at predictive factors for success and this may include age. - The criteria for accessing treatment for health-related fertility problems will be defined, and the equality assessment (which is linked to section 2 in the scope) will be used during

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			of time that a woman has been unable to conceive, as well as greater stratification of access criteria to ensure that, as a woman ages, she is not exposed to unnecessary delays in accessing IVF. Such an approach would expectedly be cost-saving since starting treatment at an earlier age increases the chances of successfully conceiving with fewer treatment cycles. Please see below our comments regarding access to treatment. **Delays in Treatment Access** • There are unnecessary delays in accessing treatment, which may reduce chances of success due to older age, if the patient does ultimately get access to treatment (Bionews, April 2022). Timelines should be shortened to enable couples to access treatment more quickly and minimise the psychological distress that can result from delays in treatment. https://www.progress.org.uk/delays-to-nhs-fertility-treatment-uncovered/ • For women > 40 years of age, the current guidelines recommend offering only 1 IVF cycle to this group, but no rationale is provided for this recommendation. We will request for NICE to review this decision, so	development to ensure that recommendations meet the needs of the groups listed within it, including whether different treatments are required based on age. - The guideline does not currently recommend other non-clinical access criteria and this is not an area included in the scope of this update, so these will not be included in the updated guideline. The intention is that the updated guideline will provide clear advice to NHS organisations on the NICE-recommended investigations and treatments for health-related fertility problems, which will then be used by NHS organisations to provide equity of treatment.

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			this patient group have access to the different strategies of investigation and management proposed for patients over 40 in order to overcome their infertility and improve the live birth rate (Cabry et al 2014). https://www.maturitas.org/article/S0378-5122(14)00065-6/fulltext Kim et al (2017) have demonstrated that the cumulative live birth rate increased in patients 40 to 42 years of age with repeated IVF cycles. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5545219/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5545219/pdf/cerm-44-111.pdf • Most private IVF clinics in UK offer ART (assisted reproductive technologies) to self-paying women aged over 40 years, but this service is not provided by NHS clinics. • Given the UK's low birth rates and the importance of valuing investment in fertility, the updated recommendations should seek greater differentiation between age groups in terms of the duration of time that a woman has been unable to	

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			conceive, as well as greater stratification of access criteria to ensure that, as a woman ages, she is not exposed to unnecessary delays in accessing IVF. Such an approach would ultimately be cost-saving since starting treatment at an earlier age does increase the chances of successfully conceiving with the help of fewer treatment cycles. **Evidence to support:** • Recent research indicates that in the UK, the average time to infertility diagnosis is 3.3 years (40.2 months), and the time to treatment is 1.9 years (23.9 months), (Domar et al., 2021) https://pubmed.ncbi.nlm.nih.gov/34756644/. This means that on average, patients are delayed by approximately 5 ½ years (64.1 months) before treatment even begins. For those that are successful, time to achieving pregnancy further extends to 1 ½ years (19.1 months), with the average overall treatment journey length equating to approximately 6.7 years. In real-terms, this length of delay can significantly impact chances of success for individuals who are experiencing infertility. It is well established that fertility declines with age, especially in women, for whom the chances of achieving pregnancy decline substantially after the age of 35.	

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			Moreover, IVF success rates decline with increasing age (Yeh et al., 2013), and in England, NHS-funded IVF does not extend to those over 43 years. https://www.fertstert.org/article/S0015-0282(13)00910-2/fulltext#relatedArticles HFEA data from 2019 showed an overall live birth rate per embryo transfer of 32% for women aged under 35 using their own eggs. See Figure 1, Fertility treatment 2019: trends and figures | HFEA • Pertinently, findings from Domar and colleagues (2021) indicate that despite the definition of infertility as 'the failure to achieve pregnancy after 1 year (12 months) of regular, unprotected sexual intercourse'(WHO 2018), respondents in the UK reported an average of 3.3 years (40.2 months) of trying to achieve pregnancy without assistance before receiving a medical infertility diagnosis (Domar et al., 2021). https://www.who.int/health-topics/infertility#tab=tab_1 https://pubmed.ncbi.nlm.nih.gov/34756644/. • Data from patients and partners in the UK, collected as part of a global survey, demonstrated that the	

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			total delay in achieving pregnancy was on average of 6.8 ± 3.4 years (Poster presented at BFS meeting, 2022 and can be shared on request). **Abstract of poster presented at the British Fertility Society Annual Meeting, 2022** **Title:** Motivational drivers and barriers for patients with infertility, and partners to patients with infertility in the UK, to seek treatment consultation and undergo treatment. **Authors:** Marie Markert, Priti Bajaj **Background and objectives** This study aims to understand the key drivers and barriers for infertile patients and partners to infertile patients to seek consultation and undergo treatment. **Methods** Data from patients and partners in the UK were collected as part of a global survey from 15th March – 17th May 2019[1]. Average time to treatment, patient and partner perspectives on the treatment journey, and drivers for, and barriers to, infertility treatment were assessed. **Results**	

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			A total of 201 respondents (101 patients and 100 partners) were included. Mean age was 35.1±9.5 years, and 89% were heterosexual. Mean time respondents attempted to achieve pregnancy before diagnosis was 3.4±2.4 years, followed by a mean time to treatment consultation of 2.0±2.2 years, and a mean of 1.6±1.0 years of treatment to achieve successful pregnancy. A total delay of 6.8±3.4 years for respondents achieving pregnancy. Most frequently reported drivers for considering treatment in respondents with seeking treatment (N=116) was an equal desire within couples to have a child (41%) and feeling that the timing was right (41%). Among partners in couples seeking treatment (N=50), 30% cited transparency of information from health care professionals (HCPs) about treatment expectations as important. Of respondents not seeking a consultation (N=29), the most frequent reasons were perceived cost (31%) and not being equally keen to have a child (31%). Most frequently reported barriers for those not seeking treatment after consultation were a determination to conceive naturally (56% (N=15)) and costs of treatment (41% (N=11)). Post consultation, 37% (N=27) of respondents not seeking treatment reported that their HCP offered supportive services, compared with 63% (N=116) of respondents seeking treatment (p=0.025).	

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			Conclusions Diagnosis, consultation and treatment were delayed for years. Motivational coherence in the wish for a child was a key driver for seeking treatment and cost was a main barrier. **References:** 1. Domar A, Vassena R, Dixon M, Costa M, Vegni E, Guiglotto J, Markert M, Boivin J. Motivational factors and barriers for infertile patients and their partners to seek consultation and treatment. Human Reproduction 2020, Volume 35, Issue Supplement_1, July 2020, Page i41 https://pubmed.ncbi.nlm.nih.gov/34756644/. • The latest published data from HFEA shows that although live birth rates have increased steadily over the past three decades for most age groups, success rates are consistently lower, the higher the age of the patient (see Figure 1; Trends in Fertility treatment 2019: trends and figures, HFEA Report). See Figure 1, Fertility treatment 2019: trends and figures | HFEA • According to a recent audit by Fertility Network UK (2021), all of England's 116 clinical commissioning	

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			groups (CCGs) are rationing access to NHS-funded fertility treatment by introducing arbitrary, non-clinical criteria or redefining what constitutes an IVF cycle. The audit indicates that: ➢ One in five CCGs (20.7%) have redefined what an IVF cycle constitutes and offer partial or reduced cycles instead of full IVF cycles where all fresh and frozen viable embryos are transferred; ➢ Over 90% of CCGs deny help if an infertile individual's partner has a child from a previous relationship; ➢ Over two-thirds of CCGs (69%) refuse to treat single women; and ➢ Over a quarter of CCGs (26.6%) deny access to same-sex couples. Of the CCGs who do offer fertility treatment to same-sex couples, the majority withhold treatment until couples have proved their infertility by paying privately for six or 12 rounds of intrauterine insemination (IUI).	

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			https://fertilitynetworkuk.org/a-complete-postcode-lottery/ • Bhattacharya et al., 2020 used prediction modelling to estimate the impact of coronavirus disease 2019 (COVID 19) related delay in starting IVF or ICSI in different groups of women. Findings indicated that a delay in starting IVF would reduce success rates in all couples across varying ages and infertility diagnoses. This would result in a lower chance of live birth in older women, especially those with a known cause of infertility. In women with unexplained infertility, the impact of delay is compensated by the chance of natural conception during a 6–12 months treatment-free interval. In the post-COVID 19 recovery period, clinics planning a phased return to normal clinical services should prioritize older women, particularly those with a known cause of infertility. https://pubmed.ncbi.nlm.nih.gov/33226080/ • A recent National Patient Survey conducted by the HFEA indicates that after speaking to a GP, it was generally another 6-18 months before treatment started (HFEA, 2022). However, around a quarter	

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			waited over 18 months. Reasons for the wait varied between NHS and privately funded patients, but NHS patients were more likely to have been affected by delays in referrals due to COVID-19 (32% vs. 18% of private patients). https://www.hfea.gov.uk/about-us/publications/research-and-data/national-patient-survey-2021/ • In the addition, the National Patient Survey indicated that around four in five (78%) patients spoke to a GP prior to starting treatment, usually within one to two years after first trying to conceive. However, less than half (47%) were satisfied with their experience of doing so, indicating a need for better quality of care at this stage of the fertility journey. https://www.hfea.gov.uk/about-us/publications/research-and-data/national-patient-survey-2021/ • Further, delays in treatment can compound the psychological distress that often co-exists with infertility treatment. A recent study was conducted in	

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			the UK, to target all fertility patients aged >18 years whose treatment had been impacted by COVID-19. Patients reported feeling 'powerless/helpless' (78.3%), 'frustrated' (59.3%) and 'anxious' (54.7%) in response to the closure of fertility clinics. The majority were 'very concerned' about time passing and not knowing when they could start treatment again (79.0%), and the length of waiting lists when clinics reopened (70.9%). While 76.8% of respondents had some concerns around contracting COVID-19, 42.9% were 'not at all concerned' about undergoing in-vitro fertilization treatment during a pandemic (Gurtin et al., 2022). https://pubmed.ncbi.nlm.nih.gov/35165660/	
Ferring Pharmaceuticals	002	024	**Referring to NICE Guidance 1.11 Access criteria for IVF** **Inequalities in Access to Treatment: Geographical** Currently, implementation of guidance is dictated by individual Clinical Commissioning Groups (CCG's) resulting in a geographical 'postcode lottery' in terms of access to treatment. As such, access to treatment may be stricter than what is recommended by NICE. Moreover, restrictions placed by CCG's disadvantages particular groups (e.g. older patients where the CCG has defined stricter age restrictions).	Thank you for your comment. The guideline does not currently recommend other non-clinical access criteria and this is not an area included in the scope of this update, so these will not be included in the updated guideline. The intention is that the updated guideline will provide clear advice to NHS organisations on the NICE-recommended investigations and treatments for health-related fertility problems, which will then be used by NHS organisations to provide equity of treatment.

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			This must be addressed to ensure that all individuals, regardless of geographical location, have consistent access to care. **Evidence to Support** • According to a recent audit by Fertility Network UK (2021): ➢ The majority of CCGs (89.9%) don't offer the recommended three full IVF cycles to clinically eligible women under 40; ➢ The majority of CCGs (72.4%) don't offer the recommended one full IVF cycle to clinically eligible women aged between 40-42; ➢ One in four CCGs (23.3%) have introduced additional age hurdles for women, with six CCGs refusing to offer help to women over 35; https://fertilitynetworkuk.org/a-complete-postcode-lottery/ "UK commissioning is unfair," said Sarah Norcross of the charity Progress Educational Trust, which wants better choices for people affected by infertility, "Scotland offers a service in line with NICE guidelines, with 60% of cycles	

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			funded, whereas in England, state funded treatment has dipped below 40%, with huge variance in treatment offered" (Howard 2018). https://pubmed.ncbi.nlm.nih.gov/29789345/ Similarly, the HFEA Trends in Fertility treatment 2019 indicated that there is a post code lottery when it comes to IVF funding, and funding has declined across England and Northern Ireland. See Figure 8, Fertility treatment 2019: trends and figures | HFEA These geographical disparities are likely to impact patients' chances of success. A population-based study that analysed the cycle data from 178,898 women in the UK indicated that the chance of a live birth after three complete cycles of IVF in UK was 42.3% for treatment commencing from 1999 to 2007 (McLernon et al., 2016), whereas, the cumulative prognosis-adjusted live-birth rate after 6 cycles was 65.3%, with variations by age and treatment type (Smith et al., 2016). These findings support extending access to treatment by IVF beyond 3 or 4 cycles. https://pubmed.ncbi.nlm.nih.gov/26783243/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4934614/	

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Ferring Pharmaceuticals	002	024	**<u>Referring to NICE Guidance 1.11 Access criteria for IVF</u>** **Inequalities in Access to Treatment: Disparities Across Patient Demographics** There has been much public discussion in recent years of health inequalities between varying demographic communities across the UK. This must be addressed to ensure that all individuals, regardless of social or ethnic background, from minority populations to single women and same sex couples, have consistent access to treatment. **Evidence to Support** • A recent HFEA Report (2014-18) highlights the disparities in access to and outcomes of fertility treatment by ethnic group. It states that: ➢ Black patients had lower IVF birth rates: for Black patients aged 30-34, the birth rate per embryo transferred was on average 23% compared to Mixed and White patients at 30% from 2014-2018. ➢ Black patients reported higher rates of tubal factor infertility, accounting for 31% of patient-based infertility compared to the 18% average from 2014-2018.	Thank you for your comment and the references provided. The evidence on 'Access criteria for IVF' will be reviewed as part of this update and new recommendations added as appropriate,. The equality assessment (which is linked to section 2 in the scope) will be used during development to ensure that recommendations meet the needs of the groups listed within it, including whether different investigations and management are required for women from Black and ethnic minority groups. In relation to your second point about same sex couples or single people, the focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone as long as the main criteria of health-related fertility problems are met, and this has now been clarified in the scope.

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			➢ Black patients had the highest multiple birth rates of any ethnic groups at 14%, compared to a national average of 12% from 2014-2018. ➢ Black patients generally started IVF at later ages than other ethnic groups at an average age of 36.4, compared to the national average of 34.6 in 2018. https://www.hfea.gov.uk/about-us/publications/research-and-data/ethnic-diversity-in-fertility-treatment-2018/ • According to a recent audit by Fertility Network UK (2021), all of England's 116 clinical commissioning groups (CCGs) are rationing access to NHS-funded fertility treatment by introducing arbitrary, non-clinical criteria or redefining what constitutes an IVF cycle. The audit indicates that: ➢ Over two-thirds of CCGs (69%) refuse to treat single women; and ➢ Over a quarter of CCGs (26.6%) deny access to same-sex couples. Of the CCGs who do offer fertility treatment to same-sex	

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			couples, the majority withhold treatment until couples have proved their infertility by paying privately for six or 12 rounds of intrauterine insemination (IUI). https://fertilitynetworkuk.org/a-complete-postcode-lottery/	
Ferring Pharmaceuticals	002	024	**Referring to NICE Guidance 1.11 Access criteria for IVF** **Inequalities in Access to Treatment: Financial** The geographical disparities in access to NHS-funded infertility treatment is further exacerbated by the fact that those in higher income groups can pay privately for access to IVF. This inequity reflects CCG funding and policy, and as such, should be harmonised across larger geographies. Recent research investigating barriers to seeking infertility consultation and treatment indicates that the most common barrier for patients was that "Fertility treatments are costly", reported by 37.5% (n = 132) of respondents (Domar et al., 2021). https://pubmed.ncbi.nlm.nih.gov/34756644/.	Thank you for your comment. The intention is that the updated guideline will provide clear advice to NHS organisations on the NICE-recommended investigations and treatments for health-related fertility problems. Thus it is hoped that the implementation of the guideline will reduce the geographical variations in the provision of fertility treatment.
Ferring Pharmaceuticals	003	001	**Referring to NICE Guidance 1.3 Investigation of fertility problems and management strategies and 1.16.1 Cryopreservation of semen, oocytes and embryos**	Thank you for your comment and the reference provided. As part of this update, the sections on investigations for female fertility problems and fertility preservation for children and

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			Elective oocyte cryopreservation for age-related fertility decline should be incorporated in women's reproductive options to ensure informed decisions and reproductive autonomy, and mitigate age related loss of fertility potential (Cronopulu et al 2021). https://pubmed.ncbi.nlm.nih.gov/33608838/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7894970/pdf/10815_2021_Article_2072.pdf	adults in situations likely to impair their fertility will both be reviewed, and new recommendations covering elective oocyte cryopreservation may be considered by the committee as part of the evidence review.
Ferring Pharmaceuticals	004	006	**Referring to NICE Guidance 1.2 Initial advice to people concerned about delays in conception** Factors beyond age should also be taken into account when considering the likelihood of success. The timelines of the treatment process likely play a role too. For instance, if patients are expected to try to conceive naturally for 2 years and have 12 IUIs before being eligible to undergo IVF, this may well affect both patient experience (potentially leading to dropouts) and treatment outcomes. Currently, the average age of starting IVF in the UK is 35.7 years (HFEA 2019 Trends Report). As such, in light of age-related declines in male and female infertility, patients should be aware of treatments timelines in order to remain fully informed.	Thank you for your comment. The guideline scope covers the treatment of health-related fertility problems and does not cover the provision of population-wide health education programmes to raise awareness of fertility issues.

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			See Section 6, Fertility treatment 2019: trends and figures | HFEA Further, an educational life-course approach should be adopted to educate the public on their fertility "timelines". Whilst infertility may, in part, be on the rise due to a changing social climate, it is also due to a lack of knowledge about infertility, its causes and its consequences, that it continues to spread. In line with a recent national report from France (Hamamah, Berlioux, 2022), an educational life-course approach should be implemented. That is, fertility education should begin in schools, and continue throughout adulthood through national campaigns. Specifically, the public should be regularly informed about the physiology of reproduction, the decline in fertility with age, the risk factors for infertility, the options for and effectiveness for social egg-freezing, and the limitations to the effectiveness of assisted reproduction. Link for English Translation of Report: https://we.tl/t-ijJdSzHmGU - This link is due to expire in 7 days. Please let us know if NICE requires for us to share the document directly with you. https://solidarites-sante.gouv.fr/ministere/documentation-et-publications-officielles/rapports/sante/article/rapport-sur-les-causes-d-infertilite-vers-une-strategie-nationale-de-lutte	

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Ferring Pharmaceuticals	004	023	**Referring to NICE Guidance 1.12 Procedures used during IVF treatment (1.12.3 Controlled ovarian stimulation in IVF)** It is stated that NICE will use predictive factors and models for the success of assisted reproduction techniques (ART) to inform recommendations on criteria for access to treatments. However, it is not clear how NICE are planning to do this? Will they be adding additional criteria to age, weight etc to restrict access? And how does this fit with their equality in access assessment? It is requested that NICE take into consideration the significant advances in the understanding of AMH as a predictive marker for ovarian response (Arce et al., 2013; Shrikhande et al., 2020), which inevitably will guide gonadotropin dosing (together with body weight) to optimise patient responses (Andersen et al., 2016; Arce et al 2016). https://pubmed.ncbi.nlm.nih.gov/23394782/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7515982/ https://pubmed.ncbi.nlm.nih.gov/27912901/	Thank you for your comment and the references provided. The evidence for 1.11 'Access criteria for IVF' will be reviewed and recommendations will be amended or added as appropriate. It is not possible to pre-suppose what the evidence may show but if there is evidence that offering treatments to certain groups is not a cost-effective use of NHS resources then this may be reflected in the access criteria. The exact details of the interventions (such as use of AMH) to be included in the reviews will be agreed by the committee when they develop the review protocol for this question.
Ferring Pharmaceuticals	004	026	• The possibility to reduce interventions associated with excessive ovarian response or to prevent early ovarian hyperstimulation syndrome (OHSS) also should be given consideration for inclusion in	Thank you for your comment and the references provided. Ovarian stimulation will only be reviewed in the context of unexplained fertility problems. For the rest of the population, the committee agreed that OHSS had been covered

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			ovarian stimulation protocols (Devroey et al., 2012; Witz et al., 2020; Andersen et al., 2016; Ishihara et al., 2021; Qiao et al., 2021). https://pubmed.ncbi.nlm.nih.gov/22244781/ https://pubmed.ncbi.nlm.nih.gov/32416978/ https://pubmed.ncbi.nlm.nih.gov/27912901/ https://pubmed.ncbi.nlm.nih.gov/33722477/ https://pubmed.ncbi.nlm.nih.gov/34179971/ • Consideration also needs to be given to the NHS burden of privately treated infertility patients who develop OHSS. Regimens that not only reduce the chance of developing OHSS but does not compromise other outcomes such as pregnancy or live birth rate should be considered, particularly for women who are at risk of developing OHSS during ART (Mourad et al., 2017). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6469542/ • Incidence of OHSS has consequences for burden on the NHS, particularly by patients who have undergone private IVF treatment and make up about 70% of the total number of patients undergoing IVF treatment.	appropriately by the comprehensive guidelines produced by the European Society of Human Reproduction and Embryology (ESHRE) relating to ovarian stimulation for IVF/ICSI (2019), therefore the guideline may cross-refer to it as appropriate. It is outside the remit of the NICE guideline to advise the HFEA on reporting criteria since this is part of its role as a regulator.

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			• There should be an expansion on the reporting criteria for OHSS by clinics to the HFEA, so that there is greater transparency on the numbers of mild, moderate and severe cases **Evidence to Support** **Efficacy and safety of Algorithm-Based gonadotrophin administration** There is ample evidence to support the use of a dosing alogorithm, as demonstrated by four randomised clinical trials clinical trials (Andersen et al. 2016; Bosch et al. 2018; Ishihara 2021; Qiao 2021), and further supported by Real World Evidence (Bachmann, 2021). https://pubmed.ncbi.nlm.nih.gov/27912901/ https://pubmed.ncbi.nlm.nih.gov/30594482/ https://pubmed.ncbi.nlm.nih.gov/33722477/ https://pubmed.ncbi.nlm.nih.gov/34179971/ https://pubmed.ncbi.nlm.nih.gov/35193799/	
Ferring Pharmaceuticals	005	007	**Referring to NICE Guidance 1.16.1 Cryopreservation of semen, oocytes and embryos** We agree with NICE to consider fertility preservation/planned oocyte cryopreservation (OC) for	Thank you for your comment and the references provided. The scope includes a review of the evidence for the preservation of fertility for children and adults undergoing treatment for cancer and other conditions or situations which are likely to impair their fertility, and this may include different

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			other chronic medical conditions where treatment can impact future Preliminary data supports that utilization of oocyte cryopreservation in both medical and planned oocyte cryopreservation results in preservation of fertility and subsequent live births in patients who return to use their cryopreserved eggs. Higher oocyte yield, with fewer ovarian stimulation cycles, and higher live birth rates are seen in patients who seek oocyte cryopreservation at younger ages, reinforcing the importance of age on fertility preservation. Oocyte yield and live birth rates are best among patients < 37.5 years old or with anti-mullerian hormone levels > 1.995 ng/dL, at the time of oocyte retrieval, (Walker et al., (2022). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8740039/pdf/12958_2021_Article_884.pdf	recommendations for the optimal techniques for preservation at different ages.
Ferring Pharmaceuticals	012	015	For the area of infertility there are some significant broader cost implications that should be considered, in addition to the costs to the NHS and Personal Social Service (PSS). There are some wider societal implications that should potentially also be considered (macroeconomic impact of declining fertility rates, impact on others than just the potential parents etc) as well as the economic impact on patients themselves, if they are not eligible for NHS funding (with reference to the NICE equality assessment document).	Thank you for your comment. This section of the scope is intended to give a very general overview to economic aspects and most of the text is standard across different NICE guidelines. It is not intended to describe methods for analysis in any detail and the actual priorities for economic appraisal are determined during guideline development, in consultation with the committee. However, the NHS and Personal Social Service (PSS) perspective reflects NICE's approach to costing as described in the NICE Guidelines Methods Manual

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				(https://www.nice.org.uk/process/pmg20/chapter/incorporating-economic-evaluation).
Ferring Pharmaceuticals	012	027	It is not clear how this assessment was done and what is to be analysed here. It will be helpful to get clarification on this for better understanding. NICE should consider cost-effective analyses, when considering specific treatment options.	Thank you for your comment. This section of the scope is intended to give a very general overview of economic aspects and most of the text is standard across different NICE guidelines. It is not intended to describe methods for analysis in any detail and the actual priorities for economic appraisal are determined during guideline development in consultation with the committee. The methods used by NICE for economic evaluation are described in the NICE Guidelines Methods Manual (https://www.nice.org.uk/process/pmg20/chapter/incorporating-economic-evaluation) but cost-utility and cost-effectiveness analyses are frequently utilised for areas prioritised for economic analysis. The particular section referred to in your comment has been deleted as this kind of detail is not typically included in the scope. Details of how this assessment was done can be found in the appendix of the CG156 (https://www.nice.org.uk/guidance/cg156/evidence/full-guideline-pdf-188539453) on page 240-41
Ferring Pharmaceuticals	014	005	**Referring to NICE Guidance 1.5 Ovulation disorders**	Thank you for your comment and the references provided. We will review evidence on ovulation induction strategies in women with ovulation disorders (WHO group I, II, III) and the

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			For women with WHO Group II ovulation disorders metformin does not increase live birth rates in PCOS patients (Wu et al., 2020; Croch et al., 2022). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7399751/?report=printable https://journals.lww.com/ebp/Citation/2022/03000/Is_metformin_effective_for_treating_infertility.28.aspx There is evidence that aromatase inhibitors (off-label) may be more effective than clomifene citrate in PCOS patients (Legro et al., 2014). https://www.nejm.org/doi/full/10.1056/nejmoa1313517 Aromatase inhibitors do not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient should provide informed consent, which should be documented.	committee will make new recommendations based on the evidence identified.
Ferring Pharmaceuticals	014	015	In the updated guidelines, factors or models that can predict success in IVF treatment, should address the algorithm-based dose calculation based on patient's age and serum AMH. https://pubmed.ncbi.nlm.nih.gov/27912901/	Thank you for your comment and the reference provided. The evidence for 1.11 'Access criteria for IVF' will be reviewed and recommendations will be amended or added as appropriate. The exact details of the interventions (such as use of AMH) to be included in the reviews will be agreed by the committee when they develop the review protocol for this question.

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Ferring Pharmaceuticals	014	023	**Referring to NICE Guidance 1.11 Access criteria for IVF** There is great variation across CCG's in terms of access to IUI as well as IVF which should be addressed. Clinicians need specific guidance to answer two main questions when treating couples with COH and IUI, and this information is not provided in current NICE Guidelines: 1. What is the chance that this treatment will result in a pregnancy? 2. When should we proceed to the next treatment strategy, namely, IVF. To evaluate the influence of female age and cause of infertility on the outcome of controlled ovarian hyperstimulation (COH) and intrauterine insemination (IUI): 2717 COH/IUI cycles were studied in 1035 subfertile couples. The cumulative clinical pregnancy rates were 39% and 58% after three and six COH/IUI cycles, respectively. The cumulative pregnancy rate significantly decreased with maternal age and differed by cause of infertility (Farhi & Orvieto, 2009). One study only looked at 2 IUI cycles. 199 women received rFSH and 110 received CC. Both cumulative clinical pregnancy and live birth rates per patient were significantly higher in the gonadotropin group (43.1% and 37.6%) as	Thank you for your comment and the references provided. The evidence for 1.11 'Access criteria for IVF' will be reviewed and recommendations will be amended or added as appropriate. It is not possible to pre-suppose what the evidence may show but if there is evidence that suggests when to proceed to the next treatment this may be reflected in the recommendations. The exact details of the outcomes to be included in the reviews will be agreed by the committee when they develop the review protocol for this question.

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			compared to CC group (28.2% and 20%) ($p < 0.05$ and $p < 0.01$, respectively). Live birth rate per cycle were significantly higher in the gonadotropin group (24.3%) in comparison with CC group (13.8%) ($p < 0.05$). However, clinical pregnancy rate per cycle was not significantly different between groups (28.4% vs 20%) ($p > 0.05$) Erdem et al., (2015). https://pubmed.ncbi.nlm.nih.gov/20540664/	
Ferring Pharmaceuticals	015	013	It has been suggested that embryo and oocyte cryopreservation may be offered in the same cycle to reduce the number of frozen embryos and provide optimal outcomes. The use of oocyte cryopreservation tends to avoid the moral objections or legal restrictions that can be associated with embryo cryopreservation and storage, as well as the disputes that can arise if a couple later separates (Shenfield et al 2017). https://pubmed.ncbi.nlm.nih.gov/30895222/ There is also some evidence from large observational studies that implantation and pregnancy rates are higher from frozen–thawed embryos than when embryos derived	Thank you for your comment and the references provided. Both oocyte and embryo preservation are covered under the planned evidence review on the preservation of fertility.

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			from frozen oocytes are used (ASRM guideline 2013; Scaravelli et al 2010). ASRM guideline Mature oocyte cryopreservation: a guideline - Fertility and Sterility (fertstert.org) https://pubmed.ncbi.nlm.nih.gov/20797902/ https://www.rbmojournal.com/article/S1472-6483(10)00321-4/fulltext	
Fertility Scotland National Network	General	General	Advanced maternal age (often the reason for IVF) also increases risk for miscarriage, stillbirth, birth defects and maternal deathand ask that consideration be given by NICE to adding the MBRRACE-UK report (November 2021 - https://www.npeu.ox.ac.uk/mbrrace-uk) recommendations to this guidance, please see details below: i) "*Guidance is needed on maternal medical assessment and screening prior to assisted reproduction, particularly for older women who are at higher risk of co-morbidities such as cardiac disease and cancer*" "*Guidance on single embryo transfer for older women undergoing in vitro fertilisation, particularly in the context of medical co-morbidities"* should be developed.	Thank you for your comment. Health-related fertility problems (where conception does not occur following a defined period of time) are more likely to occur in older women and this is reflected in the equality assessment which is linked from section 2 of the scope. This assessment will be used during development to ensure that recommendations meet the needs of the groups listed within it, including whether different treatments are required based on age, such as the number of embryos to be transferred.
Fertility Scotland National Network	General	General	We are disappointed at the exclusion of single people, same sex couples and surrogacy from the guideline scope and the lack of mention of the higher obstetric risk for	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios.

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			women undergoing fertility treatment, which include but are not exclusive to increased likelihood of: • multiple births, with accompanying risk for premature birth, high blood pressure and placenta abnormalities. • hypertensive diseases of pregnancy • gestational diabetes • preterm delivery • fetal low birth weight congenital defects/imprinting disorders	Therefore, the guideline will cover everyone, including the users of surrogates, as long as the main criteria of health-related fertility problems is met, and the scope has been clarified to state this. Consideration of the increased obstetric risk has now been added to the scope as an additional question.
Fertility Scotland National Network	002	009 and 010	This does not take into consideration same sex males couples.	Thank you for your comment. Same sex couples will need to demonstrate infertility by completing 6 cycles of artificial insemination (using a surrogate in the case of same sex male couples) before accessing investigations for fertility problems, and this will also be the case with heterosexual couples where vaginal intercourse is not possible. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios and covers all people with a health-related fertility problem. The scope has been clarified to state this.
Fertility Scotland National Network	003	001	Fertility preservation should be included in section 1 (Purpose of this guideline).	Thank you for your comment. Fertility preservation has been added to the opening section on the purpose of the guideline.

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Fertility Scotland National Network	001 and 002	012 and 007	Restricting the scope to health-related fertility problems excludes many LGBT couples who require access to fertility treatment; this also excludes single people who also access treatment.	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone as long as the main criteria of health-related fertility problems are met, and the scope has been clarified to state this.
Fertility Scotland National Network	007	1.3	The guideline does not mention Covid-19 vaccination.	Thank you for your comment. There are a wide range of treatments and vaccinations that are not mentioned in the guideline and there does not seem to be a specific reason why Covid-19 vaccination should be prioritised for inclusion.
Fertility Scotland National Network	007	1.3.1	Home testing kits for semen analysis and sperm DNA fragmentation, should also be considered.	Thank you for your comment. The current evidence base on home testing kits for semen analysis is very sparse, therefore it was not prioritised for inclusion as part of the guideline scope. DNA testing of semen may be considered in the evidence review on investigations for male factor infertility problems.
Fertility Scotland National Network	007	1.3.11	Measles should also be considered in addition to Rubella.	Thank you for your comment. There is no reason to screen women who are concerned about their fertility for measles any more than the general population.
Fertility Scotland National Network	008	1.4	Antioxidants should also be considered for management of male factor fertility problems.	Thank you for your comment. The evidence about antioxidants is of known to be of limited quality, and available systematic reviews have shown no benefit on live births. As a result of this antioxidants were not prioritised for inclusion in this guideline update.

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Fertility Scotland National Network	010	1.14	We would like the economic impact of DI treatment considered in view of the limited availability of donor sperm. A review of cumulative success rates and success rates across age ranges should be considered to ensure most efficient use of resource.	Thank you for your comment. Recommendations in section 1.14 in the current guideline on 'Donor insemination' will be retained, and no new evidence in relation to donor insemination will be reviewed, however the review on predictive factors incudes IUI and the committee will consider if an analysis of the effectiveness of donor sperm can be included as part of this review, which can be considered as part of the modelling to inform access to treatments.
Human Fertilisation Embryology Authority	002	010	This bullet point refers to health related fertility problems after 6 months of artificial insemination, however, it should be made clear that this relates to same sex couples. The failure to conceive after 6 artificial insemination cycles should trigger referral for further investigation but this should not be linked to funding for donor treatment. This does not reflect the Government's Women's Health Strategy.	Thank you for your comment. This definition is applicable to all people who are using artificial insemination to conceive (for example same sex couples, couples where vaginal intercourse is not possible). The Women's Health Strategy for England outlines that "there is no requirement for self-funding and the NHS treatment pathway for female same-sex couples will start with 6 cycles of artificial insemination, prior to accessing IVF services if necessary". However, if conception does not occur after this period of time then one or both members of the same-sex couple (as appropriate) will be eligible for investigation and treatment of health-related fertility problems. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone as long as the main criteria of health-related fertility problems are met, and this has now been clarified in the scope.

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Human Fertilisation Embryology Authority	002	021	On 1 July 2022 CCGs were abolished and replaced by Integrated Care Systems (ICS) as a result of the Health and Care Act 2022. Integrated Care Boards (ICBs) replaced CCGs in England.	Thank you for your comment. This reference to CCGs has been changed to Integrated Care Boards.
Human Fertilisation Embryology Authority	002	029	Fertility investigations and management should be tailored to Black or ethnic minority groups in light of other evidence.	Thank you for your comment. Black or ethnic minority groups are included in the equality impact assessment, which is linked to in section 2 of the scope. This assessment will be used during development to ensure that recommendations meet the needs of the groups listed within it, including whether different investigations and management are required for people from Black and ethnic minority groups.
Human Fertilisation Embryology Authority	003	004	There has also been an increase in egg freezing for fertility preservation for social reasons. This is not funded by the NHS but should this be acknowledged in this paragraph. The latest evidence on success rates of oocyte vitrification should be included. In terms of fertility preservation, the draft scope should make specific reference to the new 55 years maximum storage rules and evidence around impact of long term freezing on success rates.	Thank you for your comment. Social egg freezing is not within the remit of this guideline update because the focus is on health-related fertility problems so this has not been added to the scope. The evidence on fertility preservation will be reviewed and recommendations updated or added as needed and this is likely to reflect the new guidance on longer term storage in certain situations.
Human Fertilisation Embryology Authority	003	027	Should the guideline cover same sex couples and single patients who require treatment but do not have health related fertility problems? It would be useful to refer to the increase in IVF cycles by female same sex couples and	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone as long as the

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			single patients because increasing success rate and lowers risk of multiple birth compared to donor insemination. More information can be found in HFEA data here.	main criteria of health-related fertility problems are met and the scope has been clarified to state this.
Human Fertilisation Embryology Authority	004	001	Should the draft scope include specific transgender patients who undergo hormone therapy which may impact fertility? Should the guideline cover patients who may freeze eggs for social reasons?	Thank you for your comment. The section of the guideline on the preservation of fertility is being updated, and this will include people with any condition that impacts on their fertility, and this may include hormone treatment for transgender people, however, the specific details will be decided by the committee when they develop the detailed protocol for this review question. Social egg freezing is not within the remit of this guideline update because the focus is on health-related fertility problems.
Human Fertilisation Embryology Authority	004	026	3.2 reads as if it is covering ovarian stimulation just for unexplained fertility problems. As IUI is covered in 3.3 should 3.2 just read 'ovarian stimulation' to cover a review of stimulation for all fertility patients. The review of stimulation should include the latest evidence on mild stimulation.	Thank you for your comment. Ovarian stimulation will only be reviewed in the context of unexplained fertility problems. For the rest of the population, the committee agreed that ovarian stimulation had been covered appropriately by the European Society of Human Reproduction and Embryology (ESHRE) guideline on ovarian stimulation for IVF/ICSI (2019), therefore the guideline may cross-refer to it as appropriate.
Human Fertilisation Embryology Authority	005	004	Strategies for prevention of Ovarian Hyperstimulation Syndrome should be considered in key aspects of care	Thank you for your comment. The committee agreed that OHSS had been covered appropriately by the comprehensive guidelines produced by the European Society of Human Reproduction and Embryology (ESHRE) relating to ovarian stimulation for IVF/ICSI (2019), therefore the guideline may cross-refer to it as appropriate.

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Human Fertilisation Embryology Authority	006	1.1	It is noted that the recommendations should be retained from 2017 published guideline. However, there is no distinction between therapeutic and implication counselling. Should the guidelines be expanded to include implication counselling for those receiving donor gametes or embryos	Thank you for your comment. The updated guideline will retain recommendations on principles of care and may cross-refer to information resources from the HFEA to advise that people have access to up to date, evidence-based information and support, and this may include advice on the implications of donor gametes or embryos..
Human Fertilisation Embryology Authority	007	1.3.1	It is noted that the recommendations for semen analysis not to be updated. This should be included in the review in the light of new WHO guidance published in 2021 regarding examination and processing of human semen. Should DNA testing be included.	Thank you for your comment. The WHO guidance you are referring to is a laboratory manual relating to the examination and processing of human serum, and this level of detail on laboratory practice does not fall within the scope of the guideline. However, DNA testing of semen may be considered in the evidence review on investigations for male factor infertility problems.
Human Fertilisation Embryology Authority	010	1.12	The latest evidence on mild stimulation (mild) IVF should be considered for review	Thank you for your comment. The committee agreed that ovarian stimulation, including mild stimulation, had been covered appropriately by the European Society of Human Reproduction and Embryology (ESHRE) guideline on ovarian stimulation for IVF/ICSI (2019). Therefore the guideline may cross-refer to it as appropriate. NICE are aware that there may be new evidence recently released or imminent in this area and that if this differs from the ESHRE guideline it may be necessary to advise surveillance of this for future updates.
Human Fertilisation Embryology Authority	010	1.13	In the review of evidence for ICSI, include if there is a role for the use of calcium ionophore for oocyte activation and use of sperm stimulants eg Pentoxifylline	Thank you for your comment. A draft review question on the effectiveness of ICSI is included in section 3.5 of the scope. The exact nature of the interventions to be included in this

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				review will be agreed by the committee when the detailed review protocol is developed.
Human Fertilisation Embryology Authority	012	026	There is a reference to 'parent' here, suggested word change to patient	Thank you for your comment. As you correctly note this was a typo, however this content has now been deleted as the Economic Aspects section of the scope does not normally go into that level of detail.
Human Fertilisation Embryology Authority	015		Include – Strategies for Prevention of OHSS	Thank you for your comment. OHSS has not been prioritised for inclusion in this update as OHSS had been covered appropriately by the comprehensive guidelines produced by the European Society of Human Reproduction and Embryology (ESHRE) relating to ovarian stimulation for IVF/ICSI (2019), therefore the guideline may cross-refer to it as appropriate. It has been agreed that it is not appropriate use of NICE resources to duplicate work that has already been carried out by other reputable guideline developers.
Human Fertilisation Embryology Authority	015	006	Suggest Endometrial receptivity array, hyaluronate enriched media and intra uterine culture included. The list is limited and may suggest other add ons are appropriate to use. Wording would need to reflect other add ons may be available and that being excluded from the scope of the NICE guidance does not mean they are effective for use.	Thank you for your comment. It would not be possible to address all add-ons available, so the current list of add-ons was determined by those which are most widely used, or for which there are concerns about efficacy, risks or cost. NICE will liaise with HFEA as appropriate to ensure advice provided by the two organisations is consistent, and that there is not an incorrect perception about add-ons that have not been reviewed by NICE.

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Human Fertilisation Embryology Authority	015	006	Endometrial Scratch should be included in Fertility Treatment add-ons review	Thank you for your comment. Endometrial scratch is listed in the add-ons review.
Human Fertilisation Embryology Authority	016	006	Consider specifying OHSS and related health effects in safety of fertility treatments	Thank you for your comment. The scope includes a list of the main outcomes that the guideline may consider, and this would usually include adverse effects such as OHSS if appropriate. The guideline committee will define the outcomes that will be considered in the evidence reviews through the development of review protocols.
Merck Group	001	019-022	This statement does not seem inclusive or in line with current society needs. For example there is no mention of single parents, male same-sex couples and surrogacy.	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone, including the users of surrogates, as long as the main criteria of health-related fertility problems is met, and the scope has been clarified to state this.
Merck Group	001	012-013	Same sex couples and 'single' parents do not appear to be explicitly mentioned. It is not clear if the need for surrogacy linked to health issues is considered in here so further clarification is required.	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone, including the users of surrogates, as long as the main criteria of health-related fertility problems are met and the scope has been clarified to state this.

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Merck Group	001	015	Will this criteria be further clarified in the actual guidance later on?	Thank you for your comment. The scope has been amended to state that access criteria for health-related fertility problems will be included in the guideline.
Merck Group	001	016	We suggest NICE use a broader term instead of In Vitro Fertilisation (IVF) such as Assisted Reproductive Technologies (ART) or Medically Assisted Reproduction (MAR) that include techniques from ovulation induction to IVF and intracitosplasmatic sperm injection (ICSI, among others). Also can we infer donation is included? It would be helpful to clarify this.	Thank you for your comment. The use of IVF in this part of the scope was just as an example ('such as referral for IVF') so this has not been changed.
Merck Group	002	009	We suggest to adapt this to the World Health Organisation (WHO) definition which is: after 12 months of regular unprotected sexual intercourse for women <35 years old and after 6 months of regular unprotected sexual intercourse for women >35 years old.	Thank you for your comment. The current definition of infertility by WHO does not include an age cut-off (https://www.who.int/news-room/fact-sheets/detail/infertility) and so the definition of health-related fertility problems has not been expanded to include an age limit. Increasing age is recognised as a risk factor for infertility and, as described in the equality impact assessment linked from section 2 of the scope, this will be considered when reviewing evidence and making recommendations.
Merck Group	002	015	Male fertility problems are mainly due to these two reasons but these are not the only reasons so may be more relevant to change to '*mainly* due to issues…'.	Thank you for your comment. This change has been made to 'mainly'.
Merck Group	002	021	Please consider re-wording to integrated care systems (ICSs) to reflect recent/upcoming changes in order to future-proof this guidance.	Thank you for your comment. This reference to CCGs has been changed to Integrated Care Boards.

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Merck Group	003	002-004	It is also important to understand the settings of social egg freezing as it is an increasingly important part of fertility preservation (even if NHS funding for social egg freezing is not available).	Thank you for your comment. Social egg freezing is not within the remit of this guideline update because the focus is on health-related fertility problems.
Merck Group	003	026	Please see comments no. 1 and 8 regarding wording around same sex couples, single parents, surrogacy and donation as well as social egg freezing. Although this guideline has strong equality considerations these groups seem not to be included.	Thank you for your comments. These have been addressed individually.
Merck Group	004	026-030	We suggest the wider scope of fertility treatment protocols and patient categorisation is considered as currently the focus is mainly on Intrauterine Insemination (IUI).	Thank you for your comment. Only selected treatments for female factor fertility problems have been prioritised for inclusion in this scope where surveillance have identified new evidence, and these are detailed in section 3.5 of the scope.
Merck Group	004	023-024	Another key area for consideration here should be reducing time to live birth as well as drop-out rates.	Thank you for your comment. Reducing time to live birth and drop-out rates may be included by the committee as outcomes when they develop the detailed review protocol for this question.
Merck Group	004	018	We suggest 1.3 be included as part of point 1.2.	Thank you for your comment. Surgical sperm retrieval is not technically a treatment specifically for male factor infertility, so this has been left in a separate list.
Merck Group	005	002-003	Will the guidance consider different triggering and luteal phase support options? It would be relevant to provide some guidance on these.	Thank you for your comment. It is planned to refer to the comprehensive guidelines produced by the European Society of Human Reproduction and Embryology relating to ovarian stimulation and this is likely to include triggering and luteal phase support.

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Merck Group	005	006	Please consider the comments made on fertility preservation in comment no. 8 above, describing the settings in more detail.	Thank you for your comment. The update on the section of the guideline relating to fertility preservation will cover settings other than cancer,
Merck Group	005	009	Given recurrent miscarriage is the only confirmed topic not covered in the guideline, where will surrogacy be considered in the main points above?	Thank you for your comment. Surrogacy may form part of the treatment for a health-related fertility problem and the guideline will cover embryo creation in the context of surrogacy in people who have a health-related fertility problem. The scope has been clarified to state this.
Merck Group	007	1.3.1. in Table	Please reconsider the inclusion of semen analysis in this list as there is a new WHO laboratory manual which outlines updates to semen processing and examination Please see: https://www.who.int/publications/i/item/9789240030787	Thank you for your comment. The WHO guidance you are referring relates to the examination and processing of human serum, and this level of detail on laboratory practice does not fall within the scope of the guideline.
Merck Group	009	1.11 in Table	Please see comment no. 3 above around suggested wording for IVF.	Thank you for your comment. As the updated review will consider predictive factors for the success of ART, it is likely this section of the guideline will be renamed to reflect this.
Merck Group	010	1.12.1-1.12.7 in Table	New trends around priming, progestin-primed ovarian stimulation (PPOS) and down regulations regimens such as Duostim are being discussed in publications and congresses (at the European Society of Human Reproduction and Embryology Congress [ESHRE] for instance). If agreed, references can be provided to support the guidance development. It could also be relevant to leave these topics open for discussion for now as an	Thank you for your comment. Sections 1.12.1 to 1.12.4 and 1.12.7 have not been prioritised for update as it is planned to refer to the comprehensive guidelines produced by the European Society of Human Reproduction and Embryology relating to ovarian stimulation.

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			important Cochrane review will also be available hopefully in 2023.	
Merck Group	010	1.16 in Table	Please see comment no. 8 above around fertility preservation.	Thank you for your comment which has been responded to above.
Merck Group	013	026	Please consider the biomarkers available and issue guidance around them and the importance of treatment personalisation. Please also consider guidance on optimised patient profiling/categorisation.	Thank you for your comment. The ovarian reserve testing is likely to include measurement of biomarkers but the exact details of the tests to be included in this review will be agreed by the committee when the detailed review protocol is developed.
Merck Group	014	020-022	Will a comparison vs. IVF also be taken into account?	Thank you for your comment and for suggesting this additional comparator. The exact details of the comparator to be included in this review will be agreed by the committee when the detailed review protocol is developed.
Merck Group	014	017	Consider wider naming referred to in comment no. 3	Thank you for your comment. The broader term ART is used in the key area for this draft review question. The exact detail of the interventions to be included in this review will be agreed by the committee when the detailed review protocol is developed.
Merck Group	015	028	Live births are of course the ultimate outcome but we suggest that for the ART section, oocyte number and ongoing pregnancy are also taken into account.	Thank you for your comment. These outcomes are only suggestions and the exact details of the outcomes to be included will be agreed by the committee when they develop the review protocol for each question.
Multiple Births Foundation	General	General	Thank you for the opportunity to comment on the scope for Fertility Problems: assessment and treatment. Our comments relate to multiple pregnancy and birth as this is	Thank you for your comment. Embryo transfer strategies will be reviewed as part of this update, as described in draft review question 3.6.1: What is the effectiveness and safety of

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			the focus of the work of the Multiple Births Foundation (MBF). As the guidance is aimed at providers and commissioners of NHS fertility services in England, it is an important opportunity to remind them of the higher rates of mortality and morbidity with multiple births for mothers and babies and endorse the practice of minimising the risk of multiple pregnancy from fertility treatment.	different embryo or blastocyst transfer strategies in relation to both: • number of embryos (single versus double), • timing of transfer (cleavage versus blastocyst stage)? This review will therefore include consideration of the evidence relating to the risks and benefits of multiple pregnancies.
Multiple Births Foundation	006	1.1 no line no given	Principles of care: Although the evidence for this section will not be reviewed it would be timely to ensure that the recommendation concerning information provided to people seeking treatment includes the risks of multiple pregnancies and most importantly the need to consider the short and long term implications not only clinically but practically and financially of caring for two or more babies. At the MBF we are aware of feedback from patients that although the risk of a multiple pregnancy was part of the decision about the number if embryos to transfer it was for some extremely brief and inadequate. The HFEA patient survey has more information.	Thank you for your comment. The updated guideline will retain recommendations on principles of care and may cross-refer to information resources from the HFEA to advise that people have access to up to date, evidence-based information and support, and this may include advice on the consequences of multiple births.
Multiple Births Foundation	007	1.9 no line no given	Intra uterine insemination: we are sure that the risk of multiple pregnancy with ovarian stimulation and IUI will be part of the evidence review but suggest that the recommendation includes the need for discussing this with patients and ensuring appropriate monitoring of each cycle. .	Thank you for your comment. Multiple births has been included in the scope as a potential outcome to use in evidence reviews, and so is likely to be included in the review protocols developed for individual questions. Clinicians would be expected to warn people of the potential side-effects when

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				offering any intervention, and this would apply to the risk of multiple births.
Multiple Births Foundation	015	135	3.6 Embryo transfer: we are pleased this is a key area for evidence review. We hope the recommendations will retain the principle of a single live healthy baby being the aim of fertility treatment.	Thank you for your comment and support for the review of embryo transfer strategies, which will include consideration of single versus double transfer.
Multiple Births Foundation	017	001	Under heading 3.6 Main Outcomes: we suggest the bullet point could be hanged to "minimising multiple births "	Thank you for your comment. The aim of the intervention may be to minimise multiple births, but it is likely that studies will report outcomes as the number of multiple births, so this has not been changed in the list of possible outcomes.
National AIDS Trust	009	General	1.11 review of access criteria for IVF Current law prevents anyone living with HIV from accessing fertility treatment to start a family, where donations of gametes (eggs or sperm) are involved. Currently, the following scenarios are all unlawful: 1. Surrogacy: A couple (either with different HIV status or both living with HIV) who wish to use a surrogate. 2. Co-maternity: A lesbian couple where one is living with HIV and wishes to have her egg implanted in her partner.	Thank you for your comment. As you have stated, it is outside NICE's remit to change the legal position on fertility treatment and HIV status. NICE is aware that the British HIV association is currently updating its guidelines on sexual and reproductive health and that these may suitable for linking from the current guideline section 1.3 on 'Testing for viral status' and 'Viral transmission' in order to update this section. Consideration of HIV has now been added to the Equality Impact Assessment to recognise that separate consideration of recommendations for people who are HIV positive may be needed.

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			3. Known donation: A person wishes to receive a gamete donation from a friend or relative living with HIV. If all parties provide informed consent, there is no scientific or ethical basis to justify these rules. People living with HIV on effective treatment and with an undetectable viral load cannot sexually transmit HIV. The scientific evidence and resulting Undetectable = Untransmittable (U=U) statement (endorsed by national and international expert organisations including BHIVA, UNAIDS, WHO, CDC and The Lancet), is sufficient for clinicians to be able to advise heterosexual couples, where a partner is living with HIV, that they can conceive naturally without risk of HIV transmission to their partner or baby, provided they are adherent to at least 6 months of treatment and have an undetectable viral load. Moreover, the advice in national guidelines (including NICE's fertility guidelines) state that unprotected sex is the best method of conception and that there is zero risk of the HIV uninfected partner acquiring HIV. While NICE is not in a position to change the law (this is being considered elsewhere by SaBTO, the HFEA and Department of Health and Social Care) we do feel it is important to raise as it is an area where the advice based on scientific evidence should vary from the legal position. It	

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			would be helpful to provide clarity that, medically, there should not be a barrier to access to fertility treatment as a result of someone's HIV status. This is not something that is currently considered within the Equality Impact Assessment for this guideline. HIV diagnosis is a protected characteristic under the Equality Act 2010, as is sexual orientation. The current restrictions are both directly discriminatory towards people living with HIV and indirectly discriminatory towards same-sex couples.	
NHS England	General	General	We welcome the consultation on the guidance as there is considerable variation between geographical areas on the commissioning of fertility services and access to those services. The move to Integrated Care Boards should improve matters, but there is still a potential for geographical variation to persist.	Thank you for your comment. The intention is that the updated guideline will provide clear advice to ICBs on the NICE-recommended investigations and treatments for health-related fertility problems. Thus it is hoped that implementation of the updated guideline will alleviate some of the geographical inequalities that currently exist in the treatment of health-related fertility problems.
NHS South, Central and West Commissioning Support Unit	General	General	The draft scope does not mention surrogacy. This was specifically excluded from the scope of CG156. Suggest it is clarified whether assisted conception treatments using surrogacy are in or out of scope. It would be preferable for this to be included in the scope as there is no national guidance on NHS funding of assisted conception treatments involving surrogates.	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover surrogacy as long as the main criteria of health-related fertility problems are met, and this has now been clarified in the scope.
NHS South, Central and	001	024-025	The draft scope notes the Department of Health and Social Care (DHSC) Woman's Health Strategy for England	Thank you for your comment. The Women's Health Strategy for England outlines that "there is no requirement for self-

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Stakeholder	Page no	Line no	Comments	Developer's response
West Commissioning Support Unit			commitment to removing the requirement for self-funding for initial treatments to demonstrate a health-related fertility problem to access NHS funded care (page 1, lines 19-23). However, the scope then states the guideline will be for people who have a health-related fertility problem defined by failure to achieve a pregnancy after 12 months of unprotected sexual intercourse of 6 cycles of artificial insemination (page 2, lines 7-10) and will not make recommendations on funding arrangements for procedures to demonstrate a health-related fertility problem (page 1, lines 24-25). By requiring people trying to conceive using artificial insemination to have undergone 6 cycles prior to NHS funded fertility treatment, it is difficult to see how the DHSC Woman's Health Strategy ambitions can be realised. It would be helpful if NICE guidance could be updated to be consistent with DHSC ambitions and support implementation of these.	funding and the NHS treatment pathway for female same-sex couples will start with 6 cycles of artificial insemination, prior to accessing IVF services if necessary". However, if conception does not occur after this period of time then one or both members of the same-sex couple (as appropriate) will be eligible for investigation and treatment of health-related fertility problems. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios prior to the diagnosis of a health-related fertility problem. The scope has been clarified to state this.
NHS South, Central and West Commissioning Support Unit	002	021	Suggest replacing 'Clinical Commissioning Groups' with 'Integrated Care Boards'	Thank you for your comment. This change has been made.
NHS South, Central and West	004	011-014	It would be preferable from a commissioner's perspective if the updated guideline is published all at the same time, rather than the staggered approach suggested.	Thank you for your comment. Due to the size of this update a decision may be made to publish some sections early to facilitate earlier implementation, but a final decision is yet to be made.

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Commissioning Support Unit				
NHS South, Central and West Commissioning Support Unit	004	001-003	It may be useful to specify that 'people who may require interventions to preserve fertility' include people undergoing gender reassignment as there is sometimes some uncertainty around this. The Department of Health published guidance on this in 2019 which specifies 'all patient groups whose medical treatment may compromise fertility should be in the contemplation of a CCG when its clinical commissioning policy for fertility preservation' (NHS-England-Guidance-for-CCGs-on-Fertility-Preservation.pdf (gic.nhs.uk)). It would be helpful if this was referenced in NICE guidance.	Thank you for your comment. The section of the guideline on the preservation of fertility is being updated, and this will include people with any condition that impacts on their fertility, and this may include people undergoing gender reassignement. However, the specific details will be decided by the committee when they develop the detailed protocol for this review question.
NHS South, Central and West Commissioning Support Unit	005	001	Fertility treatment add-ons are reviewed by the Human Fertilisation and Embryology Authority (HFEA) and recommendations regarding their routine use published on the website - Treatment add-ons with limited evidence | HFEA. Consideration should be given as to whether NICE guidance on this is necessary and, if so, how NICE guidance will fit in with the HFEA recommendations.	Thank you for your comment. HFEA does not take into account cost-effectiveness evidence. Therefore there is scope for NICE to review treatment add-ons. NICE will liaise with HFEA as appropriate to ensure consistent advice is provided by both organisations.
NHS South, Central and West Commissioning Support Unit	005	002	Suggest 'Embryo transfer' should be replaced with 'embryo transfer strategies'	Thank you for your comment. The word 'strategies' has been added as you suggest.

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NHS South, Central and West Commissioning Support Unit	005	003	'Frozen embryo transfer' – please clarify specifically what this relates to? Will it be the order of fresh vs frozen cycles, or will it include consideration of freeze all cycles?	Thank you for your comment. The exact details of the interventions to be included will be agreed by the committee when they develop the review protocol for this question.
NHS South, Central and West Commissioning Support Unit	010	Section not numbered but titled 'Fertility treatment add-ons'	Fertility treatment add-ons are reviewed by the Human Fertilisation and Embryology Authority (HFEA) and recommendations regarding their routine use published on the website - Treatment add-ons with limited evidence | HFEA. Consideration should be given as to whether NICE guidance on this is required and/or how NICE guidance will fit in with the HFEA recommendations.	Thank you for your comment. HFEA does not take into account cost-effectiveness evidence. Therefore there is scope for NICE to review treatment add-ons. NICE will liaise with HFEA as appropriate to ensure advice provided by the two organisations is consistent.
NHS South, Central and West Commissioning Support Unit	010	1.16	That this section is called 'People with cancer who wish to preserve fertility'. As the scope of the updated guidance appears to be wider (as outlined on lines 1-3 of page 4), suggest the name of this section is updated accordingly to: 'People who may require interventions to preserve fertility because of clinical conditions or medical or surgical interventions'.	Thank you for your comment. This table is based on the headings used in the current guideline and will be amended in the updated guideline. to better reflect the population.
NHS South, Central and West Commissioning Support Unit	012	023-025	The example of a baby not being born and therefore not experiencing a loss of quality of life to explain why a QALY approach may not be suitable is not a good one. Quality of life measures should apply to the people receiving fertility	Thank you for your comment. This was an attempt to explain some of the difficulties with QALYs in this area and trying to make the point that quality of life measures would apply to people receiving the treatment rather than a potential life not yet conceived. However, this text has now been deleted.

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			treatments, who are the individuals with the health problems and the 'patients' in this case.	
NHS South, Central and West Commissioning Support Unit	014	018-026	In order to determine the place of IUI in the treatment pathway for people with unexplained infertility, mild endometriosis and mild male factor infertility, suggest that the comparative interventions should be IVF as well as expectant management. Note, that the addendum to the current NICE guidance states that IUI compared to IVF will be considered in a future update of the guideline (page 21 of NICE Guideline Addendum).	Thank you for your comment and for suggesting this additional comparator. The exact details of the comparator to be included in this review will be agreed by the committee when the detailed review protocol is developed.
NHS South, Central and West Commissioning Support Unit	014	031-033	Fertility treatment add-ons are reviewed by the Human Fertilisation and Embryology Authority (HFEA) and recommendations regarding their routine use published on the website - Treatment add-ons with limited evidence | HFEA. Consideration should be given as to whether NICE guidance on this is required and/or how NICE guidance will fit in with the HFEA recommendations.	Thank you for your comment. HFEA does not take into account cost-effectiveness evidence. Therefore there is scope for NICE to review it. NICE will liaise with HFEA as appropriate to ensure advice provided by the two organisations is consistent.
NHS South, Central and West Commissioning Support Unit	015	001-006	This is not a comprehensive list of add-ons – see the HFEA website Treatment add-ons with limited evidence | HFEA.	Thank you for your comment. It would not be possible to address all add-ons available, so the current list of add-ons was determined by those which are most widely used, or for which there are concerns about efficacy, risks or cost.
NHS South, Central and West	015	021-024	Suggest clarifying which fertility preservation interventions this includes as there are many including assisted conception treatments, surgical techniques, and medicines.	Thank you for your comment. This review question will cover preservation of ovarian and testicular tissues, but the exact details of the interventions covered will be defined in the

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Commissioning Support Unit			Suggest the scope of NICE guidance should include cryopreservation of sperm, embryos, eggs and ovarian and testicular tissue.	review protocol, which will be agreed by the committee during guideline development.
NHS South, Central and West Commissioning Support Unit	015	012-014	Please clarify specifically what this relates to? Will it be the order of fresh vs frozen cycles, or will it include consideration of freeze all cycles?	Thank you for your comment. The exact details of the interventions to be included will be agreed by the committee when they develop the review protocol for this question.
NHS South, Central and West Commissioning Support Unit	015	007	Suggest replacing 'Embryo transfer' with 'Embryo transfer strategies'	Thank you for your comment. 'Strategies' has been added as you suggest.
Progress Educational Trust	General	General	Surrogacy has been omitted from the scope and should be included, it is a legitimate treatment for people with infertility, whether for women with the condition MRKH or same sex male couples. The inclusion of surrogacy is particularly important given the work being carried out by the Law Commission of England and Wales and the Law Commission of Scotland to reform surrogacy law.	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover surrogacy as long as the main criteria of health-related fertility problems are met, and this has now been clarified in the scope.
Progress Educational Trust	General	General	Counselling: distinctions are missing between different types of counselling which should be offered and provided to patients, such as information counselling, therapeutic counselling and implications counselling. The latter is	Thank you for your comment. Counselling has not been prioritised for inclusion in the scope of this guideline update as it will retain the recommendations on principles of care, which includes the provision of information and the psychological effects of fertility problems. The updated

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			important for donors and also people planning to have a family using donated gametes.	guideline may also cross-refer to information resources from the HFEA to advise that people have access to up to date, evidence based information and support.
Progress Educational Trust	General	General	Investigations tailored to particular patient groups should be considered for inclusion, for example, there is a higher prevalence of fibroids in Black women and a higher prevalence of PCOS among Asian / British Asian women.	Thank you for your comment. Black and Asian women are included in the equality impact assessment, which is linked to in section 2 of the scope. This assessment will be used during development to ensure that recommendations meet the needs of the groups listed within it, including whether different investigations are required for Black and Asian women.
Progress Educational Trust	001	020	The DHSC has NOT committed to removing non-clinical access criteria imposed by commissioning bodies in the Women's Health Strategy (WHS). For example, the length pf relationship, whether one or both people have a child from a previous relationship. Further the WHS does not apply to men, and so there is no proposal to remove any non-clinical access criteria which may apply to men – for example a same-sex male couple.	Thank you for your comment. The guideline update will include the assessment and treatment of health-related fertility problems, including access to that treatment if there is failure to conceive. The guideline does not currently recommend other non-clinical access criteria and this is not an area included in the scope of this update, so these will not be included in the updated guideline. The intention is that the updated guideline will provide clear advice to NHS organisations on the NICE-recommended investigations and treatments for health-related fertility problems. Thus it is hoped that implementation of the updated guideline will alleviate some of non-clinical access criteria that currently exist.
Progress Educational Trust	002	010	In what scenario(s) does the six cycles of artificial insemination refer to? Clarification is needed otherwise it will be linked to accessing NHS-funded donor treatment for	Thank you for your comment. This definition is applicable to all people who are using artificial insemination to conceive (for example same sex couples, couples where vaginal

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			same-sex female couples. Something which the WHS is trying to move away from.	intercourse is not possible). The Women's Health Strategy for England outlines that "there is no requirement for self-funding and the NHS treatment pathway for female same-sex couples will start with 6 cycles of artificial insemination, prior to accessing IVF services if necessary". However, if conception does not occur after this period of time then one or both members of the same-sex couple (as appropriate) will be eligible for investigation and treatment of health-related fertility problems.
Progress Educational Trust	002	013	What percentage of fertility problems relate to female factor issues? This page seems to suggest that 49% of problems are female factor.	Thank you for your comment. As reflected in this section (key facts and figures) male factors account for about 26%, unknown causes around 25% and female factors about 41%.
Progress Educational Trust	002	021	The scope needs to reflect that on 1 July 2022, integrated care systems (ICSs) became legally established through the Health and Care Act 2022, and CCGs were closed down.	Thank you for your comment. This reference to CCGs has been changed to Integrated Care Boards.
Progress Educational Trust	002	024	In addition to variation about the number of cycles offered there is also significant variance as to how a 'cycle' is interpreted. For example, a commissioning body may define a cycle as one fresh and one frozen transfer.	Thank you for your comment. A full cycle of IVF is already defined in the guideline, and as part of the update, the committee will review all 'terms used' to ensure this section is still up to date.
Progress Educational Trust	003	026	Same-sex male and female couples have been missed from the list as they do not have a health-related fertility problem and so do not currently fall within the scope. This needs to be rectified. Also, does the scope include fertility	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone as long as the main criteria of health-related fertility problems are met and

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			preservation for people who are transitioning? This is not clear. This community must be included.	the scope has been clarified to state this The review on fertility preservation will cover children and adults undergoing treatment for cancer and other conditions or situations which are likely to impair their fertility. Therefore it is likely to include people who are transitioning. However the specific details will be decided by the committee when they develop the detailed protocol for this review question.
Progress Educational Trust	012	026	The word parents has been used instead of patients. This is a very unfortunate and regrettable mistake as these patients long to be parents. Has NICE considered including the cost of people resorting to fertility treatment outside the UK and then having multiple births in the UK to the NHS as part of its economic analysis?	Thank you for your comment. As you correctly note this was a typo, however this content has now been deleted as the Economic Aspects section of the scope does not normally go into that level of detail. The NICE guideline will be making recommendations for the NHS and it is beyond its remit to formally consider the unintended consequences of people resorting to fertility treatment outside the UK (when NHS funding is not available). This would not stop the committee taking this into account when making recommendations although there may be a very limited evidence base and the review questions will not elicit a systematic search for such evidence. We do note that the number of multiple births has fallen since the publication of the last guideline (ONS 2020).
Progress Educational Trust	014	031	Is NICE aware that the European Society for Human Reproduction and Embryology will soon be publishing good practice recommendations for fertility treatment add-ons.	Thank you for your comment. NICE is aware of this and will liaise with HFEA as appropriate to ensure advice provided by the two organisations is consistent.
Progress Educational Trust	015	002	Timelapse imaging needs to be reviewed both with and without the use of embryo selection software.	Thank you for your comment. Timelapse imaging is listed in the add-ons review and so will be considered. The committee will decide if any more detail is required regarding the add-on

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				interventions when they develop the detailed review protocol for this question.
Progress Educational Trust	015	006	How was the scope of this list of add-ons decided? There are many add-ons which are not included, for example those relating to endometrial receptivity, work needs to be done with the Human Fertilisation and Embryology Authority and other stakeholders to decide which add-ons should be included on this list. Including some add-ons and not others in the scope may send the wrong signal, as people may assume that an add-on is validated by not being included for consideration.	Thank you for your comment. It would not be possible to address all add-ons available, so the current list of add-ons was determined by those which are most widely used, or for which there are concerns about efficacy, risks or cost. NICE will liaise with HFEA as appropriate to ensure advice provided by the two organisations is consistent, and that there is not an incorrect perception about add-ons that have not been reviewed by NICE.
Royal College of Nursing – Fertility Nursing Forum	general	general	As an organisation, we feel that the guideline is clear and includes all areas of fertility care and investigations.	Thank you for your comment.
Royal College of Nursing – Fertility Nursing Forum	general	general	The draft does not refer to surrogacy care or treatment. Many people accessing surrogacy to build or grow their family, will do so through HFEA licensed fertility clinics. They may also have investigations and create and store embryos to use for surrogacy at a later date through NHS and private fertility clinics so we feel that the guideline should make reference to those groups which include same sex male and female couples, single people and heterosexual couples.	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone, including the users of surrogates, as long as the main criteria of health-related fertility problems are met, and this has now been clarified in the scope.

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Royal College of Nursing – Fertility Nursing Forum	003	027	'People with heath related fertility problems' we feel that this statement does not include those accessing fertility care to grow or start their family if they are in a same sex relationships or for single people. Their fertility needs may not be 'health related'. We suggest that this sentence could include those who are in same sex relationships or single people that do not have health related fertility problems.	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone as long as the main criteria of health-related fertility problems are met and the scope has been clarified to state this.
Royal College of Nursing – Fertility Nursing Forum	004	001	We feel that the reference to fertility preservation for children and young people should be included in this sentence as they are in section 4.1 of the draft document.	Thank you for your comment. 'People' covers those of all ages so we have not added children to this list.
Royal College of Nursing – Fertility Nursing Forum	005	001	We feel that this should read as 'some fertility treatment add-ons' as not all will be included in the document and as fertility care is innovative and fast changing – more evidence and further add-ons may be implemented into fertility care.	Thank you for your comment. The list of fertility treatment add-ons that will be included is provided in section 3.5 of the scope. The list of add-ons may be amended by the committee when they develop the detailed review protocol for this question.
Royal Marsden NHS Foundation Trust	General	general	introduce mandatory re-assessment of fertility & provision of counselling for patients having cancer treatment 1-2 years post treatment as best practice measure. For males if have remained fertile no longer needed to store sperm thus reducing impact on storage capacity, for females ongoing storage should be provided as not possible to predict age of premature ovarian insufficiency and/or if this will occur but best practice to offer counselling	Thank you for your comment. It is good practice to re-assess fertility as you suggest, but it is difficult to be prescriptive about the timescales as these depend on what type of therapy people have had and what regimen had been used. However, the evidence on fertility preservation will be reviewed as part of the guideline update and the committee may consider including recommendations on re-assessment of fertility.

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Royal Marsden NHS Foundation Trust	General	general	introduction of mandatory reporting by all NHS and private providers of fertility preservation as not possible to currently accurately review numbers of procedures performed and therefore funding implications	Thank you for your comment. Recording and reporting of fertility treatments and preservation is outside the remit of NICE but this comment will be passed on to the HFEA with whom NICE are liaising with over the updating of this guideline, as this may be a role that they can or do undertake.
Royal Marsden NHS Foundation Trust	010	1.16	In terms of equality impact assessment and age – with the growing importance & effectiveness of fertility preservation there are increasing referrals for the teenage & young adult group; this group need very long-term storage, we ask that the current recommendation should be strengthened to state this	Thank you for your comment. The section of the guideline on fertility preservation is being updated and this will include children and young people.
Royal Marsden NHS Foundation Trust	010	1.16	In terms of equality impact assessment and gender – disparity as recommends that if remain infertile after 10 years recommend ongoing storage for males, this should be extended to include females within child bearing window (up to 40 years?)	Thank you for your comment. It is difficult to be prescriptive about the timescales for gamete storage as these depend on what type of therapy people have had and what regimen was used. The evidence on fertility preservation will be reviewed and the committee may consider providing advice on storage and reassessment as part of this review.
Royal Marsden NHS Foundation Trust	010	1.16	Fertility preservation funding is variable around the UK and duration of funding is too short; the fertility preservation recommendation should be made into a Quality Standard for commissioners of fertility services	Thank you for your comment and for your suggestion that fertility preservation should be a quality standard. This suggestion will be passed to the NICE Quality Standards team.
Society for Endocrinology	004	1.4	Not all potential treatments are directly 'hormonal' in nature and this might exclude non-hormonal treatment.	Thank you for your comment. The second bullet point in this section refers to other treatments for ejaculatory failure which may include non-hormonal treatments, if agreed by the

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				committee when they decide exactly which interventions to include in this review.
Society for Endocrinology	004	019	Female fertility problems have two broad areas: structural and functional (i.e. anovulation) and as the issues are disparate it seems sensible to separate these within Section 2 to allow appropriate detailed assessment.	Thank you for your comment. Only selected treatments for female factor fertility problems have been prioritised for inclusion in this scope, and these are detailed in section 3.5 of the scope, so this key area has not been further sub-divided.
Society for Endocrinology	004	023	Predictive models for ART often inform access criteria to other treatments. It is important that access criteria for non-ART treatments are assessed using a separate evidence base as the population, pathology and treatments differ.	Thank you for your comment. Predictive models for IUI, IVF and ICSI have been prioritised for inclusion as these are the most commonly used techniques, for which prediction of success is likely to be most useful, but you are correct that access criteria determined by this review should not be extrapolated to other forms of treatment and this will be considered by the committee when making their recommendations.
Society for Endocrinology	008	1.5	It is not clear why cabergoline treatment for hyperprolactinaemia should be considered separately from other ovulation disorders. Safety and side effects should be a consideration of all treatment modalities.	Thank you for your comment. Hyperprolactinaemic amenorrhoea is an ovulation disorder not covered by WHO classifications I, II and III. Therefore it was added to a separate review question. The safety and side effects will also be considered as appropriate, as part of the review protocol for this question..
Society for Endocrinology	008	1.6	It is important that three key areas of clinical uncertainty, polyps, thin endometrium are CS niches are addressed and perhaps should be separate bullet points.	Thank you for your comment. It is not clear which part of section 1.6 your comment relates to, but further details of the draft review question relating to surgical interventions (for female factor fertility problems) are given in section 3.5 of the

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				scope, and the committee will decide on the exact nature of the interventions to be considered when they develop the detailed protocol for this review question.
Society for Endocrinology	009	1.11	Access criteria for ART is broadly used to inform other treatment criteria and these should be specifically looked at separately.	Thank you for your comment. Predictive models for IUI, IVF and ICSI have been prioritised for inclusion as these are the most commonly used techniques, for which prediction of success is likely to be most useful, but you are correct that access criteria determined by this review should not be extrapolated to other forms of treatment and this will be considered by the committee when making their recommendations.
Society for Endocrinology	009	1.9	Rather than just for unexplained infertility. IUI for mild male factor (and how that is defined) should be considered.	Thank you for your comment. The draft review question in section 3.5 of the scope includes the effectiveness of IUI for mild male factor fertility problems.
Society for Endocrinology	010	1.12	There is widespread variation in luteal support for non-down-regulated non-ART cycles and clarity on luteal support in the absence of down-regulation would be welcome.	Thank you for your comment. Sections 1.12.1 to 1.12.4 and 1.12.7 have not been prioritised for update as it is planned to refer to the comprehensive guidelines produced by the European Society of Human Reproduction and Embryology relating to ovarian stimulation.
Society of Radiographers	General	General	1.3 Investigations of fertility problems and management strategies Consideration of including transvaginal scan are the recommended method of ultrasound assessment and detection of structural abnormalities may be helpful. Further	Thank you for your comment. While we cannot pre-empt recommendations that will be made by the committee, the scope does allow for updating existing recommendations in section 1.3 'Investigations of fertility problems and management strategies' as needed, therefore the committee could consider the inclusion of transvaginal ultrasound as

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			detail of what should be reported could be useful for ultrasound practitioners working in fertility settings to increase standardisation of reporting.	part of the update of section 1.3.8 and this has been added to the draft scope. However, the technical specification of how the scan should be carried out is best left to professional bodies.
Society of Radiographers	General	General	1.3 In cases of chronic pelvic pain in a female, is there any value in reviewing the evidence and considering specialist referral for diagnosis/assessment of deep infiltrating endometriosis assessment and whether 3D ultrasound should be included? Is there any new evidence?	Thank you for your comment. The investigation and treatment of endometriosis is not included in the scope of this update as this is covered in the NICE guideline on Endometriosis: diagnosis and management (2017). The fertility problems update will cross-refer to this guidance to facilitate the better management of endometriosis.
Society of Radiographers	007	1.3.8	Is any consideration being given to the use of HyCoSy for the assessment of tubal patency?	Thank you for your comment. This technique (HyCoSy) is covered by the current guideline and there is unlikely to be sufficient new evidence to make a difference to the existing recommendations, therefore it has not been included in this guideline update.
Surrey County Council	General	General	Will you be providing a stance on whether sperm cryopreservation during a cycle for patients with oligozoospermia for example, is standard clinical practice ? It would make sense in specific circumstances for male patients with a low sperm count to have their sperm stored temporarily (to be used on the day of egg collection) as a backup solution to ensure the cycle can proceed as planned. There seems to be variation across ICSs.	Thank you for your comment. Sperm cryopreservation is part of fertility preservation, and the evidence on fertility preservation will be reviewed as part of this guideline update, so the use of cryopreservation for example in men going into testicular failure will be considered for inclusion in this review.

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Surrey County Council	General	General	We are aware of duplication of pathways/preliminary tests between primary and secondary care for patients wishing to access fertility treatment, with some patients being tested multiple times for the same things. Will you be producing an optimal evidence-based pathway alongside the reviewed guidance to improve clinical and shared decision-making ?	Thank you for your comment. It may be possible to produce a treatment algorithm to accompany the guideline, and although the guideline currently provides advice on generalist and specialist care, details on who should be providing different aspects of care and investigation will be considered by the committee as it makes its recommendations.
Surrey County Council	001	020 Women's Health Strategy	We welcome the reference to the Women's Health Strategy in the purpose of the guideline. In terms of equity of access into services, in particular for women in a same-sex relationship, it is important that any barriers to non-clinical access criteria for fertility treatment are removed.	Thank you for your comment. The guideline update will include the assessment and treatment of health-related fertility problems, including access to that treatment if there is failure to conceive. The guideline does not currently recommend other non-clinical access criteria and this is not an area included in the scope of this update, so these will not be included in the updated guideline. The intention is that the updated guideline will provide clear advice to NHS organisations on the NICE-recommended investigations and treatments for health-related fertility problems. Thus it is hoped that implementation of the updated guideline will alleviate some of non-clinical access criteria that currently exist.
Surrey County Council	003	019 Equality considerations	The Equality Impact Assessment has identified a series of potential inequalities affecting people with protected characteristics. On this basis will the review address the issue of gamete donation in the context of co-maternity/shared-motherhood ? It is a situation which is gradually becoming more common and it would be useful to have some guidance.	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone as long as the main criteria of health-related fertility problems are met and the scope has been clarified to state this. If co-maternity is being used as part of the treatment for a health-related

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				fertility problem the processes that is uses will be covered by this guideline update. However, gamete donation and screening is subject to HFEA regulation.
Surrey County Council	010	014 1.12.5	Does sperm retrieval include the use of Microscopic testicular retrieval (Micro TESE) of sperm ? If so would you be able to evidence the success rate of the procedure as well as define its optimal use in clinical practice.	Thank you for your comment. The scope includes an update of surgical sperm retrieval techniques so the potential inclusion of MicroTESE will be considered by the committee when they develop the review protocol for this question.
Surrey County Council	010	033 Fertility treatment add-ons	We welcome the decision to review fertility treatment add-ons. From a Public Health perspective we are concerned about the inequalities which may result if these are not funded by the NHS and therefore will only become available to those who can afford to pay. There are potentially obvious implications in terms of fairness and equity of care.	Thank you for your comment. The aim of the review on add-ons is to determine which are effective and cost-effective and should be provided by the NHS. It is hope that private clinics offering private treatment would then adhere to the NICE advice on recommended treatment add-ons. However, you are correct that private clinics could provide additional add-ons, but it is outside the scope of NICE to determine what is offered in private clinics.
The Endometriosis Foundation	General	General	In this era of modern-day medicine, the NHS must not forget this group of people with suspected or confirmed moderate – severe Endometriosis. Shouldn't referral waiting times for people with suspected or confirmed moderate – severe Endometriosis be reduced to 3 months? A quicker referral pathway, irrespective of age, would be advisable given Endometriosis can be a progressive disease, one that can have a significant impact on fertility outcomes.	Thank you for your comment. The medical and surgical management of endometriosis has not been prioritised for inclusion in the scope of this guideline as it is covered in the NICE guidance on endometriosis: diagnosis and management (2017), and this includes the options for referral. The fertility problems update will cross-refer to this guidance to facilitate the better management of endometriosis.

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The Endometriosis Foundation	General	General	The General Practitioner (GP) is usually the first line of contact for patients presenting with symptoms of Endometriosis, and therefore all GPs must be well educated about Endometriosis and the effects it can have on fertility outcomes.	Thank you for your comment. The NICE guidance on endometriosis: diagnosis and management (2017) already covers referral for women with suspected or confirmed endometriosis. The fertility problems update will cross-refer to this guidance to facilitate the better management of endometriosis.
The Endometriosis Foundation	General	General	Fertility preservation includes choices of egg, embryo or reproductive tissue freezing. Currently there is no mention of fertility preservation for this group of people. Shouldn't people with suspected or confirmed moderate – severe Endometriosis and other conditions proven to significantly jeopardise female fertility, be given the rights to preserve their fertility? Isn't it time the NHS priorities this group of people and consider reviewing their policies to include this group of people with Endometriosis, given the diagnostic times are currently averaging at 8 years? These treatments are available presently to people with a cancer diagnosis. This has recently been extended to the transgender community.	Thank you for your comment. Fertility preservation for people with confirmed moderate-severe endometriosis, as well as for people with other conditions or situations likely to impair their fertility will be covered by draft review question 4.1 What is the effectiveness and safety of fertility preservation for children and adults undergoing treatment for cancer and other conditions or situations which are likely to impair the fertility?
The Endometriosis Foundation	General	General	Those wishing to postpone their reproductive choices must also be well informed and these needs must be discussed	Thank you for your comment. The updated guideline will retain the recommendations on principles of care, which includes the provision of information and the psychological

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			thoroughly. Counselling services should also be offered to those who may need it.	effects of fertility problems, and may also cross-refer to information resources from the HFEA to advise that people have access to up to date, evidence based information and support.
The International Society for Mild Approaches in Assisted Reproduction	001	014	It is not explicitly stated here that it includes guidelines for treatment of single women and same-sex couples and also patients wishing to freeze their eggs for social reasons. It should be considered to include these categories in this section.	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone as long as the main criteria of health-related fertility problems are met, and the scope has been clarified to state this. People who wish to freeze their eggs for social reasons do not meet the criteria for health-related fertility problems and so are not included in the scope of this update.
The International Society for Mild Approaches in Assisted Reproduction	002	010	This bullet point refers to health-related fertility problems after 6 months of artificial insemination. It should be made clear that the paragraph below relates to same-sex couples. The definition about " failure to achieve a pregnancy after 6 months of artificial insemination" should not be linked to funding for donor insemination. The funding situation should reflect the position stated in the recent DHSC Women's Health Strategy	Thank you for your comment. This definition is applicable to all people who are using artificial insemination to conceive (for example same sex couples, couples where vaginal intercourse is not possible). The Women's Health Strategy for England outlines that "there is no requirement for self-funding and the NHS treatment pathway for female same-sex couples will start with 6 cycles of artificial insemination, prior to accessing IVF services if necessary". However, if conception does not occur after this period of time then one or both members of the same-sex couple (as appropriate) will be eligible for investigation and treatment of health-related fertility problems. The focus of the guideline is on health-related fertility problems, and it does not make assumptions

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				about social or personal situations or scenarios. Therefore, the guideline will cover everyone as long as the main criteria of health-related fertility problems are met, and this has now been clarified in the scope.
The International Society for Mild Approaches in Assisted Reproduction	003	004	There has also been a significant increase in egg freezing for fertility preservation for social reasons. This is not funded by the NHS but this should be recognised in this paragraph. The latest evidence on success rates of oocyte vitrification should be included. The latest changes to maximum storage rules in terms of fertility preservation should be referenced here including a link to the HFEA website. Include the evidence about safety and success of long-term storage of gametes and embryos	Thank you for your comment. Social egg freezing is not within the remit of this guideline update because the focus is on health-related fertility problems so this has not been added to the scope. The evidence on fertility preservation will be reviewed and recommendations updated or added as needed and this is likely to reflect the new guidance on longer term storage in certain situations.
The International Society for Mild Approaches in Assisted Reproduction	003	027	The guideline should cover same sex couples and single patients who require treatment but do not have health related fertility problems The draft scope should make specific reference to transgender patients who undergo hormone treatment and procedures which can have an impact on their fertility.	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone as long as the main criteria of health-related fertility problems are met and the scope has been clarified to state this. The section of the guideline on the preservation of fertility is being updated, and this will include people with any condition that impacts on their fertility, and this may include hormone treatment for transgender people, however, the specific details will be decided by the committee when they develop the detailed protocol for this review question.

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The International Society for Mild Approaches in Assisted Reproduction	004	001	The guideline should cover egg freezing for social reasons	Thank you for your comment. Social egg freezing is not within the remit of this guideline update because the focus is on health-related fertility problems.
The International Society for Mild Approaches in Assisted Reproduction	004	022	Consider the latest evidence on access and outcomes of fertility treatments in Black, Asian and Minority Ethnic (BAME) people and recommend tailored fertility investigations and management for BAME population	Thank you for your comment. Black or ethnic minority groups are included in the equality impact assessment, which is linked to in section 2 of the scope. This assessment will be used during development to ensure that recommendations meet the needs of the groups listed within it, including whether different investigations and management are required for people from Black, Asian and ethnic minority groups.
The International Society for Mild Approaches in Assisted Reproduction	004	026	Under Activities, services and aspects of care: 3.2 reads as if it is covering ovarian stimulation only for unexplained fertility problems. As IUI is separately covered in 3; we suggest that 3.2 should read 'ovarian stimulation' to cover a review of stimulation for all fertility patients. The review of stimulation should include the latest evidence on mild stimulation (see our comments below).	Thank you for your comment. Ovarian stimulation will only be reviewed in the context of unexplained fertility problems. For the rest of the population, the committee agreed that ovarian stimulation had been covered appropriately by the European Society of Human Reproduction and Embryology (ESHRE) guideline on ovarian stimulation for IVF/ICSI (2019), therefore the guideline may cross-refer to it as appropriate.
The International Society for Mild Approaches in	005	004	-Strategies for the avoidance of Ovarian Hyperstimulation Syndrome should be considered in key aspects of care for all patients undergoing ovarian stimulation for egg collection	Thank you for your comment. The committee agreed that OHSS had been covered appropriately by the comprehensive guidelines produced by the European Society of Human Reproduction and Embryology (ESHRE) relating to ovarian

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Assisted Reproduction			including those who are donating eggs and those freezing eggs/embryos for fertility preservation for social reasons. -There should a bullet point explicitly to assess the latest evidence on the effectiveness of "Freeze All Embryos (FAE) "strategy in stimulated cycles in the prevention of OHSS. -The assessment of long-term safety of ART should include the evidence of long-term safety of ovarian stimulation on patients and egg donors -The assessment of long-term safety of ART should include the use of intravenous immunology drugs administered to patients	stimulation for IVF/ICSI (2019), therefore the guideline may cross-refer to it as appropriate. The committee will decide on the exact nature of the interventions to be considered when they develop the detailed protocol for the review question on safety of ART.
The International Society for Mild Approaches in Assisted Reproduction	010	1.12	The ISMAAR Expert group recommends that the latest evidence on mild stimulation (mild) IVF should be considered under "ovarian stimulation for IVF/ICSI" in the light of the latest publications (listed below) after the ESHRE guidance for ovarian stimulation was published in 2019. References:. 1. Datta AK, Maheshwari A, Felix N, Campbell S, Nargund G: Mild versus conventional ovarian stimulation for IVF in poor, normal and hyper-responders: a systematic review and meta-analysis. Hum Reproduction Update 2020; 1-25	Thank you for your comment and the references provided. The committee agreed that ovarian stimulation, including mild stimulation, had been covered appropriately by the European Society of Human Reproduction and Embryology (ESHRE) guideline on ovarian stimulation for IVF/ICSI (2019). Therefore the guideline may cross-refer to it as appropriate. NICE are aware that there may be new evidence recently released or imminent in this area and that if this differs from the ESHRE guideline it may be necessary to advise surveillance of this for future updates.

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			2.Pennings G: Mild stimulation should be mandatory for oocyte donation: Human Reproduction 2020; 2403-2407 3.Nargund G, Datta, A.K,, Campbell, S., Patrizio, P., Chian, R., Ombelet, W., Von Woolf, M., Lindenberg, S., Frydman, R., Fauser, B.C.J.M: The case for mild stimulation for IVF: ISMAAR recommendations. RBM Online 2022 ;in press.	
The International Society for Mild Approaches in Assisted Reproduction	015	015	Include -Strategies for the avoidance of OHSS	Thank you for your comment. OHSS has not been prioritised for inclusion in this update as OHSS had been covered appropriately by the comprehensive guidelines produced by the European Society of Human Reproduction and Embryology (ESHRE) relating to ovarian stimulation for IVF/ICSI (2019), therefore the guideline may cross-refer to it as appropriate. It has been agreed that it is not appropriate use of NICE resources to duplicate work that has already been carried out by other reputable guideline developers.
The International Society for Mild Approaches in Assisted Reproduction	016	006	Specify OHSS and related health effects of ovarian stimulation in fertility treatment	Thank you for your comment. The scope includes a list of the main outcomes that the guideline may consider, and this would usually include adverse effects such as OHSS if appropriate. The guideline committee will define the outcomes that will be considered in the evidence reviews through the development of review protocols.
Wales Fertility Institute	004	009	I think a whole section on genetic is necessary. There is a need for guidance on extended genetic screening, pre implantation genetic testing not only for aneuploidies but for	Thank you for your comment and the references provided. Pre-implantation genetic testing for aneuploidy is included but other genetic tests for monogenic disorders are not related to

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			monogenic disorders and translocations. There are lots of advancements in genetic and some guidance would be beneficial. (ref: de Wert G, van der Hout S, Goddijn M, Vassena R, Frith L, Vermeulen N, Eichenlaub-Ritter U; ESHRE Ethics Committee. The ethics of preconception expanded carrier screening in patients seeking assisted reproduction. Hum Reprod Open. 2021 Feb 12;2021(1):hoaa063. doi: 10.1093/hropen/hoaa063. Erratum in: Hum Reprod Open. 2021 Apr 17;2021(2):hoab014. PMID: 33604456; PMCID: PMC7880037.)))	the treatment of fertility and so are not included in the scope of this update.
Wales Fertility Institute	005	008	To add that endometriosis will not be covered as explained at the end of the document (point 1.7 page 8)	Thank you for your comment. This has been added as you suggest.
Wales Fertility Institute	010	1.12	The guideline may cross-refer to guidance from other developers, such as the European Society of Human Reproduction and Embryology (ESHRE) guideline on oocyte pick up (The ESHRE Working Group on Ultrasound in ART, Arianna D'Angelo, Costas Panayotidis, Nazar Amso, Roberto Marci, Roberto Matorras, Mircea Onofriescu, Ahmet Berkiz Turp, Frank Vandekerckhove, Zdravka Veleva, Nathalie Vermeulen, Veljko Vlaisavljevic, Recommendations for good practice in ultrasound: oocyte pick up, *Human Reproduction Open*, Volume 2019, Issue 4, 2019, hoz025, https://doi.org/10.1093/hropen/hoz025)	Thank you for your comment. You are correct that sections 1.12.1 to 1.12.4 and 1.12.7 have not been prioritised for update as it is planned to refer to the comprehensive guidelines produced by the European Society of Human Reproduction and Embryology relating to ovarian stimulation. The decision on exactly which sections of the guideline to remove, and exactly what can be covered by the ESHRE guidelines will be discussed and agreed by the guideline committee.

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			and for embryo transfer to refer to the newly published paper on Arianna D'Angelo, Costas Panayotidis, Alessandra Alteri, Saria Mcheik, Zdravka Veleva, Evidence and consensus on technical aspects of embryo transfer, *Human Reproduction Open*, 2022;, hoac038, https://doi.org/10.1093/hropen/hoac038	
Wales Fertility Institute	010	1.16	The guideline may cross-refer to guidance from other developers, such as the European Society of Human Reproduction and Embryology (ESHRE) guideline on female fertility preservation (The ESHRE Guideline Group on Female Fertility Preservation, Richard A Anderson, Frédéric Amant, Didi Braat, Arianna D'Angelo, Susana M Chuva de Sousa Lopes, Isabelle Demeestere, Sandra Dwek, Lucy Frith, Matteo Lambertini, Caroline Maslin, Mariana Moura-Ramos, Daniela Nogueira, Kenny Rodriguez-Wallberg, Nathalie Vermeulen, ESHRE guideline: female fertility preservation, *Human Reproduction Open*, Volume 2020, Issue 4, 2020, hoaa052, https://doi.org/10.1093/hropen/hoaa052)	Thank you for your comment and providing the reference to these guidelines produced by the European Society of Human Reproduction and Embryology relating to female fertility preservation. The decision on exactly which sections of the guideline to remove, and exactly what can be covered by the ESHRE guidelines will be discussed and agreed by the guideline committee.
Wales Fertility Institute	011	1.17	Ref: D'Angelo, A., Rodriguez-Wallberg, K.A., & Nogueira, D. (Eds.). (2022). Long Term Safety of Assisted Reproduction (1st ed.). CRC Press. https://doi.org/10.1201/9781003052524	Thank you for the reference and the background information.
Welsh Health Specialised	General	General	With the success rates for IVF increasing year on year, the number of viable embryo's available for transfer increasing,	Thank you for your comment. A full cycle of IVF is already defined in the guideline, and as part of the update, the

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Services Committee			an increasing number of freeze all cycles and there being a wide range of interpretations of what a cycle of IVF is across the UK - would the review of the guideline consider how a cycle is defined?	committee will review all 'terms used' to ensure this section is still up to date.
Welsh Health Specialised Services Committee	009	1.10 Prediction of IVF success	Consider an evidence review and reference to In Vitro Maturation(IVM) and Natural cycles of IVF	Thank you for your comment. In Vitro Maturation is not widely used in the UK, and therefore it was not prioritised for inclusion in the guideline scope. Natural cycle IVF is covered by the comprehensive guidelines produced by the European Society of Human Reproduction and Embryology (ESHRE) relating to ovarian stimulation for IVF/ICSI (2019), therefore the guideline may cross-refer to it as appropriate.
Welsh Health Specialised Services Committee	009	1.9 Intrauterine insemination	The guideline would benefit from a review of clinical access criteria for IUI. For example, should there be an upper age limit for accessing IUI? Are there any patients who would benefit from accessing IVF in the first instance and not IUI?	Thank you for your comment. The guideline update will include a review question on criteria for access to treatments and if there is any evidence relevant to an upper age limit or that older people would benefit from accessing IVF in the first instance, the committee would use this information in drafting their recommendations.
Welsh Health Specialised Services Committee	010	1.14 Donor insemination	Review the clinical effectiveness evidence when using donor sperm; what is the ideal age for sperm donation, the genetic screening required for donor sperm and the quality of donated sperm?	Thank you for your comment. Genetic and quality screening for donor sperm is governed by HFEA regulations, which also includes advice on the selection of donors. The guideline update will cross-link to this resource as appropriate, so no other evidence reviews on the use of donor sperm have been prioritised for inclusion in the scope.

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Welsh Health Specialised Services Committee	010	1.15 Oocyte donation	Review the clinical effectiveness evidence when using donor eggs. What is the ideal age for egg donation? Consider if there would be benefit in using egg donation for women over a certain age. What genetic screening is required for donated eggs? Consider what number of donated eggs should be used in a cycle of IVF to give the patients the best opportunity of a positive outcome?	Thank you for your comment. A review of the effectiveness of donor eggs has not been prioritised for inclusion in the scope because the age of the recipient has only a minor effect on the success rate of donor egg treatment and the number of eggs to be used is very unlikely to be answered by an evidence review.
Welsh Health Specialised Services Committee	010	1.16 People with cancer who wish to preserve fertility	Review the evidence in terms of utilisation of stored material following preservation. Should patients who store material need to meet the access criteria at the point of using the stored material? How many cycles should a patient who requires storage be able to access given the time critical nature of their condition? An evidence review of non-standard IVF treatment and duo stimulation protocol for preservation.	Thank you for your comment. For people who have stored gametes to preserve fertility due to medical conditions or treatment, the guideline already states that 'eligibility criteria used for conventional infertility treatment' do not apply and this is unlikely to change. The number of cycles is likely to be a clinical decision that will need to be made based on the cancer diagnosis, gametes stored and personal preference. This use of duo stimulation will be considered as a possible intervention for inclusion in this review.
Welsh Health Specialised Services Committee	012	3.4 Economic Aspects	Accumulative success rates - are there any gold standard accumulative success rate models which could be used in the economic appraisal?	Thank you for your comment. This section of the scope is intended to give a very general overview to economic aspects and most of the text is standard across different NICE guidelines. It is not intended to describe methods for analysis in any detail and the actual priorities for economic appraisal are determined during guideline development, in consultation with the committee. We would anticipate using the best available evidence on success rates in any economic analysis. This could potentially include real world evidence from the HFEA.

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Welsh Health Specialised Services Committee	012	3.5 Key issues and draft questions	Are there any predictive success indicators which would indicate a patient should access IVF over IUI? Does using e-cigarettes have an impact on fertility? Preservation of fertility is not restricted to gametes/ embryos. There are an increasing number of children accessing wedge procedures. Are there any clinical effective data on the use of the stored samples post treatment? Should the evidence for the utilisation of preserved material used in a cycle of IVF post treatment be reviewed? Should patents on a fertility preservation pathway need to meet the suggested access criteria when the stored material is being used?	Thank you for your comments. These have been addressed these in order: - Whether there are any predictive success indicators which would indicate a patient should access IVF over IUI will be guided by the evidence reviewed as part of predictive factors and models for the success of ART. - There is limited evidence on the effect of e-cigarettes on fertility, therefore the other topic areas more likely to inform decision-making in a meaningful way have been prioritised for inclusion in this update. - Wedge resection of the ovary is no longer a procedure commonly carried out and so no evidence review is planned on the use of preserved material obtained from this procedure. - The evidence review on preservation of fertility will include a review of the effectiveness of different techniques so this will encompass the utilisation of preserved material. - For people who have stored gametes to preserve fertility due to medical conditions or treatment, the guideline already states that 'eligibility criteria used for conventional infertility treatment' do not apply and this is unlikely to change.

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The following comments were also sent to NICE as part of the consultation but were not received. They were added to the table at the stakeholder's request in January 2023.

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Scottish Government	General	General	The Scottish Government notes with disappointment, the exclusion of single people, same sex couples and surrogacy from the guideline scope and is concerned at the lack of mention of the higher obstetric risk for women undergoing fertility treatment, which include but are not exclusive to increased likelihood of: • multiple births, with accompanying risk for premature birth, high blood pressure and placenta abnormalities. • hypertensive diseases of pregnancy • gestational diabetes • preterm delivery • fetal low birth weight • congenital defects/imprinting disorders	Thank you for your comment. The focus of the guideline is on health-related fertility problems, and it does not make assumptions about social or personal situations or scenarios. Therefore, the guideline will cover everyone, including the users of surrogates, as long as the main criteria of health-related fertility problems is met, and the scope has been clarified to state this. Consideration of the increased obstetric risk has now been added to the scope as an additional question.
Scottish Government	General	General	Advanced maternal age (often the reason for IVF) also increases risk for miscarriage, stillbirth, birth defects and maternal death. Additionally, the MBRRACE UK – Saving Lives, Improving Mothers' Care report, published in November 2021 highlighted maternal deaths in women who had received	Thank you for your comment. Health-related fertility problems (where conception does not occur following a defined period of time) are more likely to occur in older women and this is reflected in the equality assessment which is linked from section 2 of the scope. This assessment will be used during development to ensure that recommendations meet the needs of the groups listed within it, including whether

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			fertility treatment and states that "*Guidance is needed on maternal medical assessment and screening prior to assisted reproduction, particularly for older women who are at higher risk of co-morbidities such as cardiac disease and cancer*" and "*Guidance on single embryo transfer for older women undergoing in vitro fertilisation, particularly in the context of medical co-morbidities"* should be developed. We would support this for women of any age with comorbidity and ask that NICE consider adding to their guidance.	different treatments are required based on age, such as the number of embryos to be transferred.