National Institute for Health and Clinical Excellence

Fertility (update)
Guideline Consultation Comments Table
22 May - 3 July 2012

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
1.	Association of Biomedical Andrologists (ABA)	38	NICE Version	9	1.2.13.4	Should read "woman or man" or "person" for consistency – many men are just as distressed about inability to conceive and considering 30-50% infertility has a male factor, investigation must include men	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
2.	Association of Biomedical Andrologists (ABA)	39	NICE Version	19	1.3.1.1	The guidelines state that the results of semen analysis should be compared with the WHO reference values. It might be useful to consider how many UK lab services have switched to these ranges. Although ABAsupport this recommendation perhaps it would be prudent to ask the question should NICE be recommending a standard against which semen analysis results should be reported before assessing the uptake in practice?	Thank you for your comment. Your query is outside the scope of the guideline update to address. However, an essential change has been made to ensure the recommendation is consistent with current WHO standards. Furthermore, it has been clarified that the figures only apply to WHO recommended tests.
3.	Association of Biomedical Andrologists (ABA)	40	NICE Version	20	1.3.1.2	There may be no "treatment" for anti-sperm antibodies but knowing of their presence has several benefits: • The couple may be given a reason for their infertility. Not knowing why is a major cause of stress amongst infertile couples. • In discussions withpatients, men are often relieved to be able to tell their partners that the problem is male-related, in a protective response towards their partner's own infertility distress.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

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						• Assisted conception techniques may be adjusted if the presence of antibodies is known, i.e.asking the patient to produce a sample into a container withculture medium in it, or performing ICSI instead of IVF, etc.	
4.	Association of Biomedical Andrologists (ABA)	41	NICE Version	24	1.3.6	Patients cannot be diagnosed accurately on symptoms alone (UK Guidelines for the use of thyroid function tests, 2006) and as females are 7x more likely to suffer this disorder than men, surely they should be screened as part of the initial work-up?	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Thyroid testing was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
5.	Association of Biomedical Andrologists (ABA)	42	NICE Version	25	1.3.9.1	Should have been amended to "IUI and IVF" (risk is just as high in IUI and also protects staff).	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Viral screening was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
6.	Association of Biomedical Andrologists (ABA)	1	Full	27	83	The comment about the significance of antisperm antibodies is dismissive. We accept	Thank you for your comment.

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						that corticosteroids may be ineffective, but the two issues in one sentence may be misleading.	The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
7.	Association of Biomedical Andrologists (ABA)	43	NICE Version	34	1.9.1.1	Define "routinely" – IUI may not be funded by the NHS in England but is a less expensive route for couples who cannot afford IVF and has been shown to be effective if OI/IUI in clinical practice.	Thank you for your comment. The term 'routine' relates to women who may have social, cultural or religious objections to IVF or where the balance of clinical judgement is that a single cycle of IUI will be as effective as a single cycle of IVF. NICE guidelines relate to treatment that is funded by the NHS, so costs for the couples are not taken into account. People who are self-funding their treatment can still opt to use IUI.
8.	Association of Biomedical Andrologists (ABA)	44	NICE Version	47	1.16.1	Cryopreservation should not be limited to cancer patients but include all men at iatrogenic risk of infertility associated with clinical treatments and also chronic disease such as men with raised FSH and oligozoospermia, which if diagnosed early, as primary testicular failure may progress to azoospermia and may become more costly and less successfully treated by micro-TESE.	Thank you for your comment. The scope of this guideline was to only make specific recommendations for cancer patients. We have, however, added text (below) to make sure that the guideline is explicit on the context of the recommendation the GDG made but does not to preclude their use for other patient groups.

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							"The scope of this guideline states that recommendations are to be outlined for people undergoing cancer treatment who wish preserve their fertility. The interpretation of the evidence was based on this and recommendations have been written specifically for this population. No recommendations are made for other groups who may prematurely lose their fertility. However, the GDG highlighted that the fact recommendations were not made for other groups should not be used as a justification for not funding cryopreservation in these groups and that the recommendations made in the guideline could be extrapolated to other population who may be at risk of losing their fertility due to treatment."
9.	Association of Biomedical Andrologists (ABA)	2	Full	63	14	Typographical error "this is process" should read "this process".	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
10.	Association of Biomedical Andrologists (ABA)	3	Full	63	19	Continuity issue, "one" should read "1" to be in keeping with the rest of the format of the section	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
11.	Association of Biomedical Andrologists (ABA)	4	Full	63	20	Continuity issue, "seven" should read "7" to be in keeping with the rest of the format of the section	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
12.	Association of Biomedical Andrologists (ABA)	5	Full	63	28	Typographical error, 'in10' should read 'in 10'	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
13.	Association of Biomedical Andrologists (ABA)	6	Full	63	35	Typographical error 'age 35 years of age' should read '35 years of age'.	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended

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14.	Association of Biomedical Andrologists (ABA)	7	Full	64	4-5	Table title is confusing ,should it be: "Cumulative probability of achieving a clinical pregnancy by increasing the number of menstrual cycles in women from 4 different age categories."?	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
15.	Association of Biomedical Andrologists (ABA)	8	Full	64	7-8	Table title is confusing ,should it be: "Cumulative probability of achieving a clinical pregnancy by increasing the number of menstrual cycles in women from 4 different age categories."?	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
16.	Association of Biomedical Andrologists (ABA)	9	Full	81	Rec 44	The threshold of 58% vitality is of negligible use and in direct conflict with the threshold of 32 progressive motility. A man may have plenty of progressive sperm e.g. 40% but insufficient vitality e.g. 50%. There is no practical value in testing vitality unless there is <5% motility.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
17.	Association of Biomedical Andrologists (ABA)	10	Full	81	Rec 44	There should be emphasis that the WHO reference ranges are only valid if WHO recommended methods for semen analysis are used.	Thank you for your comments. This recommendation was edited for accuracy as WHO have outlined new standards. Furthermore, it has been clarified that the figures only apply to the tests used by WHO when defining these criteria.
18.	Association of Biomedical Andrologists (ABA)	11	Full	81	7-16	There is no mention of best practice in the extraction of sperm from urine. The 'Liverpool solution' is the only properly documented and (partially) validated method for retrieving sperm	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard

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						after the adjustment of urine pH and osmolarity (Aust *et al*., 2008).	scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
19.	Association of Biomedical Andrologists (ABA)	12	Full	177	14	Text suggests endometriosis may be present without symptoms apart from infertility. Then it says minimal and mild endometriosis should be removed by laparoscopic resection as it will improve live birth rate P178; line3-5. This might suggest every infertile woman should be investigated by laparoscopy to discover and treat symptomless endometriosis. However chapter 6.4 Investigation of suspected tubal and uterine abnormalities recommendation 62, p104 advises laparoscopy to investigate tubal patency only if co-morbidities are thought. Perhaps it should be clearer as to when to do laparoscopy for endometriotic women.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Neither of these sections was selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline. A new introduction was added to clarify the management options for endometriosis. This included a description of endometriosis. This is not meant to be used as a management strategy, and is not the basis for any recommendations.
20.	Association of Biomedical Andrologists (ABA)	13	Full	178	Rec 108	Recommendation 108 suggests the removal of ovarian endometriomas. However it may reduce ovarian reserve significantly and there is no evidence that it could improve IVF outcome. This	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was

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						would warrant caution with endometrioma removal. Gelbaya*et al.*(2011) Evidence-based management of endometrioma.RBMOnline. 2011 Jul;23(1):15-24 Kennedy*et al.*., (2005) ESHREguidelines for the diagnosis and treatment of endometriosis. Hum. Reprod. 20, 2698–2704.	held and the scope was subject to a period of public consultation before it was finalised. Endometrioma was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
21.	Association of Biomedical Andrologists (ABA)	14	Full	192	15	The evidence which compares stimulated IUI with expectant management (EM) is limited and does not truly represent IUI in its best light. Indeed the guidance reads: *"IUI with ovarian stimulation versus expectant management (evidence profile 12.2)* *The evidence quality was very low due to limitations in the study design and wide confidence intervals."* P199 L6 We feel this could be re-written.	Thank you for your comment. A systematic review was undertaken comparing IUI (with or without stimulation) against expectant management. The review only included RCTs. Therefore, this represents the highest quality evidence that is available.
22.	Association of Biomedical Andrologists (ABA)	15	Full	204	Rec 115	The guidelines recommend that IUI (with ovulation induction) should no longer be used as first treatment for unexplained infertility in favour of expectant management (EM). A flaw in this assessment is that: 1. Only 2 papers were used to arrive at these conclusions – indeed the guidance suggests that quality evidence is either low or very low 2. One paper Tummon *et al*. (1997) actually suggests that IUI is effective with an LBR of 11% in endometriosis patients 3. The main paper used was: Steures *et al. (*2006) which showed EM to be as	Thank you for your comments. The GDG has considered all your points and reassessed the evidence in light of these. They have concluded that the recommendations should not be changed. However, the GDG wished to highlight that the recommendation states that IUI should not be used routinely, not that it should never be used as a first line treatment. With regards to the methods used, these are outlined in the NICE technical manual and represent current best practice in terms of systematic reviewing. To summarise the process and results:

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						effective as IUI in 253 couples. However: a. The IUI pregnancy rate was only 6.5% with a miscarriage rate of 33% and an ongoing PR 4%. In contrast in the clinical setting, Queens Medical Centre (QMC) in Nottingham has an overall 16% PR and 14% LBR. This suggests that the selected isolated paper was operating a 'less than' effective service and should not be used for comparative purposes b. In their patients with multifollicular growth the reported PR is only 5% - at QMC this group has an LBR of 23% c. Some patients were shown to have tubal infertility d. The study must be regarded as weak with a poor quality treatment service and we prefer that it is not cited to influence national policy Moreover Goverde *et al*. (2000) in the Lancet demonstrated using an RCT that IUI was more cost-effective than IVF in the treatment of unexplained infertility. The papers cited appear to have been carefully selected to portray IUI as ineffective.	• The comparisons being assessed were: Is IUI (with or without stimulation) more effective than expectant management or one another? • Papers were selected for inclusion based on pre-specified criteria. Data was then extracted and analysis undertaken, again using pre-specified and standardised methods. This work was undertaken by an independent technical team. • It is important to remember that GRADE is used to assess the quality of the evidence for answering the specific review question posed by the GDG members. This is contributed to not only by the quality of the study, but also by how useful the evidence is in answering the question posed for the guideline. The quality grading is on the basis of the value of the evidence reported in the study in answering the research question. • The results were then presented to the GDG for discussion. • Based on the available data (IUI with stimulation vs expectant management & IUI with stimulation vs IUI without) and using their primary outcome of achieving live full-term singleton births, the GDG concluded that: IUI with stimulation would result higher

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						There is no economic evaluation or accurate costing for IUI with stimulation. There is no similar comparison to show the effectiveness of IVF treatment vs EM for unexplained infertility.	pregnancy rates than IUI alone, but a significant proportion of these would be multiple births (relative risks of about 10 and many of these would be higher order births). The GDG was aware that the regimens used in these studies involved higher drug doses than would be used in current UK practice. The GDG believed that the Steures et al figures showed the likely outcome if current UK doses of ovarian stimulants were used and this showed no difference in pregnancy rates or multiple birth rates compared to expectant management. However, the risk of higher order multiple pregnancies when using stimulated IUI still exists and was a major concern for the GDG. For these reasons the GDG concluded that stimulated IUI should not routinely be used. • No economic evaluation was undertaken on IUI with stimulation compared to expectant management. The reason for this was any such analysis would use the Steures et al study figures showing expectant management is superior to IUI with stimulation, as expectant management has much lower costs it would automatically be more cost-effective. In relation to the Steures paper:

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							• Firstly, the Steures et al paper is an RCT. The GDG agreed that if a population had been selected for IUI then it is likely that pregnancy rates would have been higher than those reported. However, randomised trials are undertaken to avoid this patient selection bias and to provide an estimate of the relative effect between treatments. • Secondly, the Steures et al l study was undertaken in 26 units across the Netherlands, so it is unlikely that results are due to poor standards in a single unit. • Finally, Steures et al acknowledged that the pregnancy rate was lower than expected and hypothesised this was due the characteristics of the population not being selected for IUI. However, due to randomisation these women were equally distributed between the groups, so the expectant management arm would be equally affected. Finally, • The Goverde et al (2000) paper compares IUI and IVF, but this was not a comparison included in this review so this paper was not reviewed. • The GDG agreed that data is lacking on IVF compared to expectant management. However, in chapter 14

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							considerable efforts has been made to compare IVF against expectant management in a health economic model. The GDG have also made a research recommendation that further work is undertaken in this area to confirm the findings of existing RCTs.
23.	Association of Biomedical Andrologists (ABA)	16	Full	229	12-21	There is no inclusion of sperm morphology as a characteristic in the male factor assumption. This could be a limitation of the IVF Predict model and if so should be documented for clarification.	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
24.	Association of Biomedical Andrologists (ABA)	17	Full	279	11	Typographical error 'GnRH Antogonist' should read 'GnRH Antagonist'	Thank you for pointing out this typographical error. We have made the necessary correction.
25.	Association of Biomedical Andrologists (ABA)	18	Full	279	43	Therefore the use of GnRH antagonist and short GnRH agonist protocols should be considered in women who are at a higher risk of OHSS." The benefit of short protocol over reduction of OHSS was not studied.	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
26.	Association of Biomedical Andrologists (ABA)	19	Full	311	24	Nonsensical statement "The available evidence shows that unstimulated cycles result in lower clinical pregnancy rates than unstimulated cycles."	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
27.	Association of Biomedical Andrologists (ABA)	20	Full	320	41	"hCG also resulted in less cases of OHSS when compared with 42 GnRH agonist, although the GDG acknowledged that the absolute number of cases was low." This is the opposite what was concluded on p320; line 14. GnRH agonist trigger was found to reduce the risk of OHSS to almost 0%. Used together with elective cryopreservation is an effective way to achieve acceptable pregnancy rate. As this is a widespread practice it should be mentioned.	Thank you for your comment. The paragraph has now been amended to say: *"The evidence showed that hCG was associated with more live births and clinical pregnancies than GnRH agonist. Although the evidence showed that hCG resulted in more cases of OHSS when compared to GnRH agonist, the GDG acknowledged that the absolute number of cases was low. The GDG*

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							was also aware that there is uncertainty regarding luteal phase support when using GnRH agonist as a trigger. Based on the increased the number of clinical pregnancies and live births, as well as considering the role of luteal phase support, the GDG recommended the use of hCG to trigger ovulation." The GDG was aware that the evidence suggests GnRH agonist results in fewer cases of OHSS, but also less pregnancies. The evidence base is not large enough to make a recommendation for their use. The section dealing with elective cryopreservation in cases of OHSS is in chapter 15. The GDG did not consider this topic as it is a part of the original Guideline that was not updated. The text makes it clear that in 2004 there was insufficient evidence to support routine cryopreservation in cases with a high risk of OHSS.
28.	Association of Biomedical Andrologists (ABA)	21	Full	346	Rec 159	This recommendation makes no difference in embryo quality or stage although its importance is highlighted in the analysis	Thank you for your comment. The GDG believed that embryo quality and stage are embedded in this and other recommendations in this section. Where embryo quality is not mentioned it is because after evaluation of the evidence the GDG concluded that it should not be used.
29.	Association of Biomedical Andrologists (ABA)	22	Full	347	Rec 164	"Use cryopreservation to store any remaining good-quality embryos after embryo transfer." It might be against some people's conviction to store embryos. So wording should perhaps be "cryopreservation should be offered"	Thank you for your comments. Your comments have been considered by the GDG and the relevant recommendation has been amended

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30.	Association of Biomedical Andrologists (ABA)	23	Full	363	4	The sperm does not need to be motile, and may indeed by immotile, therefore the term 'preferably motile' is recommended	Thank you for your comment The GDG agreed with your comment and the text of the introduction has been amended.
31.	Association of Biomedical Andrologists (ABA)	24	Full	363	7	Typographical error 'techniquel'. This sentence also omits sperm motility and polyspermy. This it might read better as: "ICSI is routinely used as an extension to conventional IVF treatment and is a commonly used technique in cases with low sperm number, motility or quality, surgically recovered sperm or in IVF cases where fertilisation rate is unexpectedly low or the polyspermy rate is unexpectedly high."	Thank you for pointing out this typographical error. We have made the necessary correction. We have also amended the text in the introduction to reflect your comment.
32.	Association of Biomedical Andrologists (ABA)	25	Full	363	11-12	This sentence is misleading, as there is substantial evidence to indicate that the origin of the sperm, especially epididymal versus testicular, impacts on the pregnancy and live birth rate, e.g. Sibler 2010.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. ICSI was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
33.	Association of Biomedical Andrologists (ABA)	26	Full	363	28-29	The reference cited defines moderate teratozoospermia inaccurately as 'a minimum concentration of 5 million/ml and morphology of 4–20%.'	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of

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							public consultation before it was finalised. ICSI was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
34.	Association of Biomedical Andrologists (ABA)	27	Full	364	18-21	This statement contradicts lines 16-17. Contradictory evidence makes the guidelines difficult to read.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. ICSI was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
35.	Association of Biomedical Andrologists (ABA)	28	Full	365	Rec 170	Recommendation 70 does not include high polyspermy rate recognised indication for treatment by ICSI. There is sufficient evidence and practice to include this.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. ICSI was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

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36.	Association of Biomedical Andrologists (ABA)	29	Full	365	42	Recommend this sentence begins with the term 'Surgically retrieved sperm from azoospermic men...' to make it clear that this is the origin of the sperm that is being assessed.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. ICSI was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
37.	Association of Biomedical Andrologists (ABA)	30	Full	366	25 & 29	The reference '1018' needs superscripting.	Thank you for pointing out this typographical error. We have made the necessary correction.
38.	Association of Biomedical Andrologists (ABA)	31	Full	366	27	What is a Y-deleted man? Recommend this is reworded to 'men with deletion of the Y-chromosome'.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. ICSI was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
39.	Association of Biomedical Andrologists (ABA)	32	Full	366	23-37	As it reads this section seems disjointed, as if deletions of AZF are separate from Y-chromosome deletions.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was

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							held and the scope was subject to a period of public consultation before it was finalised. ICSI was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
40.	Association of Biomedical Andrologists (ABA)	33	Full	366	38-40	Screening for aneuploidy is not the same as screening for Y-chromosome deletions. This paragraph reads as if they are the same test. Rewording is recommended.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. ICSI was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
41.	Association of Biomedical Andrologists (ABA)	34	Full	369	12	The reference still used today to define the rate of male infertility at 25% (Hull *et al*., 1985) is almost 30 years out of date. The data is based on WHO reference ranges of the time: sperm concentration 20 millions per ml, 50% progression and 50% normal forms which do not compare well with the recently revised reference range of 2010.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Donor insemination was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

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42.	Association of Biomedical Andrologists (ABA)	35	Full	377	40	Typograpical error, 'use' should read 'used'	Thank you for your comment. We have amended the text in the light of your suggestions.
43.	Association of Biomedical Andrologists (ABA)	36	Full	378	Res Rec39	ABA strongly support this research recommendation	Thank you for your comment.
44.	Association of Biomedical Andrologists (ABA)	37	Full	422	Section 21.1	The references from the 2004 guideline are not in alphabetical order – it is extremely hard to find a particular reference as they are not numbered in the text.	Thank you for your comment. As this is only a partial update we are obliged to retain the original reference list formatting for the 2004 reviews. We understand that this may be confusing.
45.	Association of Clinical Embryologists	1	Full	23	98	This suggests that Antral follicle count alone would be an adequate predictor of ovarian response for IVF. There is some evidence that AMH is less variable and a more accurate predictor than AFC and FSH. AMH can be used in conjunction with AFC and FSH if necessary The NHS currently does not fund AMH testing. We believe this should be a standard baseline test in all patients considering IVF to optimise success and reduce cancellation due to over or under response	Thank you for your comment. The GDG did discuss the use of tests in isolation and combination. Based on the available evidence and their own clinical experience, the GDG concluded that it would be best if individual clinical judgement was used in deciding which combination of tests, if any, are required.
46.	Association of Clinical Embryologists	2	Full	111	15	The guidelines only recommend the viruses to be screened. The HFEA have recently stated that patients should be screened for HBV by serological testing for HBsAg and anti-HBc. If this does not occur it will be a breech of compliance. Therefore we feel this should be included or a reference to standards which should be followed included as a minimum.	Thank you for your comment. The guideline's update scope was limited only to consider the transmission of viral disease through sperm washing. Therefore, the GDG was unable to review or make recommendations about screening. The GDG was, however, aware of the new legislation for screening of HBV and have made the following statement within the

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							evidence to recommendation text of the chapter: *"The GDG was aware of ongoing developments of the screening of HBV, specially the HFEA consultation on the serological testing for HBsAg and anti-HBc. The GDG was content that the recommendations made within this chapter are complementary to new screening initiatives and would be adequately supportive to those found positive for hepatitis B."*
47.	Association of Clinical Embryologists	3	Full	204	115	This may be controversial in many centres that offer IUI as a first line less invasive treatment. Some patients opt to choose the treatment of least invasiveness and it is an alternative to those with objections to IVF on religious or moral grounds. The NHS currently supports the use of IUI for the groups which are now being recommended to move directly to IVF. We are concerned that the evidence is based on low quality trials and whilst the guidelines specify use of clomifene citrate, letrozole or anastrozole there are no studies comparing the use of gonadotophins. The studies are also several years old and better well designed stimulation regimens for IUI using gonadotrophins now exist and are in use. Stimulated IUI is also less expensive than IVF.	Thank you for your comment. The overarching conclusion of the GDG was that IUI without stimulation was no more effective than expectant management, and that IUI with stimulation increased the risk of multiple pregnancies. The term 'routine' allows IUI to be performed under certain 'non-routine' circumstances. For example, it could apply to women who may have social, cultural or religious objections to IVF or where the balance of clinical judgement is that a single cycle of IUI will be as effective as a single cycle of IVF. The evidence used was the highest quality available, and the Steures et al study included stimulation with gonadotrophin. The GDG was aware that the method of IUI has changed over time and varies between countries, and this was taken into account when they made their recommendation.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
48.	Association of Clinical Embryologists	8	Full	254	125	Welcome the definition of a full cycle	Thank you for your comment
49.	Association of Clinical Embryologists	4	Full	346	157	This statement is not possible in many cases. Ie. If a patient produces only 3 embryos of medium quality it would be inappropriate management to go beyond 3 days of culture as the embryos may likely arrest. Suggest rewording to " Culture embryos to blastocyst where possible and clinically appropriate"	Thank for your comment. The recommendation has been amended to clarify that if available only a single top-quality blastocyst should be transferred:
50.	Association of Clinical Embryologists	5	Full	346	159	Clinics should have the flexibility to make clinical decisions with regards to number of embryos for transfer, so long as they are compliant with the HFEA's multiple birth rate (10% from Oct 2012). It is **inappropriate** to state all patients under 37 should have single embryo transfer in their first cycle. This will compromise some patients chance of success, if for example there are only poor quality embryos available. Although blanket policies (used in a number of clinics to introduce single embryo transfer) have reduced multiple pregnancies, they have also dramatically reduced pregnancy rate. This is not the case in clinics that have been given more flexibility.	Thank you for your comments. The GDG have outlined an IVF strategy based on a woman receiving three full cycles of IVF, and wish to highlight that individual parts should not be viewed in isolation. Furthermore, the primary outcome for the guideline was live full-term singleton births. This particular part was based on the available evidence and clinical experience. The GDD concluded that a single embryo in the first of three full cycles in women aged under 37 would optimise the chances of a full-term live singleton birth for an individual woman. If this fails then the next 2 full cycles allows more than one embryo to be transferred dependent on embryo quality. Therefore, in this instance no change will be made to the recommendation.
51.	Association of Clinical Embryologists	6	Full	347	161	Women over 40 should be allowed to consider 3 embryos to be replaced in certain circumstances. (ie. previous failed attempts, or very poor embryo quality.). As above, as long as clinics multiple rate is within HFEA guidelines	Thank you for your comment. The GDG was tasked with examining the effectiveness and safety of treatment for the individual woman. Based on the evidence and

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							their clinical experience, the GDG concluded that triple embryo transfer in those over age 40 years would put a woman and any resulting infants at an undue risk of complications especially in relation to the increase in multiple births including triplets.
52.	Association of Clinical Embryologists	7	Full	347	162	In certain patients it may be valid to transfer two top quality blastocysts. For example in the case of 2 previous failed cycles and patient nearing or over 40, this may be their best chance of achieving a healthy singleton. We believe following this guideline strictly would result in a decline in pregnancy rates in older patients. Suggest putting an age guideline attached to this statement and for first 2 cycles only. Again, clinic multiple rates must be under 10% which demonstrates they manage their patients appropriately.	Thank you for your comment. Based on the available data the GDG concluded that transferring two top quality blastocyst embryos significantly increased a woman's chances of a multiple pregnancy compared to a single blastocyst or lower quality embryos. Given that multiple pregnancy is the greatest risk to the health to a mother and unborn children, the GDG concluded that the two top quality blastocysts should not be transferred. Therefore, whilst this recommendation has been reworded for clarity, its meaning has not been changed.
53.	Association of Clinical Embryologists	9	Full	367	177	It should not be implied that ICSI improves fertilisation rates compared to IVF alone. This would encourage all patients to have ICSI which is clearly inappropriate. Suggested that this section be reworded to reflect evidence of increased birth defects compared with IVF/naturally conceived children. **ICSI should not be used for men with normal semen parameters unless otherwise**	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. ICSI was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						clinically indicated ie low fertilisation in a previous cycle.	forward or make any substantive changes to the existing topic in the final version of the Guideline. However, the GDG did note that the recommendation is accurate, and does not suggest that ICSI is superior to IVF where there are normal semen parameters. In order make this clear in the guideline the following text has been added: *"Whilst the evidence for this recommendation has not been updated for the 2012 edition of the guideline, it should be noted for clarification that in the absence of male factors (see recommendation 170), ICSI is not proven to confer a benefit in terms of increased pregnancy rates and should not be offered in the first treatment cycle"*
54.	Association of Clinical Embryologists	10	Full	391	205	We would support some guidance in this area. A number of clinics currently have men with stored samples on rolling ten year consents. They are often reluctant to return for analysis or discussion (This is a problem nationally that very few men return to use their sperm) and it is not clear at which stage we could determine their fertility was recovered? Would this be the detection of sperm in a sample or if they have fathered children following the completion of chemotherapy treatment. Clearly if their consents have expired then we would need to discard	Thank you for your comments. The GDG agreed that the wording would make the recommendation difficult to implement. They have subsequently changed the recommendation so that the indication is to retain the sample (after 10 years) if the man has a diagnosis of significant infertility or is at risk of significant infertility. The change of wording now is consistent with the guidance offered within the Human Fertilisation and Embryology (HFE) Act 1990 (as amended by the HFEA).

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
55.	Association of Clinical Embryologists	11	Full	391	203	It is very controversial to recommend that vitrification should replace slow rate freezing There is no robust evidence to state that vitrification results in better outcomes especially as there are very few long term follow up studies of children. Initial studies are promising (Noyes et al) but the numbers are too small to reach conclusions. The problem with the studies is that although there is an increased survival rate this does not necessarily translate into more clinical pregnancies (Wood et al 2011, Borini et al 2006) and there is no data yet on the cumulative pregnancy rates with vitrification. Data in oocyte cryopreservation studies which show improved survival, fertilisation and pregnancy rates are often incomplete and do not take into account the number of embryos transferred, the number of oocytes thawed and the degree of embryo selection. Furthermore much of the evidence comes from a few clinics most of which have been involved in the development of vitrification eg Kuwayama et all; Cobo et al, Rienzi et all, Nagy et al. The meta analysis (Kolibianakis (2009) collated all evidence available from RCTs but whilst survival increased there were no differences in pregnancy rates. The strength of the evidence is also questionable as the method of randomisation is not always clear.	Thank you for your comments: The evidence shows that there was a significantly higher rate of post-thaw survival after vitrification of oocytes compared to controlled rate freezing of oocytes and an indication that the same is true in embryo cryopreservation. Furthermore, there were significantly more embryos with abnormal morphology after controlled rate freezing compared with after vitrification. The GDG was aware that the amount of RCT evidence comparing controlled rate freezing and vitrification is small. They were also aware that there is no long-term data on vitrification use or indeed the primary outcome for the review, live singleton birth. However, the evidence that was available supported the consensus that vitrification should be the preferred technique, but only where it is available. Because of the limitations of the evidence, controlled rate freezing can still be offered without restriction if this is the only option within a clinic. We agree that there is not enough robust evidence for a more definitive recommendation of one technique over the other. Finally, the GDG has written a research recommendation to reflect such sentiment and it is hoped that these areas will be addressed within the next review of the guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						There is very little data on vitrifying cleavage stage embryos and most are not randomised studies. Evidence is conflicting; Raju et al (2005) found vitrification improved survival, implantation rates and pregnancy rates but the method of randomisation was unclear and the sample size was very small. Li (2007) saw no difference in post thaw survival rates. Vitrification uses much higher concentrations of cryoprotectants which may have safety implications and therefore as with all new technology we should be cautious. The cost effectiveness also needs assessing. There are many different methods available and the variety of solutions and carriers need further evaluation. The problems with using open and closed systems needs addressing. Should not be a recommendation yet as it is too early to conclude the efficiency of vitrification and there are issues with the methodology which need to be resolved. New freezing protocols are emerging which may improve survival rates with slow freezing. Gook and Edgar (2012) reported similar implantation rates with fresh and frozen embryos after freezing. Properly conducted randomised control trials should be carried out before recommending 1 method over another. It is not enough to build on early studies and we should only use good evidence. From the best practice meeting held by ACE in 2011 (paper in review) it was clear	

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						that no one defined method is producing consistently good results, some centres had concerns and were not achieving the published survival rates and some centres are getting better results with slow freezing. There is a strong feeling that there is a learning curve when implementing vitrification. Further data needs to become available before this is made a recommendation.	
56.	Barts and The London Centre for Reproductive Medicine	1	Full	general		If the evidence is weak the executive summery need to reflect that as most readers will only read this. Many of the recommendations fall under this.	Thank you for your comment. Once the GDG has reviewed and discussed the quality and implications of evidence on a given topic, the resultant recommendations are phrased in ways that reflect the strength and quality of that evidence. Thus, for example, if there is good quality evidence to support a particular intervention then 'offer' is the form of verb used; if the quality of the evidence is not as strong then 'consider' is used.
57.	Barts and The London Centre for Reproductive Medicine	6	Full	general		Throughout the document there is emphasis that couple with unexplained subfertility need to try for 2m or 3 years before going through IVF. This can be true in young women less than 33 years. For older women the number of years trying needs to be limited to 1 year as the chances of IVF will be significantly lower the longer they try, so negating the full advantage of IVF. This delay will cause quite a problem too to some minority group in whom the social pressure is so great that it may cause disharmony. Research is required in those minority group to identify if the rate of pregnancy over time is the same as others.	Thank you for your comments. The GDG have recommended that women that are 36 years or more are offered an earlier referral. If they are then diagnosed with unexplained infertility, however, the GDG did not agree that these women should be referred for IVF treatment any sooner than younger women. By being referred earlier at the outset they would be able to access discussion of and consideration for IVF more promptly than younger women. Women who are 36y or more with no apparent cause for their infertility after full assessment an

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							investigation still have about a 90% of conceiving after 2 years of expectant management (see Table 5.1 and Figure 5.2, in the full Guideline). It is possible that one or both of those 2 years occur before the women presents with difficulty in conceiving. However, the implication of this and other recommendations in the Guideline is that women should not defer pregnancy until their late 30's as this means that if they do not conceive naturally their therapeutic options are limited.
58.	Barts and The London Centre for Reproductive Medicine	3	Guideline summery, Full	8,83-96		Tests for ovarian reserve: AFC values in the summery of 2 AFs not specified if in one ovary or both? The level of ≤2 is extreme and only limited evidence presented for using this number as lower limit, specially as the assessments of AFC need good experience. Furthermore the definition does not include the size of the AF in mm that define and AF. The group identified serum FSH as a measure of ovarian reserve yet they have not stated as physiologically well known that the measurement need to be "basal" that is measured in very early menstrual date (2±1) and best wit measuring serum estradiol to ensure it is low (<200 pmol/l) to reduce variability when measured at different days in the menstrual cycle. While the group need to state that measuring serum AMH have the advantage that it can be assayed any day of the cycle with little variation. The group is to be commended in stating that all these test are only related to ART and can only predict number of oocytes retrieved. But They	Thank you for your comment. The GDG agreed with your comment. After discussion it has been agreed that the aim of the recommendation is the safe management of women. Therefore, a higher false positive rate will be accepted. The result of this is that the AFC will rise from 2 to 4 for a low response. The text does highlight the differences between measuring FSH and AMH. However, this section has been expanded for clarity.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						also need to stress more that gonadotrophin dose manipulation may help to overcome this in women with younger age.	
59.	Barts and The London Centre for Reproductive Medicine	2	Guideline summery	6	B2	The wording may confuse many as it seem to read like supporting IUI to "people" yet "people" not defined. Later in the document IUI is only recommended for specific indications.	Thank you for your comments. The guideline only restricts the use of IUI as a fertility treatment, i.e. in women with unexplained infertility. IUI remains the recommended insemination technique where intercourse is not in an option for women (for example in same sex women using donor sperm). As discussed within the initial advice and donor insemination chapters (5 and 17, respectively), IUI has been shown to be the most effective and safe way of insemination in these women requiring assisted reproduction On this basis the GDG have made the decision not to change the wording.
60.	Barts and The London Centre for Reproductive Medicine	4	Full	103	13	There is an advantage in cost efficacy of HyCoSy over HSG in that an ultrasound of the pelvis is done at the same time. The group need to express this in the summery and in the full text. Saline instillation Sonography which is part of HyCoSy has a very high sensitivity for diagnosing uterine abnormalities similar to hysteroscopy leading to further cost cutting.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
61.	Barts and The London Centre for Reproductive Medicine	5	Full	175	14-25	There is accumulating evidence that removal of hydrosalpinges may result in diminishing ovarian reserve through disruption of vascular supply, in some cases. Disconnecting the fallopian tube(s) from the corneal end have been reported to give same advantage as salpingectomy with less trauma and no disruption to vascular connection of the ovaries.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Tubal and uterine surgery was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
62.	British Acupuncture Council	1	Full	73	13-23	For complementary therapy as a whole there is mention of only four RCTs evaluating 'substances' and one on prayer. This is surprising as we know that for acupuncture alone there are numerous RCTs on aspects of fertility. Most of these are for acupuncture delivered in addition to some form of assisted conception treatment (mostly IVF). A recent meta-analysis paper (Zheng et al, 2012) lists more than 30 such published studies. Some at least of these are of reasonable methodological quality, and they have been the subject of numerous systematic reviews, including Cochrane, in the last 4 years. Outside of IVF the research is much sparser, though a few RCTs exist both for female (e.g. Song et al, 2008; Chen et al, 2007) and male (e.g. Dieterle et al 2009; Pei et al 2005) infertility. Nevertheless there is substantial experimental evidence to indicate plausible biological mechanisms (Stener-Victorin and Wu, 2010).	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						References Chen D. Chen SR. Shi XL. Guo FL. Zhu YK. Li S. Cai MX. Deng LH. Xu H. [Clinical study on needle-pricking therapy for treatment of polycystic ovarial syndrome]. [Chinese] Zhongguo Zhenjiu. 27(2):99-102, 2007 Feb Dieterle S et al. A prospective randomized placebo-controlled study of the effect of acupuncture in infertile patients with severe oligoasthenozoospermia. *Fertility and Sterility* 2009; 92: 1340-3. Pei J et al. Quantitative evaluation of spermatozoa ultrastructure after acupuncture treatment for idiopathic male infertility. *Fertility and Sterility* 2005; 84: 141-7. Song FJ. Zheng SL. Ma DZ. [Clinical observation on acupuncture for treatment of infertility of ovulatory disturbance]. [Chinese] Zhongguo Zhenjiu. 28(1):21-3, 2008 Jan Stener-Victorin E, Wu X. Effects and mechanisms of acupuncture in the reproductive system. *Auton Neurosci* 2010 Mar 27. [Epub ahead of print] Zheng CH, Huang GY, Zhang MM, Wang W.Effects of acupuncture on pregnancy rates in women undergoing in vitro fertilization: a systematic review and meta-analysis.Fertil Steril. 2012 Mar;97(3):599-611.	

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
63.	British Andrology Society	22				**Quoted References** Bhattacharya S, Hamilton MP, Shaaban M, Khalaf Y, Seddler M, Ghobara T, Braude P, Kennedy R, Rutherford A, Hartshorne G, Templeton A.Conventional in-vitro fertilisation versus intracytoplasmic sperm injection for the treatment of non-male-factor infertility: a randomised controlled trial Lancet 2001 357 2075-79 Gharagozloo P, Aitken RJ. The role of sperm oxidative stress in male infertility and the significance of oral antioxidant therapy. Hum Reprod. 2011 Jul;26(7):1628-40. Epub 2011 May 5. Review. PubMed PMID: 21546386. Hammiche Fatima, Joop S.E. Laven, John M. Twigt, Willem P.A. Boellaard, Eric A.P. Steegers, and Régine P. Steegers-Theunissen. Body mass index and central adiposity are associated with sperm quality in men of subfertile couples. Hum. Reprod. first published online June 12, 2012. doi:10.1093/humrep/des177 S.E.M Lewis R. Paro, L. Borriello, L. Simon, L. Robinson, Z Dincer, G. Riedel, N. Battista and M. Maccarrone. Long Term Use of HU210 Adversely Affects Spermatogenesis in Rats by modulating the Endocannabinoid System International Journal Andrology 2012 advance online Ross C, Morriss A, Khairy M, Khalaf Y, Braude P, Coomarasamy A, El-Toukhy T. A. Systematic	Thank you for providing these references

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						review of the effect of oral antioxidants on male infertility. Reprod Biomed Online. 2010 Jun;20(6):711-23. Epub 2010 Mar 10. Review. PubMed PMID:20378409. Showell MG, Brown J, Yazdani A, Stankiewicz MT, Hart RJ. Antioxidants for male subfertility. Cochrane Database Syst Rev. 2011 Jan 19;(1):CD007411. J.M. Twigt, M.E.C. Bolhuis, E.A.P. Steegers, F. Hammiche, W.G. van Inzen, J.S.E. Laven, and R.P.M. Steegers-Theunissen. 2012. The preconception diet is associated with the chance of ongoing pregnancy in women undergoing IVF/ICSI treatment. Hum. Reprod. first published online May 15, 2012. doi:10.1093/humrep/des157 Van Rumste M M E; Evers J L H; Farquhar C M 2003 Intra-cytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in patients with non-male subfertility. Cochrane database of systematic reviews (Online) Issue: 2 CD001301 Whan LB, West M, McClure N, Lewis SEM. The effects of Delta–9–Tetrahydrocannabinol, the primary psychoactive cannabinoid in marijuana, on human sperm function in vitro. Fertility and Sterility 2006 85(3):653-660 WHO Manual for the Standardized Investigation, Diagnosis and Management of the Infertile Male. ISBN:9780521774741 Publication date:March 2000	

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
64.	British Andrology Society	1	Full	7		[C2] Smoking We believe they should be informed that paternal smoking (especially around conception) has also been indicated as a risk of childhood cancers	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Paternal smoking was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline. However, this comment will be logged for the next update of the guideline.
65.	British Andrology Society	2	Full	7		[C6] Tight underwear The BAS agree that spermatogenic impairing effects of tight underwear are suggested from animal models, though as yet in the human any direct effect remains not scientifically proven. If this matter is to be discussed then oral antioxidant supplementation – which is supported by recent systematic reviews (Ross et al., 2010, Showell et al, 2011) – should also certainly be listed. These should also be addressed in Section 7 (Line 24, p128). This could be under a more formal 'healthy diet' title as advice beyond folic acid on the pre-conception diet for the female partner may also be desirable as evidenced by Twight et al., 2012 (Human Reproduction, Papers online in press).	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Neither this topic nor oral anti-oxidant supplementation was selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						The latter may be more appropriate under lifestyle factors at section 122.	
66.	British Andrology Society	3	Full	7		[C8] Prescribed, over-the-counter and recreational drug use Cannabinoid substances have also been reported to affect male reproduction adversely (e.g. Whan et al, 2006; Lewis et al, 2012). Specific reference to the use and abuse of androgens in sports training should be included. These are generally not regarded as 'recreational' drugs and they may have substantial impact on male fertility factors.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Cannabinoid use was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline
67.	British Andrology Society	4	Full	8		[D6] Semen analysis In the event of an abnormal semen analysis more discretion to the course of action is required. A very poor semen analysis is extremely unlikely to change over three months in the absence of any clear external causal factor which would have been detected in a medical history. In all cases a standard semen analysis is only able to identify a sub-set of the sperm problems that may be present. Semen from many men in pathway ([G3] Normal semen analysis as per WHO, 2010) would actually reveal other potential sperm defects (for example DNA damage) if subjected to advanced investigation. It would therefore not be appropriate to further delay treatment in these cases if the couple had displayed infertility as defined.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
68.	British Andrology Society	5	Full	11		[G4] Mild male factor This is a misnomer and should not be used. There can be no such thing as a mild male factor. Either a factor exists or it does not. Any phenotype which can be detected by the low-tech means of standard semen analysis reflects a male factor which has an underlying cause.	Thank you for your comments. We have now defined mild male factor, this has now been added to the Glossary.
69.	British Andrology Society	6	Full	17		Section M. Cryopreservation for patients with cancer who wish to preserve their fertility This section should be clarified. There are now many diseases beyond cancer which have chemotherapeutic or other interventions which can affect fertility; Cancer is just one amongst them. The section should be called ***Cryopreservation for patients where their disease or its treatment may affect their future fertility***. This would be a responsible move by NICE to assist the role out of relevant care to all those who may require it.	Thank you for your comment. The scope of this guideline was to only make specific recommendations for cancer patients. We have, however, added text (below) to make sure that the guideline is explicit on the context of the recommendation the GDG made but does not to preclude their use for other patient groups. *'The scope of this guideline states that recommendations are to be outlined for people undergoing cancer treatment who wish preserve their fertility. The interpretation of the evidence was based on this and recommendations have been written specifically for this population. No recommendations are made for other groups who may prematurely lose their fertility. However, the GDG highlighted that the fact recommendations were not made for other groups should not be used as a justification for not funding cryopreservation in these groups and that the recommendations made in the guideline could be extrapolated to other population who may be at risk of losing their fertility due to treatment.'*
70.	British Andrology Society	7	Full	21	15	People should also be provided clear information that use of vaginal lubricants such	Thank you for your comment.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						as KY jelly may seriously compromise their attempts at natural conception as they have biocidal effects upon sperm.	The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
71.	British Andrology Society	8	Full	28	87	87 Management of ejaculatory failure The statement as stands is true, though there should be caution that interventions, such as imipramine, have been reported to work well, for example for some diabetics, and are in standard use by urologists. This statement may imply to gynaecologists seeing the guideline that no action is worth investigating. For this and other reasons it is possible that the statement should say investigation and management by a urological specialist could be beneficial.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
72.	British Andrology Society	9	Full	36	170	Indications for intracytoplasmic sperm injection *Severe deficits in semen quality* is a difficult and unquantifiable phrase. It would be better phrased as ***Deficits in semen quality which support the use of ICSI as opposed to IVF***. This allows for professional interpretation by scientific and medical staff according to the level and quality of testing performed on a given patient, which will vary greatly from clinic to clinic.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. ICSI was not part of the 2012 update scope, therefore the GDG was unable to amend previous recommendations or include new ones.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							However, the GDG did note that clarification of the indications of ICSI within the relevant recommendation would be useful for clinicians: Within this clarification text we have suggested that severe defects should be described using the WHO (2010) criteria. *"Whilst the evidence for this recommendation has not been updated for the 2012 edition of the guidelines, it should be noted for clarification that in the absence of male factors (see recommendation 170), ICSI is not proven to confer a benefit in pregnancy rate and should not be offered in the first treatment cycle."*
73.	British Andrology Society	10	Full	36	177	177. Intracytoplasmic sperm injection versus IVF The BAS would be interested to see the latest data analysed to support this statement. Many clinics report higher rates for ICSI patients. Even if this is due to the number of failed fertilisations at IVF it is a misleading statement to make to a patient who will wish to know the chance that they leave with a live birth from walking through the door of a clinic. Simple reading of the current latest data on the HFEA website which encompasses all UK cycles would suggest better rates for ICSI (e.g. the latest 2010 Q2 Yr Aggregate data for under 35 yrs old, fresh cycles with own eggs, Live Births per cycle started are 30.6% for IVF,	Thank you for your comments and for taking the time to provide these references. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. ICSI was not part of the 2012 update scope, therefore the GDG was unable to amend previous recommendations or include new ones. However, the GDG did note that clarification of the indications of ICSI within the relative recommendation would be useful for clinicians: In order to do this the following text

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						34.3% for ICSI). This difference has grown larger not smaller since 2008 and equates to hundreds if not thousands of children across the number of cycles in the UK. Therefore Section 16.2 related to this is also misleading. It states that this recommendation is based on ten RCTs comparing ICSI with other types of IVF and that the review showed no difference in fertilization or pregnancy for couples with normal semen. In fact, it is based on a Cochrane review by van Rumste et al, 2003 1 that actually seems to include results from just one paper (Bhattacharya et al, Lancet 2001 357 2075-79). However, our key criticism would be that this does not seem to revaluate the latest data as ICSI practice has spread and evolved over the last twelve years. BAS would like to suggest that cases of 'failure' should include failure to obtain good embryos, or failure to achieve a pregnancy and NOT be limited to failed or poor fertilization. In any of these cases where clinics should not be prohibited from offering these couples ICSI. As it stands, this NICE recommendation removes clinical judgment by imposing a 'one case fits all' strategy, preventing clinics from making clinical decisions based on individual couples' history, tests and previous IVF outcomes.	has been added to explain recommendation 170: *Although ICSI was not reviewed within the 2012 guideline update, to improve the implementation of the recommendation the GDG have included a note of clarification on the indications of when to use ICSI. ICSI should be offered as part of the first IVF cycle where there is a clear indication for its use (for example azoospermia) or where there are severe deficits in semen quality, normally determined using WHO semen criteria (WHO, 2010).* *ICSI can also be offered to a potentially wider group, in whom previous IVF cycles have failed. It should be noted that the evidence within this chapter shows that unless there is an indication for the use of ICSI, IVF is equally effective. Therefore the decision to offer ICSI after IVF failure should involve consideration of' the added value that ICSI would have. For example, ICSI could be offered where there the previous IVF cycle demonstrates it may be of value (such as failure of the sperm to bind to the oocyte) or where the fertilisation rate is unexpectedly poor (a common value used is less than a 50% fertilisation rate).*
74.	British Andrology Society	11	Full	39	198	When deciding to offer fertility preservation to people diagnosed with cancer, take into account the following factors: This section should stress that fertility preservation is not really at the discretion of a member of laboratory staff. The Clinician treating the patient for their disease is best	Thank you for your comments. We do agree that the best treatment will often involve open communication between oncology and fertility teams. To support this view we have subsequently written supportive text within the evidence to recommendations

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						placed to consider whether offering banking is appropriate and helpful. This can be discussed with that clinician by the clinic, but it is not for a fertility centre to reassess the clinical diagnosis or treatment findings and in any case they may be irrelevant should the patient wish for someone to have posthumous treatment.	to indicate that the options to consider when offering cryopreservation should come from a multi-disciplined team.
75.	British Andrology Society	12	Full	40		Key Research Recommendations The BAS support the present key recommendations but believe that they fall very short in only being related to the female partner and later factors. The role of the male gamete needs to be examined and therapy here may well be the cheapest and most tractable in providing healthy birth outcomes with or without intervention. In line with the papers commented on above (Ross et al., 2010 and Twight et al., 2012) This should therefore include KEY RR What are the effects of diet and dietary supplementation upon fertility, particularly with respect to the male? Why this is important Where there is no known cause for infertility, there may be underlying male causes which can have cheap treatment (Ross et al., 2010). This management increases the cumulative chances of successful conception. Systematic reviews have also demonstrated that the likely related male factor of sperm DNA damage significantly increases miscarriage rate (Robinson et al., 2012, HR in Press). As both inability to conceive and miscarriage could therefore benefit from	Thank you for your comments. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. The section on initial management was not selected to be included in the 2012 update of the Fertility Guideline. As no review has been undertaken the GDG could not make a recommendation on if research is needed in this area.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						low-tech antioxidant therapies these require urgent investigation. Further work on the incredible 65% increased chance of pregnancy reported by Twight et al., 2012; due to healthier female diet is also clearly urgent and requires in depth examination. As obesity and poor diet are recognised as UK wide priorities work in this area matches key national research strategies beyond the field of reproduction.	
76.	British Andrology Society	13	Full	43		Research Recommendations The BAS would seek the addition of the following recommendations / changes: *RR 14 Research into the optimum dose and duration of alpha blockers to improve semen parameters in infertile men is needed.* BAS would suggest that this should be reworded to: Research drug interventions that improve semen parameters, or restart spermatogenesis allowing infertile men who otherwise could not have their own genetic offspring to father children is needed. RR ADDITIONAL Research is needed into management of the potentially infertile male as to implementation and use of the WHO and EAU guidelines. Currently few men have the full array of diagnosis and management beyond semen analysis and the utility of these in determining prognosis or finding other medical problems requires examination. RR ADDITIONAL As sperm viability and motility are key factors in reaching the oocyte naturally and a major cause of infertility, research into	Thank you for your comments. As male factor fertility and ICSI were not in the updated scope, the GDG was unable to change research recommendation 14 unless they believed that the 2004 recommendation has been completed and is therefore redundant, which in this case they did not. Similarly, without reviewing the evidence the GDG was unable to make new research recommendations and so cannot add your suggestions. It should be noted, however, that the GDG did review the safety of IVF and have made a research recommendation similar to your final suggestion:

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						improving or maintaining sperm motility whilst protecting or maintaining the genetic integrity of the gamete both for cryopreservation or lower technology treatments are highly desirable. RR ADDITIONAL Research into selecting male gametes of the highest quality for treatment, particularly for ICSI are desirable. For example, around 10% of sperm are aneuploid being able to identify and not use these will directly benefit healthy embryo rates. RR ADDITIONAL Further research to identify effects of consanguinity in risks to offspring born through ART, particularly via ICSI, is required. This is important as subfertility is widely accepted as an early phenotype in consanguinity before more severe phenotypes emerge, yet many patients presenting for ICSI have a high level of consanguinity.	
77.	British Andrology Society	15	Full	62		4.4 Specialist and generalist care The BAS would like to highlight that specialist care for the male is required and directions for this care are clearly provided in and should be according to: The WHO Manual for the Standardized Investigation, Diagnosis and Management of the Infertile Male. This may involve referral to Urologists as certain aspects sit outside the specialism of gynaecology.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Principles of care was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
78.	British Andrology Society	16	Full	80	32	The BAS strongly agree that development and investigation of further reliable sperm function tests is urgent and request therefore that this be added to the Key Research Recommendations.	Thank you for your
79.	British Andrology Society	20	Full	81	5	CBAVD is not associated with renal tract abnormalities. Renal tract abnormalities occur with unilateral vasal or seminal vesicle absence.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
80.	British Andrology Society	21	Full	81	22	As part of the investigation for azoospermic or severely oligozoospermic patients a Karyotype and Y chromosome microdeletion should be performed as this will determine appropriate counselling for patients undergoing ICSI as the male offspring will also potentially carry the Y deletion.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. ICSI was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
81.	British Andrology Society	17	Full	130		The role of varicocele surgery remains unclear although more recent randomised publications have indicated that varicocele correction can result in a better pregnancy rate. Therefore	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						varicocele surgery should not be entirely excluded as part of the management of patients with impaired semen parameters	scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. The surgical treatment of varicoceles was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
82.	British Andrology Society	18	Full	325	12	The guidelines are unclear as to the techniques of surgical sperm retrieval. The use of microdissection TESE as a technique has resulted in a higher sperm retrieval rate in patients with non obstructive azoospermia and is therefore considered a gold standard. Although the majority of fertility units still perform a TESA in men who are azoospermic, this should not be viewed as the definitive technique.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Sperm recovery was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
83.	British Andrology Society	19	Full	369		Recommendation 178. To advocate the use of donor sperm in cases of obstructive azoospermia is contradictory as the sperm retrieval rates from the testicles is almost 100%. Therefore using assisted conception these men can father their own biological children.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Donor insemination was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							changes to the existing topic in the final version of the Guideline.
84.	British Andrology Society	14	Full	391	205	*Do not continue to store cryopreserved sperm, beyond 10 years, for a man whose normal fertility has restored by the time he is discharged from oncology follow-up. [new 2012]* The BAS are extremely concerned that this is misleading and prone to be misinterpreted – the only true assessment of 'natural fertility' would be that the man has fathered a child of proven paternity. It should be made clear that a return to 'normal' semen parameters is not a return to natural fertility and in this scenario the option to continue sperm storage should, at the very least, be offered.	Thank you for your comments: The evidence shows that there was a significantly higher rate of post-thaw survival after vitrification of oocytes compared to controlled rate freezing of oocytes and an indication that the same is true in embryo cryopreservation. Furthermore, there were significantly more embryos with abnormal morphology after controlled rate freezing compared with after vitrification. The GDG was aware that the amount of RCT evidence comparing controlled rate freezing and vitrification is small. They were also aware that there is no long-term data on vitrification use or indeed the primary outcome for the review, live singleton birth. However, the evidence that was available supported the consensus that vitrification should be the preferred technique, but only where it is available. Because of the limitations of the evidence, controlled rate freezing can still be offered without restriction if this is the only option within a clinic. We agree that there is not enough robust evidence for a more definitive recommendation of one technique over the other. Finally, the GDG has written a research recommendation to reflect such sentiment and

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							it is hoped that these areas will be addressed within the next review of the guideline.
85.	British Association for Sexual Health and HIV	3	Full	121	67	Recommendation 67: We welcome this recommendation but suggest change wording to man consistently has a stable VL<50 for greater than 6 months. This deals with the issue of a single VL<50 (Note: flow diagram will also need to be amended)	Thank you for your comments. Your comments have been considered by the GDG and the relevant recommendation has been amended
86.	British Association for Sexual Health and HIV	4	Full	121	69	We are slightly concerned with the following recommendation (no. 69) which advises: "For couples where the man is HIV positive and either he is not compliant with HAART or his plasma viral load is 50 copies/ml or greater, measure the man's seminal viral load. If the seminal viral load is undetectable, advise couples that the risk of transmission to the female partner is negligible through unprotected SI at the time of ovulation. If there is detectable virus in semen, use sperm washing." We do not agree with this recommendation. From a practical level, seminal viral loads are not routinely performed; patients and clinicians may have no access to these tests on a routine basis, and most importantly, there is no evidence base for this suggestion (particularly at a single time point). We feel that most HIV Clinicians looking after couples trying to conceive would feel uncomfortable if the male positive partner had detectable plasma viraemia (particularly if on treatment). Note that flow diagram would also need to be amended	Thank you for your comment. The GDG agreed with your comment. The recommendation no longer makes reference to seminal viral load. In its place, the GDG recommended that the viral load of 50 copies/ml or less should be maintained for 6 months or more. If this measurement is not met then sperm washing is offered. If the plasma viral load is maintained at a level of 50 copies/ml or less for 6 months it would confer a clinical confidence that HAART has been effective in every body compartment, including the seminal fluid therefore making testing seminal fluid redundant.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
87.	British Association for Sexual Health and HIV	5	Full	122	72	Recommendation 72: Whilst we broadly agree with the statement that there may be a lack of additional benefit of PrEP where the HIV positive male is undetectable on HAART, it might be helpful to acknowledge that there are limitations of the data. We are unable to confidently exclude a potential benefit given the benefits in terms of acquisition of HIV reported using PreP in clinical trials to date. Such a broader statement would permit clinicians to have a more informed discussion with couples around the use of PrEP for conception.	Thank you for your comment. The GDG broadly agreed with you and have added this additional text to support this argument. *"The GDG did note that while the evidence for pre-exposure prophylaxis showed no additional benefit for a man with an undetectable viral load, the evidence base was limited. Furthermore, this is an area where the evidence base is new and more research is expected and needed. Currently PrEP is occasionally offered in clinical practice, the cost is relatively low and the perceived extra security it provides is welcomed by some. The GDG concluded that the evidence was not sufficient to make a recommendation for or against the use of PrEP."*
88.	British Association for Sexual Health and HIV	1	Full	123	28	The ligase chain reaction test for Chlamydia is no longer available. I suggest this be changed to 'transcription mediated amplification'.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Chlamydia screening was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
89.	British Association for Sexual Health and HIV	2	Full	123	26	'to' rather than 'o'	Thank you for pointing out this typographical error. We have made the necessary correction.
90.	British Association of Urological Surgeons	15	General			Overall, we welcome the updated NICE guidance and in particular acknowledge the extensive review on female fertility. We note that in 2004 there was no recognised Urological Surgeon on the guideline development group, although Anthony Hirsch is listed as an Andrologist and David Ralph was an external advisor. We note with dismay that no Urological Surgeon has been consulted on either the GDG membership or as External Advisors in the current guidance, which reflects poorly on the clarity of the guidance regarding male factor infertility. We feel that the lack of current evidence base in this area will give mis-leading advice to both clinicians and patients. Urological problems occur commonly in men with sub-fertility and we believe that this guidance, in its current format, has serious omissions, is inappropriate and not in the best interest of the infertile male. In summary we find that the draft guidance does not deal with male factor infertility in a substantial or informative manner. In particular the supporting literature search is outdated without the appropriate levels of evidence. Without modification patients will be ill informed and as a result of this they will have inappropriate treatments dictated, largely, by the needs of the female partner. We recommend that this document is re-written in the context of male factor infertility and that the British Association of Urological Surgeons section of	Thank you for your comments. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. After which it was deemed that a urological surgeon was not considered applicable to the 2012 update GDG. Furthermore, male factor infertility was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						andrology and genito-urethral surgery are directly involved in the development of the finalised guidance. In commenting we have given the page numbers but as our comments relate to whole sections, or in some cases to the flow charts, it was not practicable to give line numbers. We have clearly stated the sections we are referring to in the text.	
91.	British Association of Urological Surgeons	1	Full	General		Overall, we welcome the updated NICE guidance and in particular acknowledge the extensive review on female fertility. I note that in 2004 there was no recognised Urological Surgeon on the guideline development group, although Anthony Hirsch is listed as an Andrologist and David Ralph was an external advisor. We note with dismay that no Urological Surgeon has been consulted on either the GD membership or as External Advisors in the current guidance, which reflects poorly on the clarity of the guidance regarding male factor infertility. We feel that the lack of current evidence base in this area will give mis-leading advice to both clinicians and patients. Urological problems occur commonly in men with sub-fertility and we believe that this guidance, in its current format, has serious omissions, is inappropriate and not in the best interest of the infertile male.	Thank you for your comments. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. After which it was deemed that a urological surgeon was not considered applicable to the 2012 update GDG. Furthermore, male factor infertility was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
92.	British Association of Urological Surgeons	9	Full	General		We note that in the section on research there is no reference made to research in male factor infertility.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Male factor infertility was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline. It should be noted, however, that although there are no male factor key research recommendations. Research recommendations were made (and have been retained) in the 2004 guideline. These can be found in section 1.7 of the full guideline.
93.	British Association of Urological Surgeons	13	Full	General		There are no references made throughout the whole document of any surgical techniques used for non-obstructive azoospermia. This is a major reason for couples seeking help for male factor infertility, particularly from men desiring to parent after previous vasectomy. The role of vasectomy reversal in the treatment of male factor infertility in the guidance is derisory and does not include any guidance on results, surgical techniques, cost benefit analyses or counselling guidance about the role of sperm retrieval and IVF with ICSI as a viable alternative procedure, or as an adjunct, to vasal reconstruction. Additionally, there are no references to the likely outcome from, and surgical techniques available for retrieval of sperm from men with primary and secondary obstructive azoospermia or any reference to the accepted gold standard technique of micro-dissection TeSE in the management of men	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. The surgical techniques used for non-obstructive azoospermia were not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						with NOA, when up to 50% of men may have sperm retrieved by appropriate surgical intervention. The current lack of evidence in this document, in this area, promotes variation in surgical which, we believe is contrary to the basic principles of NIHCE guidance	
94.	British Association of Urological Surgeons	14	Full	General		In summary we find that the draft guidance does not deal with male factor infertility in a substantial or informative manner. In particular the supporting literature search is outdated without the appropriate levels of evidence. Without modification patients will be ill informed and as a result of this they will have inappropriate treatments dictated, largely, by the needs of the female partner. We recommend that this document is re-written in the context of male factor infertility and that the British Association of Urological Surgeons section of andrology and genito-urethral surgery are directly involved in the development of the finalised guidance.	Thank you for your comments. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. After which it was deemed that a urological surgeon was not considered applicable to the 2012 update GDG.
95.	British Association of Urological Surgeons	2	Full	11		Suspected male factor infertility algorithm. The authors have referred to the fact that men with abnormal semen analysis who have mild male factor infertility (G4) should be offered an IVF pathway. We would disagree with this as a number of men will have urological problems including accessory gland infection, varicocele and potential partial obstruction to account for their sub-fertility which may be best assessed by an appropriate specialist able to discern and manage these problems.	Thank you for your comments. We have now defined mild male factor, this has now been added to the Glossary. The option of expectant management was considered within the review of IVF and IUI. In both of those reviews mild male factor (in comparison IUI) and male factor (In comparison of using ICSI) was considered. It was found that IUI had no additional benefit in comparison to expectant management in mild male factor infertility. Within the IVF review if was concluded that it would not be cost effective to offer ICSI/IVF in male factor

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							infertility before a minimum duration of 2 years expectant management. Therefore, on the basis of this evidence, the GDG made the recommendation that mild male factor should follow the same pathway as unexplained infertility and mild endometriosis before IVF is offered.
96.	British Association of Urological Surgeons	3	Full	11		On the management of ejaculatory failure (statement G5) is both confusing and ambiguous. Statement G8 refers to the fact that non-obstructive azoospermia and severe defects in semen quality, patient's should be offered donor insemination. This would be completely inappropriate as there is extensive data within the literature outlining the fact that almost 50% of men with obstructive azoospermia will have foci of spermatogenesis, which means sperm may be retrieved by techniques such as micro-dissection TESE with successful ensuing pregnancy when used in conjunction with IVF and ICSI. Therefore, the algorithm's suggestion to simply progress straight to donor insemination is wholly inappropriate.	Thank you for your comments. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Donor insemination was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline. However, to clarify the recommendation the GDG has added the following text: *'Donor insemination was not included within the updated scope of 2012 guideline. The GDG, however, noted that in some men with azoopsernia, semen can be surgically extracted and be used in ICSI procedures. The GDG wished to clarify that recommendation 178 does not list the clinical indications for when donor insemination should be offered; it lists when donor insemination can be*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							considered as an option (where the evidence shows it is effective).'
97.	British Association of Urological Surgeons	4	Full	27		Section 83 that men should be informed .....antibodies and effect of systemic cortico-steroids is uncertain, contradicts the statement on previous pages that anti-sperm antibodies should not be measured in semen analyses. This is therefore unclear and does not offer clear guidance.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
98.	British Association of Urological Surgeons	5	Full	28		Regarding section 85, there is reference to where appropriate expertise..... should be offered surgical correction of epididymal blockages. Whilst we agree with this statement age of the female partner should also be considered within the context of this statement.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
99.	British Association of Urological Surgeons	6	Full	28		Section 86, the statement that men should not be offered surgical varicocele and does not improve pregnancy rates is wholly inaccurate. There are a number of extensive systemaic reviews, published in European Urology and Journal of Urology suggesting that varicocele	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						ligation does improve semen parameters and DNA fragmentation and may in fact improve natural pregnancy rates as well as outcome from ICSI.	public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
100.	British Association of Urological Surgeons	7	Full	36		Section 176 Testing for Y chromosome deletions. We believe this should be mandatory in patients undergoing ICSI treatment with both severe oligoasthenoteratozoospermia and non-obstructive azoospermia as a significant portion of men as outlined within the contemporary literature will have Y-deletions. The implications of this will of course be that a male child conceived by ICSI will have the same fertility problems as that of the father and therefore we find that the patient should be counselled and informed of this. We therefore believe that Y-deletion analyses should be mandatory in the above patients.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. ICSI was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
101.	British Association of Urological Surgeons	8	Full	36		Section 178 the use of donor insemination is considered effective management of fertility problems associated following conditions; obstructive azoospermia, non-obstructive azoospermia. This would seem rather illogical given the previous statements made within this guideline. It would normally be the patient's choice as to whether or not they would undergo donor insemination rather than the actual pathological conditions themselves excluding them from ICSI using their own genetic sperm. Furthermore, sperm retrieval rates of 100% can be achieved in patients with Obstructive Azoospermia (OA) and 50% of those with non-Obstructive Azoospermia (NOA). This statement	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Donor insemination was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						is again misleading and, in our opinion, dangerous.	
102.	British Association of Urological Surgeons	10	Full	80		section 53. There is no effective treatment to restore fertility in primary testicular failure. This is in contradiction to the algorithm previously presented in the summary page. This section outlines that surgical sperm retrieval can be performed in patients whilst the algorithm does not refer to this.	Thank you for your comment. The algorithm (in box G5) does repeat the recommendation found in section 7.4 of the guideline, regarding sperm retrieval. It states: *'Treatment of ejaculatory failure can restore fertility without the need for invasive methods of sperm retrieval or the use of assisted reproduction procedures. However, further evaluation of different treatment options is needed.'* We note that within the investigations chapter you have directed us to there is a contradiction. Therefore we have deleted the following sentence: *'Alternatively, surgical sperm retrieval with assisted reproduction or donor sperm may be considered (see chapter 7)'.*
103.	British Association of Urological Surgeons	11	Full	81		Sections 17-21. The description on varicoceles and levels of evidence needs expansion as outlined above. The section is uninformative and does not discuss in detail the current evidence base for varicocele ligation or fixation in the management of male factor sub-fertility including its effect on DNA fragmentation.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Varicoceles surgery was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
104.	British Association of Urological Surgeons	12	Full	130		Section 18-45regarding surgical treatment of varicocele. We again disagree with the conclusion,there are a number of systematic reviews and prospective randomised controlled studies comparing varicocele ligation and pregnancy rates compared to control groups. The levels of evidence referred to within this section relate to historical studies which have been criticised historically for their poor methodology. This would need to be outlined within the context of this guidance as we would regard these studies (particularly that of Evers and Collins) as misleading as outlined in more contemporary analysis. Furthermore there is substantial evidence in the literature suggesting varicocele ligation improves DNA fragmentation may have an impact on subsequent IVF outcome.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. The surgical treatment of varicoceles was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
105.	British Fertility Society	1	Full	General		The British Fertility Society welcomes the updated Guidance. We do, however, have certain concerns that relate to the short period of time for the consultation given the size of the document and the complexities of the economic modelling. The funding of fertility therapy is a highly charged political issue. Whilst we appreciate that the NICE Guidance is an attempt to provide an evidence base for the provision of NHS funded fertility treatment, there is still a significant "post code lottery" throughout England, Wales and Northern Ireland. The 2004 recommendations have still not been adopted by the majority of commissioners and so as a general point we are concerned that the new guidance was presented into the public arena with an emphasis on extending the age of	Thank you for your comments. The time available for consultation on NICE Clinical Guidelines is 6 weeks. That period is set by NICE and is considered to be a reasonable period of time for review and reflection by stakeholders.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						provision to 42 (presumably a woman's 43rd birthday) which was inevitably going to detract from many of the other key areas and yet is not really based on robust evidence. What does "absolute infertility" mean at this age - using a strict definition this would suggest that a woman has to be menopausal or have absent Fallopian tubes. And why then only offer one cycle of treatment when logic would suggest that older women require more treatments and not fewer to provide an equitable chance of success? The BFS feels that such guidance is likely to lead to a reduction in the overall provision for those for whom the treatment is actually going to work.	
106.	British Fertility Society	2	Full	General		Surrogacy is a real issue and it is wrong to exclude it from the review. Women with congenital absence of the uterus and those who have needed a hysterectomy for various reasons (and for a small number for whom pregnancy would be dangerous) have a legitimate right to receive fertility treatment and it is inequitable not to include surrogacy in the review.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Surrogacy was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
107.	British Fertility Society	3	Full	General		In a number of places AMH is promoted as a marker of the ovarian reserve. This seems appropriate but we are unsure how useful the precise numbers given in the NICE guideline actually are. The guideline group will be aware of the differences in AMH results from the assays currently available and with development of the Gen II assay now becoming more widely used these numbers are set to change again. Giving such specific numbers without any discussion as to the assays in which they were derived is therefore potentially misleading and will lead to errors in clinical practice.	Thank you for your comments. In summary. you are correct and we have added references to the assay tests from which the figures are derived. The GDG also highlighted that the figures are provided as general guidance to assist implementation of management strategies.
108.	British Fertility Society	4	Full	Research section		The guidelines do not make any recommendations to the use of screening for a methodology for selecting embryos for transfer (PGS) i.e. FISH, CGH array etc. This is a rapidly expanding field where patients could be charged thousands of pounds for a treatment with little evidence base. In addition, there are many adjuvant therapies used in some centres which have not been recommended for use by professional guidelines (Nardo *et al.,* 2009) The BFS believes this is an opportunity for NICE to recommend that they should only be used in conjunction with a RCT.	Thank you for your comments. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
109.	British Fertility Society	50				**References cited in this response** Abdel-Meguid TA, Al-Sayyad A, Tayib A, Farsi HM. (2011) Does Varicocele Repair Improve Male Infertility? An Evidence-Based Perspective From a Randomized, Controlled Trial. *European Urology* 59: 455–61	Thank you for providing these references

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
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Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
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Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
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Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
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Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
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Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
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Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
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Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
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Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
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110.	British Fertility Society	8	Full	67-73	Various	The discussion of individual lifestyle choices in males (e.g. alcohol, smoking, recreational drug use is largely reliant upon univariate analyses. NICE should consider the recent publication by Povey *et al.,* (2012) as more up to date evidence than the current literature cited.	Thank you for your comments and additional up to date reference. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. These topics were not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topics in the final version of the Guideline.
111.	British Fertility Society	5	Full	5		Pathway M Cancer Therapy. It is good to see this clear pathway, which is referred to throughout the document. We think that it should be acknowledged that this is relevant to other diseases other than just cancer where gonadotoxic therapy is used (e.g. some rheumatological conditions, and sickle cell disease where treated with bone marrow transplantation). The application of cryopreservation to other diseases is acknowledged much later in the document	Thank you for your comments. The scope of this guideline was to only make specific recommendations for cancer patients. We have, however, added text (below) to make sure that the guideline is explicit on the context of the recommendation the GDG made but does not to preclude their use for other patient groups. *"The scope of this guideline states that recommendations are to be outlined for*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						(Section 19) but it is rather in the small print and should be highlighted earlier.	*people undergoing cancer treatment who wish preserve their fertility. The interpretation of the evidence was based on this and recommendations have been written specifically for this population. No recommendations are made for other groups who may prematurely lose their fertility. However, the GDG highlighted that the fact recommendations were not made for other groups should not be used as a justification for not funding cryopreservation in these groups and that the recommendations made in the guideline could be extrapolated to other population who may be at risk of losing their fertility due to treatment."*
112.	British Fertility Society	6	Full	28		Guidelines 90 - 92. It seems surprising that these 3 guidelines are listed first when they don't address the primary treatment modalities in these patients. Some reordering would be appropriate. Thus recommendations 93 and 94 would seem to be the primary ones.	Thank you for your comment. These recommendations have been moved to be presented after the other recommendations dealing with women who are resistant to clomifene citrate.
113.	British Fertility Society	7	Full	41 45 348 361	11 2 10 5	Typos *Prednisoline* should read *prednisolone*.	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
114.	British Fertility Society	10	Full	69	8	There's a huge amount published on obesity and reproductive health since 2004. The BFS appreciate this topic isn't being revised, but feel it would be helpful to add some more recent references that fit with the guidance and also strengthen it: The RCOG Scientific Study Group: *Obesity and Reproductive Health.* And the BFS Guidelines: Balen *et al*., (2007).	Thank you for your comment and additional up to date reference. As you say, this topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
115.	British Fertility Society	9	Full	71	34-35	Again, in multivariate analyses many of these occupational risks disappear. A better paper to cite is Cherry *et al.,* (2008) which looks	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
116.	British Fertility Society	11	Full	74	6	**34** Please mention that a higher dose of folic acid (5mg) may be more effective for obese women.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
117.	British Fertility Society	12	Full	75	13	Whilst we recognise that lesbian couples may embark upon 'do-it-yourself methods' including home insemination we feel there should be a stronger statement by NICE discouraging this practice. We should not condone this "treatment" as it is unregulated and uses unscreened, fresh sperm. There is almost an inference here that NICE is suggestion that DIY Methods should be	Thank you for your comments. However, the Scope makes it clear that the Guideline is for people who have a possible pathological problem (physical or psychological) to explain their infertility. Women in same sex relationships can only be considered to be possibly in that category and

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						undertaken prior to NHS funded treatment NHS. Greater clarity is required in the wording here. Lesbian couples may receive NHS funding for treatment straight away if other infertility factors are identified (e.g. anovulation). Given that it is recognised that DI for lesbian couples has excellent outcomes we believe that it would be simpler, more straightforward and justifiable to avoid confusion and offer a set number of cycles of treatment at the outset after appropriate investigation, rather than expect lesbian couples to either home-inseminate or pay for 6 cycles of DI before having access to NHS care.	be considered to be 'infertile' if they have a known cause or have a period of unsuccessful artificial insemination (AI). How that AI is provided and funded are outside the Scope of the Guideline. However, the GDG did discuss the issue of 'do-it-yourself' AI before referral was indicated. Many shared your concerns about the potential hazards of this approach and the text reflects this discussion.
118.	British Fertility Society	13	Full	78	8	Section 6.2 comments on the relevance of physical examination findings, but as this is perhaps the most cost-effective intervention then it should recommend examination of male genitalia in cases of male factor infertility, to emphasize the importance of this intervention.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
119.	British Fertility Society	14	Full	81		Diagnostic semen analysis: Recommendation 44. The threshold of 58% vitality is of little or no use and in direct conflict with the threshold of 32 progressive motility. A man may have plenty of progressive sperm (e.g. 40%) but insufficient vitality (e.g. 50%). There is no practical value in testing vitality unless there is low motility (ABA, 2012). A figure of <5% is suggested.	Thank you for your comments. The GDG has updated the recommendation to reflect the WHO figures that have also been updated since the 2004 version. As the WHO values are the recognised standard the GDG did not sought to make any further amendments.
120.	British Fertility Society	15	Full	81		There should be emphasis that the WHO reference ranges are only valid if WHO	Thank you for your comments.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						recommended methods for semen analysis are used. It would be appropriate also to have some mention that sperm concentration is a better predictor of fertility than motility or morphology and that there is also debate as to whether concentration or total sperm number is the more appropriate parameter. The text also appears to be written from the point of view that spermatogenesis is either normal or abnormal while of course it is shades of grey and indeed recognition of this is the basis for the current WHO guidelines based upon 95% confidence intervals rather than distinct diagnostic categories (Cooper *et al.,* 2010).	This recommendation was edited for accuracy as WHO have outlined new standards. Furthermore, it has been clarified that the figures only apply to the tests used by WHO when defining these criteria.
121.	British Fertility Society	16	Full	81		There is no mention of best practice in the extraction of sperm from urine. The Liverpool solution is the only properly documented and (partially) validated method for retrieving sperm after the adjustment of urine pH and osmolarity (Aust *et al.,* 2008).	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
122.	British Fertility Society	17	Full	100		Recommendation 56. The timing of gonadotrophin assessment should be commented on as measurement outside the early follicular phase will at times detect spontaneous ovulation and these results are frequently misinterpreted.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
123.	British Fertility Society	18	Full	101	1	Whilst the following may not have been included in the review it is wrong not to have done so if there is evidence to support a change in practice. This is one of the great limitations of a selective review of a rapidly changing field. The prevalence of disorders of thyroid dysfunction in women of reproductive years is approximately 5%, which is high enough to warrant a simple assessment of thyroid function – especially if one considers the potential implications for the developing fetus. (Stratford *et al.,* 2000). The use of Chlamydia screening – indication / methods / male and female / should be mentioned. This informs the method of tubal patency assessment. It is mentioned briefly below but needs expansion. The BFS recently published guidance on this topic see Akande *et al.,* (2010).	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
124.	British Fertility Society	19	Full	105	5	**63** The guidelines only recommend the viruses to be screened. The HFEA have recently stated that patients should be screened for HBV by serological testing for HBsAg and anti-HBc. If this does not occur it will be a breech of compliance. Therefore this should be included and a reference to standards which should be followed included as a minimum.	Thank you for your comment. The guideline's update scope was limited only to consider the transmission of viral disease through sperm washing. Therefore, the GDG was unable to review or make recommendations about screening. The GDG was, however, aware of the new legislation for screening of HBV and have made the following statement within the

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							evidence to recommendation text of the chapter: *"The GDG was aware of ongoing developments of the screening of HBV, specially the HFEA consultation on the serological testing for HBsAg and anti-HBc. The GDG was content that the recommendations made within this chapter are complementary to new screening initiatives and would be adequately supportive to those found positive for hepatitis B."*
125.	British Fertility Society	20	Full	121	4	**66 and 67** Advising on unprotected sex where the male partner is positive may cause anxiety and be met with reluctance. The document states the evidence was low in quality which may not be robust enough to base a guideline on. On some samples where a positive result was still found after washing the couple were given the choice whether to proceed. Patient choice is not possible if intercourse is the only line of treatment. It stated that it could be considered if the patient is anxious but their chance of conception may not be lower with IUI than natural conception. We believe that poorly designed studies have influenced the conclusion that sperm washing produces a poorer pregnancy rate compared with natural intercourse and that a well designed RCT would need to be carried out to help determine this.	Thank you for your comments. We agree with the sentiment that sperm washing should be retained for anxious couples, despite the man meeting the criteria we outline for safe unprotected sex. The opinion of the GDG was that sperm washing would reduce the pregnancy rate. As demonstrated in other parts of the guidance, donor insemination (using IUI) is shown to be inferior to expectant management. The first year of intercourse will produce a pregnancy rate of 82% (within in the 30-34 age range), its equivalence (in the same age range) of 6 cycles of IUI has a pregnancy rate of 63%. As donor insemination (through IUI) would be the most common route of administration for washed sperm it was concluded that the pregnancy rate would be reduced.
126.	British Fertility Society	21	Full	123	14	Reference should be made to Akande *et al.,* (2010). Also, no reference is made to Chlamydia screening in the male, yet we know that men who have the infection have reduced semen quality	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						(Al-Mously *et al.,* 2009) and that sperm function can be compromised (Eley *et al.,* 2005). Strategies for screening males in a fertility context have been proposed (Eley and Pacey, 2011).	scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Chlamydia screening was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
127.	British Fertility Society	22	Full	125	1	Surely donor insemination is the **only** option for such couples.	Thank you for your comment. This section of the Guideline was not updated but we think the statement is satisfactory. It follows a paragraph discussing surgical sperm recovery for use in assisted conception methods in some men with male factor infertility. Thus "*Donor Donor insemination (see Chapter 17) is an alternative treatment option..."* is a valid statement.
128.	British Fertility Society	23	Full	128	24	Can the Cochrane review by Showell *et al.,* (2011) be better incorporated into the section on antioxidants as it would seem to be more robust than the current literature cited and is lost as a footnote.	Thank you for your comment. The footnote was added to this chapter as an explanation for the removal of antioxidants from the relevant 2004 research recommendation. Male factor infertility was not included in the 2012 update scope and therefore no changes can be made to the chapter. In this case however, an exception was made as this RCT was used to correct a proven factual error. We have subsequently moved the footnote to sit alongside the research recommendation and not the text within the chapter.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
129.	British Fertility Society	24	Full	130	18	With regard to surgical treatment of varicoceles. more recent evidence should have been discussed including an RCT (Abdel-Mequid *et al.,* 2011) and a meta-analysis (Baazeem *et al.,* 2011). The impact of treatment on sperm quality should be discussed specifically, even if the conclusions remain unchanged. The European Association of Urologists has recently published updated guidelines on Male Infertility (Jungwirth *et al.,* 2012), which discusses these topics in detail. They discuss MicroTESE, which is not mentioned in the NICE guidelines and the guidelines have a good overview of male genetics. They recommend varicocoele treatment in the context of infertility in certain instances, which is a view contrary to NICE. They also state the importance of including the need for male patients with subfertility to be examined.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. The surgical treatment of varicoceles was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
130.	British Fertility Society	25	Full	132	11	The comment on anxiolytics is not backed up by evidence and is not cited in the referenced article. If the point is to consider the minority of men who have a psychological cause for their ED, then other psychological treatments (i.e. sexual counselling) should be mentioned. Anxiolytic drugs can cause erectile and ejaculatory dysfunction and are not considered a treatment for straightforward erectile dysfunction. It might be better just to remove the entire reference to anxiolytics.	Thank you for your comments. Medical treatment for male factor infertility was not included within the 2012 guideline scope. Therefore, unfortunately, the GDG was unable to make this change to the chapter.
131.	British Fertility Society	26	Full	133	28	Kallmann is miss spelt should have 2 n's.	Thank you for pointing out this typographical error. We have made the necessary correction.
132.	British Fertility Society	27	Full	134	16	There is frequent recommendation of the use of pulsatile GnRH. The guideline group will know that this is unlicensed, and appropriate expertise is rare. Furthermore the current formulation of	Thank you for your comments. The GDG was aware that the current formulation is expensive to use. However, the

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						GnRH used for this therapy makes it extremely expensive. While it is clear that this is an extremely effective therapy in women (and also in men as mentioned in the relevant section), in the right hands, it would appear appropriate to mention these caveats rather than the straightforward across the board recommendation as presently phrased.	guideline recommends this treatment for a small number of women with WHO group 1 disorder and the evidence shows it is effective as you concur. The GDG has added to the guideline text to highlight that the appropriate expertise is needed for this procedure.
133.	British Fertility Society	28	Full	135	22	This section seems to be omitting a clear statement on the efficacy and safety of clomiphene alone as first line therapy in anovulatory women.	Thank you for your comments. Your comments have been considered by the GDG and the relevant recommendation has been amended
134.	British Fertility Society	29	Full	169	1	It would be helpful to give specific guidance on the number of allowable follicles in Ovulation Induction. For example BFS and ESHRE suggest "no more than a total of 2 follicles greater than 14mm in diameter, with at least one of 17mm" (The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2008). In order to reduce multiple pregnancy rates.	Thank you for your comments. The GDG believed that making a recommendation on the number of allowable follicles would make the guideline too prescriptive, and so chose not to do so.
135.	British Fertility Society	30	Full	170	26	The BFS suggests that an additional comment should be added to this paragraph to indicate that women who have a body mass index of more than 29, and who are not ovulating, should be informed that losing weight is likely to increase their chance of conception ***and this should be considered as part of their fertility treatment and not as a ''barrier' to treatment***. This is in line with The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2008).	Thank you for your comments. The GDG agreed that BMI should not be seen as a barrier to treatment. Thus, the text of the full guideline has been amended.
136.	British Fertility Society	31	Full	170	14	**94** It is wrong to present metformin as a first line therapy for anovulatory PCOS. This flies in the face of all international consensus groups	Thank you for your comments.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						(ESHRE, ASRM, RCOG, BFS, WHO). Metformin only has a first line role for those with IGT or Type 2 DM. Can NICE really explain how metformin induces ovulation or justify its use as first line therapy? Metformin is not appropriate as first line therapy for anovulatory PCOS and should be used only in those with CC resistance (combined with CC) or those with IGT/Type 2DM (this was agreed in ESHRE/ASRM Consensus (The RotterdamESHRE/ASRM-sponsored PCOS consensus workshop group, 2004; The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008), the 2010 RCOG Scientific Group on PCOS (Balen *et al.,* 2010) and the Cochrane Database (Tang *et al*., 2012).	It is worth noting that the review of this topic in the Guideline includes the studies presented in the 2010 Cochrane review, with additional studies that were published after the Cochrane review. The cut off date for literature searches for the guideline was prior to the publication of the 2012 Cochrane review, and so it could not be included in the guideline. However, as outlined in table 8.2 in the full guideline, there was no significant difference in the number of live births or clinical pregnancies when studies comparing clomifene citrate to metformin were combined. Based on this, the GDG recommended that metformin or clomifene or a combination of the two could be used in WHO Group II women, taking into account various factors such as the need for monitoring and ease of use. The key point is that for the review all the studies comparing clomiphene with metformin were combined and not subgroup analysed by BMI. The text within Section 8.3, emphasises this point namely that different BMIs were included in the reviewed studies. Although a subgroup analysis by BMI was not undertaken, the GDG noted that the studies that only included women with a BMI of 32 or less (Johnson et al., 2010 [32 or less], Karimzadeh et al., 2010 [25 to 29.9], Palomba et al., 2005 [30 or less]) showed a trend towards the effectiveness of metformin over clomifene citrate for live birth and clinical

							pregnancy rates (although this was not significant). Of the two studies that did not apparently restrict BMI, one found a significant advantage of clomifene over metformin for live birth but not clinical pregnancy (Zain et al, 2009) whilst the other found a significant advantage of clomifene over metformin for clinical pregnancy but not live birth (Legro et al., 2007) (both of the non-significant effects were trending towards clomifene). When these five studies were meta-analysed together, no significant difference was found between clomifene citrate and metformin. Metformin Clomiphene citrate Study or Subgroup Events Total Events Total W Johnson 2010 10 35 13 36 Legro 2007 3 38 6 39 Palomba 2005 26 50 9 50 Zain 2009 15 208 47 209 **Total (95% CI) 331 334** Total events 54 75 Heterogeneity: Tau² = 1.03; Chi² = 26.26, df = 3 (P < 0.00001); I² Test for overall effect: Z = 0.41 (P = 0.68)

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							Metformin / Clomiphene citrate Study or Subgroup: Johnson 2010 14 35 14 36; Karimzadeh 2010 13 90 11 90; Legro 2007 18 208 50 209; Palomba 2005 31 50 16 50; Zain 2009 3 38 6 39 **Total (95% CI) 421 424** Total events 79 97 Heterogeneity: Tau² = 0.54; Chi² = 25.65, df = 4 (P < 0.0001); I² = Test for overall effect: Z = 0.35 (P = 0.73) The GDG has now clarified, in the guideline text, this discussion on the effect of BMI of included women on the results of the studies. They have also added BMI to the list of things to consider when choosing which treatment to use. The GDG agreed that the order of the bullet points could be misinterpreted as recommending metformin above clomifene citrate. The bullets have been reordered so that clomifene citrate is top of the list, reflecting its status as the current standard treatment for these women.
137.	British Fertility Society	32		170	25	**96** No evidence is presented for limiting clomiphene treatment to 6 months, This seems to derive entirely from the duration of the licence of this therapy. This also seems at odds with the lengthy discussion and justification of 12 cycles of donor insemination for women who require that therapy. There is also no mention of the management of women who are not clomiphene	Thank you for your comments. The GDG acknowledged that there was no evidence addressing the stopping of clomfene citrate after 6 months, however, the main reason the GDG recommended limiting treatment with clomifene citrate to six months is because of the possibility of clomifene

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						resistant but who do not conceive on clomiphene therapy despite have regular ovulation.	citrate resistance. The GDG did not believe that women who are resistant to clomifene citrate should continue to be offered clomifene citrate alone beyond six months. If the woman has not responded to clomifene citrate after six months, other treatment options for these women should be explored. This will also help reduce the costs that result from the additional monitoring needed with the use of clomifene citrate. Text has been added to the full guideline to clarify this. With respect to your comparative statement regarding 12 cycles of DI, please note that the Guideline recommendations that the 12 cycles of donor insemination would include 6 unstimulated cycles and 6 stimulated cycles, and so restricting clomifene citrate treatment to 6 months is not at odds with the donor insemination recommendations.
138.	British Fertility Society	33	Full	171	12	**99** "…dopamine agonists such as bromocriptine *or cabergoline…"* The addition of cabergoline is based on the text that appears later in the document, giving numbers indicating that cabergoline may be even more effective than bromocriptine. In the full discussion of this it would be appropriate to mention current guidelines on echocardiography to assess mitral valve fibrosis in patients taking bromocriptine. The manufacturer's view is that cabergoline should be stopped a month before conception and therefore it cannot be used in women attempting to conceive. This seems to be accepted without question despite the finding that it is associated with improved pregnancy	Thank you for your comments. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in Scope of the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						rates as well as a rather better side effect profile. This seems to be without any analysis of whether cabergoline does indeed carry a risk of teratogenicity and the guideline group will be aware that it has been widely used for many years in women at the time of conception without apparent clinical risk.	
139.	British Fertility Society	34	Full	189	12	**110** This may be controversial in many centres that offer IUI as a first line less invasive treatment. The NHS currently supports the use of IUI for the groups which are now being recommended to move directly to IVF. Some BFS members are concerned on the evidence being based on low quality trials and whilst the guidelines specify use of clomifene citrate, letrozole or anastrozole there are no studies comparing the use of gonadotrophins. The studies are also several years old and better well designed stimulation regimens for IUI using gonadotrophins now exist.	Thank you for your comments. The GDG was aware that the recommendation on IUI will have an impact on service delivery in the NHS. The evidence included in the review was the best available to answer the question that was set: namely comparing IUI against expectant management.
140.	British Fertility Society	35	Full	189	9-22	It is clear that fertility declines with age and the graphical representations clearly show this, yet the statements in the document seem to bracket all women up to the age of 40 within the same spectrum of potential chance of success, which we find misleading. The BFS believes that the age groups should be separated and that women in their late 30's warrant earlier investigation and treatment. The age limit for offering 2 years of expectant management could be stated more clearly. Is it really as high as 40 years? On page 189 (lines 21-22 in particular), the document refers to good figures, 80% and 90% chances of conception after 1 and 2 years expectant management, respectively and merges all age groups together	Thank you for your comments. The GDG agreed that the decline of fertility is a continuum; however, to make practical and implementable recommendations, they have grouped women together by age. The GDG has recommended that women that are 36 years or more are offered an earlier referral for specialist consultation to discuss their options for attempting conception, further assessment and appropriate treatment. If they are then diagnosed with unexplained infertility, however, the GDG did not agree that these women should be referred for IVF treatment any sooner than younger women. By being

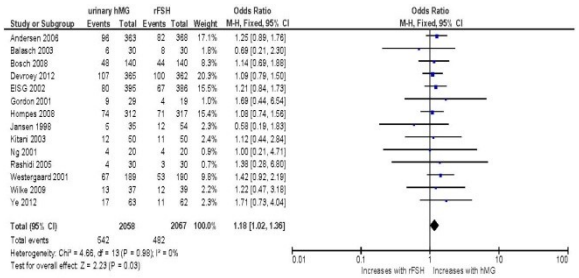
Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						as one group. However, many women over the age of 37 would benefit from a more proactive approach to their management and delaying a further year is likely to reduce the chance for many to have a live birth. The decline in fertility is a continuum and not quite as simply stated in the document.	referred earlier at the outset they would be able to access discussion of and consideration for IVF more promptly than younger women. Women who are 36y or more with no apparent cause for their infertility after full assessment an investigation still have about a 90% of conceiving after 2 years of expectant management (see Table 5.1 and Figure 5.2, in the full Guideline). It is possible that one or both of those 2 years occur before the women presents with difficulty in conceiving. However, the implication of this and other recommendations in the Guideline is that women should not defer pregnancy until their late 30's as this means that if they do not conceive naturally their therapeutic options are limited
141.	British Fertility Society	36	Full	192 199	15 6	The evidence which compares stimulated IUI with expectant management (EM) is extremely thin and does not truly represent IUI in its best light. Indeed the guidance reads: *"IUI with ovarian stimulation versus expectant management (evidence profile 12.2).* *The evidence quality was very low due to limitations in the study design and wide confidence intervals. P199 L6"* The guidelines recommend that IUI (w ovulation induction) should no longer be used a first treatment for UNEXPLAINED INFERTILIT in favour of expectant management (EM). The major flaw in this assessment is that:	Thank you for your comments. The GDG have considered all your points and reassessed the evidence in light of these. They have concluded that the recommendations should not be changed. However, the GDG wish to highlight that the recommendation states that IUI should not routinely be used, not that it should never be used as a first line treatment. An explanation for this decision is given below. With regards to the methods used, these are outlined in the NICE technical manual and represent current best practice in terms of

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						1. Only 2 papers were used to arrive at these conclusions – indeed the guidance suggests that quality evidence is either low or very low; 2. One paper Tummon *et al.,* 1997 actually suggests that IUI is effective with an LBR of 11% in endometriosis patients; 3. The main paper used was: Steures *et al.,* 2006 which showed EM to be as effective as IUI in 253 couples. However: a. The IUI pregnancy rate was pitiful at only 6.5% with an incredible miscarriage rate of 33% and an ongoing PR 4%. In contrast, BFS members have reported they have pregnancy rates of (approx.) 16% PR and 14% LBR. This suggests that this isolated paper 'selected' was operating a 'less than' effective service and should not be used for comparative purposes; b. Within the Steures paper the patients with multifollicular growth the PR is only 5%, whereas BFS members reported that they have achieving a LBR of 23%; c. Some patients were shown to have tubal infertility; d. Basically the study is weak with a poor quality treatment service and should not be cited to influence national policy. Goverde *et al.,* 2000 in the Lancet demonstrated using an RCT that IUI was more cost-effective than IVF in the treatment of unexplained infertility. There is no economic evaluation or accurate costing for IUI with stimulation within the papers cited, which appear to have been carefully selected to portray IUI as ineffective.	systematic reviewing. To summarise the process and results: • The comparisons being assessed were: Are IUI (with or without stimulation) more effective than expectant management or one another? • Papers were selected for inclusion based on pre-specified criteria. Data was then extracted and analysis undertaken, again using pre-specified and standardised methods. This work was undertaken by an independent technical team. • It is important to remember that GRADE is used to assess the quality of the evidence for answering the specific review question posed by the GDG members. This is contributed to not only by the quality of the study, but also by how useful the evidence is in answering the question posed for the guideline. The quality grading is on the basis of the value of the evidence reported in the study in answering the research question. • The results were then presented to the GDG for discussion. • Based on the available data (IUI with stimulation vs expectant management & IUI with stimulation vs IUI without) and using their primary outcome of achieving live full-term singleton births, the GDG concluded that: IUI with

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						There is no similar comparison to show the effectiveness of IVF treatment vs EM for unexplained infertility.	stimulation would result higher pregnancy rates than IUI alone, but a significant proportion of these would be multiple births (relative risks of 10 and many of these would be higher order). The GDG was aware that the regimens used in these studies involved higher drug doses than would be used in current practice. The GDG believed that the Steures et al figures showed the likely outcome if current doses of ovarian stimulants were used, and this showed no difference in pregnancy rates or multiple birth rates compared to expectant management. However, the risk of higher order multiple pregnancies when using stimulated IUI still exists and was a major concern for the GDG. For these reasons the GDG concluded that stimulated IUI should not routinely be used. • No economic evaluation was undertaken on IUI with stimulation compared to expectant management. The reason for this was any such analysis would use the Steures figures showing expectant management is superior to IUI with stimulation, as expectant management has much lower costs it would automatically be more cost-effective. In relation to the Steures paper:

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							• Firstly, the Steures et al paper is an RCT. The GDG agreed that if a population had been selected for IUI then it is likely that pregnancy rates would have been higher than those reported. However, randomised trials are undertaken to avoid this patient selection bias and to provide an estimate of the relative effect between treatments. • Secondly, the Steures et l study was undertaken in 26 units across the Netherlands, so it is unlikely that results are due to poor standards in a single unit. • Finally, Steures et al acknowledge that the pregnancy rate was lower than expected and hypothesised this was due the characteristics of the population not being selected for IUI. However, due to randomisation these women were equally distributed between the groups, so the expectant management arm would be equally affected. Finally, • The Goverde et al (2000) paper compares IUI and IVF, but this was not a comparison included in this review so this paper was not reviewed. • The GDG agreed that data is lacking on IVF compared to expectant management. However, in chapter 14 considerable efforts has been made to

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							compare IVF against expectant management in a health economic model. The GDG has also made a research recommendation that further work is undertaken in this area to confirm the findings of existing RCTs.
142.	British Fertility Society	37	Full	204	4	**115** Whilst it is clear when not to use IUI and clear when un-stimulated IUI should used it is not clear when stimulated IUI could be used. Studies are classified as low quality and are contradictory, some studies showed a statistical difference with gonadotrophin stimulation but this is not represented in the recommendations.	Thank you for your comments. It was the conclusion of the GDG that IUI with stimulation should not routinely be used because of the risk of multiple pregnancy compared to expectant management and IVF. The GDG has changed the order of recommendations for clarity.
143.	British Fertility Society	38	Full	284	2	In the review by Coomarasamy *et al.,* (2008) and in the updated Cochrane review by Van Wely *et al.,* (2011) there was a statistically significant but 'small' increase in live birth/ongoing pregnancy in favour of hMG. Although a small effect size (3% in the updated review), there is good evidence that patients regard this as an important difference (the patient preference work was an international study, with a focus on America and Australia, and showed that patients regard a 3% difference in live birth as important, and would rank this as a key factor when deciding on clinics). In the NICE review it appears that the figures have been rounded off, giving a non-significant result. However, the true figures show significantly less live births occurred with rFSH when compared	Thank you for your comments. The OR figure has been rounded in the GRADE table, in line with all of the GRADE tables, which for ease of reading report to one decimal place. However, for live birth rate, the absolute effect figure reported next to the OR shows a significant advantage of hMG over rFSH and the GDG said in the evidence statement: *"There were significantly more live full-term singleton births with the use of hMG or hphMG compared with rFSH."*The guideline developers agree that this should be made clearer in the text, and have added a footnote to clarify that the OR is significant. The rationale behind why this evidence was given a very low grade by the GDG is

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						with hMG/HP-hMG (**OR 0.84; [95% CI: 0.72–0.99]**; p=0.04; 11 trials; n=3197) http://dx.doi.org/10.1002/14651858.CD005354.pub2 What is also important about this evidence is its consistency across the study. There was virtually no evidence of heterogeneity (p-value 0.96, highly non-significant for heterogeneity; and I-squared statistics of 0%, indicating the absence of heterogeneity). It is therefore not surprising that Cochrane GRADE-ed this evidence as ++++, but NICE has given it a very low grade. Furthermore, three randomised trials have been published since the Cochrane Review, which all confirm the increase in livebirth with hp-HMG. The forest plot of the updated meta-analysis is given below:  	explained in the footnotes of the full GRADE profile (in the appendix). This is noted in the full GRADE profiles, where the GDG graded the inconsistency for this study as 'None'. It is important to remember that GRADE is used to assess the quality of the evidence for answering the specific review question posed by the GDG members. This is contributed to not only by the quality of the study, but also by how useful the evidence is in answering the question posed for the guideline. The quality grading is on the basis of the value of the evidence reported in the study in answering the research question. Thus, a study that is of high quality in general terms can provide low quality evidence when considering a specific research question set by the GDG. Given that background, the Cochrane review was Graded as 'very low' by guideline developers for the following reasons: • As reported in the Cochrane review, there were serious limitations in the included studies – they did not all clearly report blinding, allocation concealment or the method of randomisation used. • There was serious indirectness in using the Cochrane review for the guideline review. The Cochrane review authors used ongoing pregnancies (beyond 20 weeks) as the outcome/endpoint but live birth rate was not reported. However, the guideline review specified 'live full-

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							term singleton birth' as their main outcome. It was not possible to separate out the data in the Cochrane review into 'true' live births, and ongoing pregnancies. Therefore, including ongoing pregnancies beyond 20 weeks is an indirect measure of the outcome the GDG deemed most relevant to the guideline. • A Cochrane review of RCTs with no limitations or indirectness would be Graded as 'High' by the guideline developers. However, as there were very serious limitations, the evidence was downgraded twice (from high to 'moderate', and from moderate to 'low'). The serious indirectness resulted in an additional downgrading, from low to 'very low'.
144.	British Fertility Society	39	Full	313	14	**141** The BFS believe that clinical presentation should be taken into account especially now day 5 embryo transfers are being carried out. Clinical assessment, a full blood count and urea and electrolyte assessment would confirm the patient's suitability for transfer if carried out periodically after egg collection and the morning of embryo transfer. There is recent evidence that triggering antagonist cycles with agonists (Humaidan *et al.,* 2011) plus low dose hCG or the use of cabergoline reduces risk. The meta analysis 2010 (Youseef *et al.,* 2010) concluded that dopamine agonist used as a preventative treatment leads to significantly lower OHSS in high risk patients without compromising pregnancies. This guideline is too rigid.	Thank you for your comments. The GDG did not review or make any comments about the use of clinical appraisal, full blood count and urea and electrolytes to assess a patient's suitability for embryo transfer as it was not in the Scope for the Guideline update. The GDG was aware of the use of cabergoline and dopamine agonists, but believed that the evidence base is not yet robust enough to make a recommendation on its use. The GDG was aware that the evidence suggests GnRH agonist results in fewer cases of OHSS, but also less pregnancies. However, they believed further

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						The issue with the use of GnRH agonist trigger in antagonist cycles is more complex as it relates to luteal phase issues and if embryos are cryopreserved (as many would do if there is risk of OHSS) and transferred in a subsequent FERC cycle then the pregnancy rates appear to be satisfactory.	research was needed to confirm these findings before a recommendation could be made. The procedures in the IVF procedures chapter are described with the aim of fresh embryo transfer. As outlined on in the full Guideline, there is insufficient evidence to support routine cryopreservation in cases with a high risk of OHSS. The GDG therefore did not make any recommendations on the use of triggers when the cryopreservation of all embryos is planned.
145.	British Fertility Society	40	Full	325	1	No comment is made on the quality retrieved sperm between the various techniques. There is some evidence that the quality and quantity of retrieved sperm is higher in MESA than PESA (The Practice Committee of the ASRM, 2008) and therefore male patients may need fewer interventions with this approach.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Sperm recovery was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
146.	British Fertility Society	41	Full	325	16	Failure rates of recovery. The differences in sperm recovery between TESE techniques in non-obstructive azoospermia should be discussed (single site v multi site v microTESE) numerous references including review by Pantke *et al.,* (2008).	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Sperm recovery was not selected to be included in the 2012 update of the Fertility

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
147.	British Fertility Society	42	Full	346	15	**159** Whilst the BFS are fully supportive of reducing multiple pregnancy rates this should be in line with the HFEA target which will be 10% from Oct 2012. It is inappropriate to state all patients under 37 should have single embryo transfer in their first cycle. This will compromise some patients' chance of success. NICE should follow the professional guidance (Cutting *et al.,* 2008) and allow flexibility as long as the HFEA targets are met. Whilst IVFPredict can be used as guidance to give the chance of success there are still many variables which need to be taken into account which can make the figure inaccurate. In a study, introducing an eSET policy across the board in women under the age of 38, irrespective of embryo quality, resulted in a halving of live birth rates compared to DET (Van Montfoort *et al.,* 2006). Age of the woman, the first cycle of treatment, the number of embryos available for selection, embryo quality, and the stage at which the embryos are transferred are all factors that appear to influence the chance of a multiple pregnancy if more than one embryo is replaced. Of these, embryo quality and age are the most influential (Gerris, 2005). The BFS therefore feels it is inappropriate to have a blanket policy.	Thank you for your comments. The GDG has outlined criteria based on people receiving 3 full cycles of IVF. Based on the available evidence on effectiveness and safety, it is the conclusion of the GDG that using a single embryo in the first full cycle optimises the chance of a live full-term singleton birth. If this fails then the next 2 full cycles allows more than one embryo to be transferred dependent on embryo quality. This strategy was based on that outlined by Cutting et al. *"Initially a table (see table 15.30) was outlined based an algorithm outlined by Cutting et al., 2008. The algorithm included women's age, number of failed IVF cycles, the number and the quality of embryos. In total, there were 27 different clinical scenarios. In addition, the survey contained a number of questions and statements related to embryo transfers, such as the need for information provision to couples about the risks of multiple births."* However, this was amended as it is based on a single cycle and the recommendation is based on three full cycles. The GDG accepted that this will lead to a reduction in the pregnancy rates in the first

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							cycle for those aged 37 or under, but this would also lead to a significant reduction in multiples which with a DET policy would be approximately 30% to 40% of all pregnancies. With regards the Van Montfoort study. This result was driven by an extremely high spontaneous abortion rate in the SET group. However, the HTA report by Roberts et al (2010) shows that using an age restriction alone could reduce twinning rates from 25% to 10% whilst reducing live births rates from 24% to 20%.
148.	British Fertility Society	43	Full	347	8	**161** In certain cases women over 40 years old it may be appropriate to consider replacing 3 embryos.	Thank you for your comment. The GDG was tasked with examining the effectiveness and safety of treatment for the individual woman. Based on the available evidence and their clinical experience the GDG concluded that triple embryo transfer in over 40s would put a woman (and any resulting infants) at undue risk of complications and mortality. For example, evidence from Sweden shows the odds of peri/neonatal mortality is 2.42 greater when using DET compared to the general population. Therefore, whilst this recommendation has been reworded for clarity, its meaning has not been changed.
149.	British Fertility Society	44	Full	366	31	The team have completely misinterpreted the referenced article (1020) that states (correctly) that only AZFc carriers have the potential for	Thank you for your comment.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						spermatogenesis. The remainder (AZFa, AZFb and combinations involving these two) have no proven capacity for sperm production and therefore have a fertilization, implantation and lbr of zero. This conflicts with the comment written in the review, which should be amended. Men with genotypes containing AZFa and b should not be offered surgical sperm-retrieval and this should be the conclusion.	The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. ICSI was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
150.	British Fertility Society	45	Full	367	20	**177** The BFS do not agree that couples should be informed that ICSI improves fertilisation rates compared to IVF alone. This would encourage all patients to have ICSI which is clearly inappropriate given the associated risk of birth defects (ref). If this recommendation stays then it should be clear that this is only when ICSI is clinically relevant and ICSI should not be used for men with normal semen parameters unless otherwise clinically indicated i.e. low fertilisation in a previous cycle. This statement will be taken by some to mean that ICSI should be used in all cases of IVF. This is misleading and should be removed.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. ICSI was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline. However, the GDG did note that the recommendation is accurate, and does not suggest that ICSI is superior to IVF where there are normal semen parameters. In order make this clear in the guideline the following text has been added: *"Whilst the evidence for this recommendation has not been updated for the 2012 edition of the guideline, it should be noted for clarification*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							that in the absence of male factors (see recommendation 170), ICSI is not proven to confer a benefit in terms of increased pregnancy rates and should not be offered in the first treatment cycle"
151.	British Fertility Society	46	Full	369		Donor Insemination: The reference still used today to define the rate of male infertility at 25% (Hull *et al.,* 1985) is almost 30 years out of date. The data is based on WHO reference ranges of the time: sperm concentration 20 millions per ml, 50% progression and 50% normal forms which do not compare well with the recently revised reference range of 2010.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Donor insemination was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
152.	British Fertility Society	47	Full	370	11	**180** This guideline could be misleading in that it could imply the use of ICSI with donor sperm as opposed to partner sperm which we assume is the intent. This is important because it could lead sperm banks to relax their donor recruitment criteria for donor selection and accept men with poor quality sperm as donors. The ABA, ACE, BAS, BFS and RCOG (2008) donor screening guidelines specifically outline that donor should not be selected on this basis and that ICSI should not be used with donor sperm, except in cases of known donation where it might be unavoidable.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Donor insemination was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
153.	British Fertility Society	49	Full	390	37	**204** Patients considering whether to have oocytes or embryos frozen should be informed of the legalities of having to have partner consent to use frozen embryos in the future and the benefits of having oocytes frozen if consent is withdrawn. This is an important point in the counselling process in pre chemotherapy treatment	Thank you for your comments. The GDG agreed with your comments, and have added the text below to further clarify the regulations that should be followed within the implementation of the recommendations. No recommendations have been made on this as it is not NICE policy to instruct on legislation that should be in place irrespective of our guidance. *"The cryopreservation of any fertility material should follow the Human Fertilisation and Embryology (HFE) Act 1990 (as amended by the HFEA). This particularly pertinent to the consent and use of stored gametes, embryos or human admixed embryos."* Furthermore, earlier within the chapter we make specific comments about counselling and consent. *"This counselling should cover the issues surrounding the choose of whether to have oocytes or embryos frozen given the need to have partner consent to use frozen embryos in the future and the benefits of having oocytes frozen if that consent is withdrawn."*
154.	British Fertility Society	48	Full	391	34	**203** It is very controversial to recommend that vitrification should replace slow rate freezing. There is no robust evidence to state that vitrification results in better outcomes especially as there are very few long term follow up studies of children. Initial studies are promising	Thank you for your comments: The evidence shows that there was a significantly higher rate of post-thaw survival after vitrification of oocytes compared to controlled rate freezing of oocytes and an

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						(Noyes *et al.,* 2009) but the numbers are too small to reach conclusions. The problem with the studies is that although there is increased survival rates this does not necessarily translate into more clinical pregnancies (Borini *et al.,* 2006) and there is no data yet on the cumulative pregnancy rates with vitrification. Data in oocyte cryopreservation studies which show improved survival, fertilisation and pregnancy rates are often incomplete and do not take into account the number of embryos transferred, the number of oocytes thawed and the degree of embryo selection. Furthermore much of the evidence comes from a few clinic most of which have been involved in the development of vitrification (e.g. Kuwayama *et al.,* 2007; Cobo *et al.,* 2011; Rienzi *et al.,* 2010; Nagy *et al.,* 2009) The meta analysis (Kolibianakis, 2009) collated all evidence available from RCTs but whilst survival increased there were no differences in pregnancy rates. The strength of the evidence is also questionable as the method of randomisation is not always clear. There is very little data on vitrifying cleavage stage embryos and most are not randomised studies. Evidence is conflicting; Raju *et al.,* (2005) found vitrification improved survival, implantation rates and pregnancy rates but the method of randomisation was unclear and the sample size was very small. Li (2007) saw no difference in post thaw survival rates.	indication that the same is true in embryo cryopreservation. Furthermore, there were significantly more embryos with abnormal morphology after controlled rate freezing compared with after vitrification. The GDG was aware that the amount of RCT evidence comparing controlled rate freezing and vitrification is small. They were also aware that there is no long-term data on vitrification use or indeed the primary outcome for the review, live singleton birth. However, the evidence that was available supported the consensus that vitrification should be the preferred technique, but only where it is available. Because of the limitations of the evidence, controlled rate freezing can still be offered without restriction if this is the only option within a clinic. We agree that there is not enough robust evidence for a more definitive recommendation of one technique over the other. Finally, the GDG has written a research recommendation to reflect such sentiment and it is hoped that these areas will be addressed within the next review of the guideline.

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	**Comments** Please insert each new comment in a new row.	**Developer's Response** Please respond to each comment
						Vitrification uses much higher concentrations of cryoprotectants which may have safety implications and therefore as with all new technology we should be cautious. The cost effectiveness also needs assessing. There are many different methods available and the variety of solutions and carriers need further evaluation. The problems with using open and closed systems needs addressing. The BFS agree with the GDG that evidence is strong in favour for the use of vitrification but disagree that it should be a recommendation. It is too early to conclude if the efficiency of vitrification can be concluded and there are issues with the methodology which need to be resolved. New freezing protocols are emerging which may improve survival rates with slow freezing. Edgar and Gook (2012) reported similar implantation rates with fresh and frozen embryos after freezing. Properly conducted randomised control trials should be carried out before recommending one method over another. It is not enough to build on early studies and we should only use good evidence. From the best practice meeting held by ACE in 2011 (Brison *et al.,* 2012) it was clear that no one defined method is producing consistently good results, some centres had concerns and were not achieving the published survival rates and some centres are getting better results with slow freezing. There is a strong feeling that there is a learning curve when implementing vitrification.	

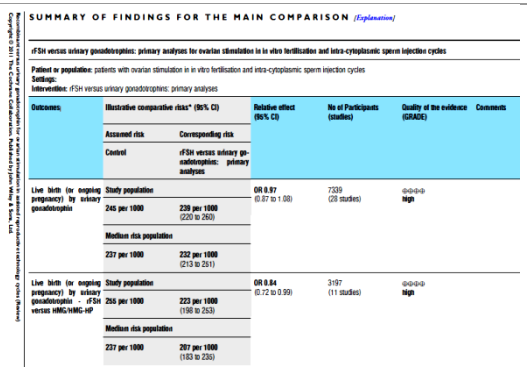
Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						Further data needs to become available before this is made a recommendation.	
155.	Coeliac UK	1	Full	General		There is evidence that undiagnosed maternal coeliac disease has a negative affect on intrauterine growth and birth weight, and is associated with increased preterm birth and caesarean section rates (NICE Clinical Guideline 86, 2009).	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. The section on initial management was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
156.	Coeliac UK	2	Full	General		Patients presenting to subfertility clinics should routinely be tested for coeliac disease.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. The section on initial management was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
157.	Coeliac UK	3	Full	General		There needs to be a cross reference to the NICE Clinical Guideline 86, 2009.	Thank you for your comment. Causes of infertility were outside the Scope of the guideline remit. Furthermore, there is no reference to coeliac disease within this guideline's recommendations or supporting

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							text and therefore will cannot link to this NICE guideline.
158.	Department of Health	2	Full	General: Sections 5.13 and11.2:		We welcome earlier access for investigation and IVF.	Thank you for your comment.
159.	Department of Health	3	Full	General: Section 12.2		Ensure that language in main guideline in not so prescriptive, that precludes reasonable clinical judgement that IUI might be appropriate.	Thank you for your comment. The GDG has tried to ensure that the recommendations are clear and easy to follow, but still allowing clinical judgement to be used in situations that do not fit within the recommendations.
160.	Department of Health	1	Full	General: Section 13.3		We welcome clarification of the definition of a cycle to include fresh and frozen embryos.	Thank you for your comment
161.	Department of Health	6	Full	General: Section 15.4		Ensure that language in main guideline in not so prescriptive that it precludes reasonable clinical judgement that natural IVF approaches might be appropriate in individual cases.	Thank you for your comment. As stated on in the full guideline: *"This guideline has been fully funded by NICE. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient."* The GDG believed that these recommendations do not prevent natural IVF

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							being used where it is appropriate in individual cases.
162.	Department of Health	4	Full	General: Section 15.7		We welcome firm recommendations on Single Embryo Transfer in IVF treatment but have concerns that the wording in full text of recommendations is too prescriptive and might preclude clinical judgment in particular individual cases.	Thank you for your comment. The GDG wished to highlight that the strategy they have outlined is based on a woman receiving three full cycles of IVF, and is worded to allow clinical judgement to be used where appropriate.
163.	Department of Health	5	Full	General: Section 19.2		Cryo-preservation sections should take account of Independent Medical Expert Group recommendations in respect of armed forces service personnel and veterans with fertility issues as a result of active service.	Thank you for your comment. Our scope for this chapter was specifically for people with cancer, as such our evidence review and recommendations have been completed within this context. Therefore, we are unable to make cryopreservation recommendations for the armed forces within this chapter.
164.	Dudley PCT	1	Full	38	125	The statement that the cycle will include the transfer of any resultant frozen embryos will bring some practical issues. What if there are still frozen embryos but the woman is older than the maximum age stated in the local IVF policy?	Thank you for your comments. Your comments have been considered by the GDG and the relevant recommendation has been amended
165.	Dudley PCT	2	Full	38	127	We are concerned that the cost implications of funding 3 full cycles for all women under 40 years will impact on other services areas and remove resources from other interventions with lower QALY thresholds. It may also remove funding from areas that are considered a higher priority by the local population.	Thank you for this comments. We appreciate your concern but note that nearly all recommendations in NICE guidelines have an opportunity cost. Our mandate is to produce an evidence based guideline based on clinical and cost-effectiveness. The guideline discusses at some length the difficulty of valuing the benefits of fertility treatment but by using a QALY we have tried

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							to be consistent with NICE's favoured approach.
166.	Dudley PCT	3	Full	38	128	We are concerned that the cost implications of funding 1 full cycles for women from 40 to 42 years will impact on other services areas and remove resources from other interventions with lower QALY thresholds. It may also remove funding from areas that are considered a higher priority by the local population	Thank you for your comments. We think that this recommendation will mean that women age 40-42y who get offered IVF will stand the best chance of conceiving.It is likely that the majority of women who are considered for IVF in this age group will not be eligible because of a low ovarian reserve. However, in practice health service commissioners will set their own rules about funding IVF irrespective of the guideline recommendations as evidenced by the variable implementation of the 2004 guideline when there was a less liberal recommendation about IVF. Please note that the wording of this recommendation has been amended to read: *In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled:* • *they have never previously had IVF treatment* • *there is no evidence of low ovarian reserve*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							• *there has been a discussion of the additional implications of IVF and pregnancy at this age.*
167.	Dudley PCT	4	Full	240	21	The cost modelling does not include additional costs which will occur with older females who have a higher risk of congenital defects such as Down's.	Thank you for your comment. We accept the point being made here and it applies equally to the increased risk of adverse outcomes from multiples. Our explanation for not including such costs is outlined in the text: *"To what extent these "downstream" costs should or should not be included is not a straightforward matter and arbitrary cut-offs can be made at various time points. IVF leading to live birth will impose costs to the NHS throughout the conceived individual's lifetime and not just during pregnancy and birth. However, it would not be fair to count these longer term costs without some consideration of the contribution or benefit that individual has to society….For this analysis for IVF we are not considering the QALY of the potential life because at the time of decision there is no QALY loss to a non-existent being if treatment is not offered but future "downstream" costs do have that QALY as an end-point because they are then dealing with decisions affecting an existing life."*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
168.	Dudley PCT	5	Full	245	17	Guidance assumes a willingness to pay of £20,000 per QALY. This value does not reflect affordability criteria. It also does not reflect local views on funding of fertility treatment when discussed with patient and clinician groups.	Thank you for your comment. The use of a willingness to pay threshold as an aid to decision making does, albeit imperfectly, have regard to affordability. We were tasked with producing evidence based guidelines on management of fertility within pre-specified limits. We do not have any input on the local implementation of these guidelines.
169.	Dudley PCT	6	Full	245	23	See comment above	Thank you for your comment. The use of a willingness to pay threshold as an aid to decision making does, albeit imperfectly, have regard to affordability. We were tasked with producing evidence based guidelines on management of fertility within pre-specified limits. We do not have any input on the local implementation of these guidelines.
170.	Ferring Pharmaceuticals Ltd	4					Thank you for your comment.

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						Figure 1. Extract from Cochrane review showing live birth rates with rFSH versus hMG and evidence grade	
171.	Ferring Pharmaceuticals Ltd	5				**References** 1. Coomarasamy A, Afnan M, Cheema D *et al*. Urinary hMG versus recombinant FSH for controlled ovarian hyperstimulation following an agonist long down-regulation protocol in IVFor ICSI treatment: a systematic review and meta-analysis. *Hum Reprod* 2008; **23:** 310–315. 2. van Wely M, Kwan I, Burt AL *et al*. Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles. *Cochrane Database Syst Rev* 2011**:** CD005354 3. Clarke JF, van Rumste MM, Farquhar CM *et al.* Measuring outcomes in fertility trials: can we rely on clinical pregnancy rates? *Fertil Steril* 2010; **94:** 1647–1651. 4. Devroey P, Pellicer A, Nyboe Andersen A*et al.*A randomized assessor-blind trial comparing highly purified hMG and recombinant FSH in a GnRH antagonist cycle with compulsory single-blastocyst transfer. *Fertil Steril* 2012; **97**: 561–571. 5. Ye H, Huang G, Pei L, Zeng P, Luo X. Outcome of in vitro fertilization following stimulation with highly purified hMG or recombinant FSH in downregulated women of advanced reproductive age: a prospective, randomized and controlled trial. *Gynecol Endocrinol* 2012; **28:** 540–544. 6. Wilke G, Dieterle ST, Ledger W *et al.*Prospective, open-label, randomized, parallel	Thank you for providing these references

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						group multinational, multicenter pilot trial comparing the efficacy and safety of Menotropin (high purified) with follitropin alpha in GnRH-antagonost protocol in subfertile woman with IVF-treatment (unpublished data).	
172.	Ferring Pharmaceuticals Ltd	1		284	2	In the review by Coomarasamy *et al* (2008),[1] as well as in the updated Cochrane review by Van Wely *et al* (2011),[2] there was a 'small' but statistically significant increase in live births/ongoing pregnancies in favour of human menopausal gonadotrophin (hMG). Although a small effect size (3% in the updated review), there is good evidence that patients regard this as an important difference (the patient preference work was an international study, with a focus on America and Australia, and showed that patients regard a 3% difference in live birth rate as important, and would rank this as a key factor when deciding on clinics). In the draft NICE guideline, it seems that the figures have been rounded off, giving a non-significant result. However, the true figures show that significantly fewer live births occurred with recombinant follicle-stimulating hormone (rFSH), when compared with hMG or highly purified hMG (hp-hMG): (OR 0.84; 95% CI 0.72–0.99; p=0.04; 11 trials; n=3,197).[2] What is also important about this evidence is its consistency across the study. There was	Thank you for your comments. The OR figure has been rounded in the GRADE table, in line with all of the GRADE tables, which for ease of reading report to one decimal place. However, for live birth rate, the absolute effect figure reported next to the OR shows a significant advantage of hMG over rFSH and the GDG said in the evidence statement *"There were significantly more live full-term singleton births with the use of hMG or hphMG compared with rFSH."* The guideline developers agree that this should be made clearer in the text, and have added a footnote to clarify that the OR is significant. This is noted in the full GRADE profiles (in the appendix), where the GDG Graded the inconsistency for this study as 'None'. Again, the OR figure has been rounded in the GRADE table, in line with all of the GRADE tables, which for ease of reading report to one decimal place. However, for clinical pregnancy rate, the absolute effect figure reported next to the OR shows a significant advantage of hMG over rFSH and the GDG said in the evidence statement *"There were significantly more clinical pregnancies after hMG or hp-hMG compared to after rFSH..."*.The guideline developers agree that this should be made

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						virtually no evidence of heterogeneity (p-value 0.96, highly non-significant for heterogeneity; and I-squared statistics of 0%, indicating the absence of heterogeneity). Moreover, there were significantly fewer clinical pregnancies after rFSH compared with hMG/hp-hMG (OR 0.85; 95% CI 0.74–0.99; 12 trials, n=3,775).[2] A recent meta-analysis, based on results of 142 randomised controlled trials, has concluded that treatment effect based on the endpoints (clinical pregnancy and live birth) is usually comparable, without compromising the comparison between treatment groups.[3] It is, therefore, not surprising that the Cochrane GRADE given to this evidence was ++++, but NICE has given it a very low grade. Furthermore, three randomised trials have been published since the publication of the Cochrane review, which all confirm the increase in live birth rate with hp-HMG.[4-6]	clearer in the text, and have added a footnote to clarify that the OR is significant. The rationale behind why this evidence was given a very low grade by the GDG is explained in the footnotes of the full GRADE profile (in the appendix). It is important to remember that GRADE is used to assess the quality of the evidence for answering the specific review question posed by the GDG members. This is contributed to by the quality of the study, but also by how useful the evidence is in answering the question posed for the guideline. The quality grading is for the evidence presented by the study, not the study itself and so a high quality study can provide low quality evidence. Given that background, the Cochrane review was Graded as 'very low' by guideline developers for the following reasons: • As reported in the Cochrane review, there were serious limitations in the included studies – they did not all clearly report blinding, allocation concealment or the method of randomisation used. • There was serious indirectness in using the Cochrane review for the guideline review. The Cochrane review authors used ongoing pregnancies (beyond 20 weeks) as the outcome/endpoint but live birth rate was not reported. However, the

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							guideline review specified 'live full-term singleton birth' as their main outcome. It was not possible to separate out the data in the Cochrane review into 'true' live births, and ongoing pregnancies. Therefore, including ongoing pregnancies beyond 20 weeks is an indirect measure of the outcome the GDG deemed most relevant to the guideline. A Cochrane review of RCTs with no limitations or indirectness would be Graded as 'High' by the guideline developers. However, as there were very serious limitations, the evidence was downgraded twice (from high to 'moderate', and from moderate to 'low'). The serious indirectness resulted in an additional downgrading, from low to 'very low'. We are unable to include the three studies you reference (Devroey et al., 2012; Ye et al., 2012; and Wilke et al., unpublished). The first two were conducted after the cut-off date for our literature searches (December 2011). The third is unpublished data, and we restricted this search to published trials.
173.	Ferring Pharmaceuticals Ltd	2	Full	285		The draft guideline does not discuss the difference in live birth rate between rFSH and hMG. Two meta-analyses[1,2]have demonstrated that significantly more live births were achieved in women undergoing *in vitro* fertilisation (IVF) or	Thank you for your comments. This is discussed in chapter 15. The evidence is presented in table 15.9, and the evidence statement says: *"There were significantly more live full-term singleton births with the use of hMG or hphMG*

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						intracytoplasmic sperm injection (ICSI) with hp-hMG than those treated with FSH. Although the evidence is considered in Table 15.9 of the draft guidance (page 285), the evidence quality is regarded as 'very low'; however, the 2011 Cochrane review[2] cites the quality of the evidence as 'high' (see Figure 1 below). Ferring Pharmaceuticals Ltd would like to request that the evidence grade of the Cochrane review[1] is amended in the final guideline.	*compared with rFSH."* In the evidence to recommendations section, the GDG discussed urinary and recombinant products further: "*The GDG acknowledged that there was no overwhelming evidence in favour of a particular recombinant or urinary product, and that some urinary products are in short supply or are no longer available. They therefore recommended that either urinary or recombinant gonadotrophins can be used".* The Coomarasamy (2008) review (reference 1 in your comment) was excluded from the review for the guideline as it was superseded by the Van Wely (2011) review. The Van Wely (2011) Cochrane review (reference 2 in your comment) was discussed in detail by the GDG, as outlined in the full guideline. The rationale behind why this evidence was given a very low grade by the GDG is explained in the footnotes of the full GRADE profile (Table 1.14.9 on p421 of the appendix). It is important to remember that GRADE is used to assess the quality of the evidence for answering the specific review question posed by the GDG members. This is contributed to by the quality of the study, but also by how useful the evidence is in answering the question posed for the guideline. The quality grading is for the evidence within the study, not the study itself, and so a high quality study can provide low quality evidence.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							Given that background, the Cochrane review was Graded as 'very low' by guideline developers for the following reasons: • As reported in the Cochrane review, there were serious limitations in the included studies – they did not all clearly report blinding, allocation concealment or the method of randomisation used. • There was serious indirectness in using the Cochrane review for the guideline review. The Cochrane review authors used ongoing pregnancies (beyond 20 weeks) as the outcome/endpoint but live birth rate was not reported. However, the guideline review specified 'live full-term singleton birth' as their main outcome. It was not possible to separate out the data in the Cochrane review into 'true' live births, and ongoing pregnancies. Therefore, including ongoing pregnancies beyond 20 weeks is an indirect measure of the outcome the GDG deemed most relevant to the guideline. A Cochrane review of RCTs with no limitations or indirectness would be Graded as 'High' by the guideline developers. However, as there were very serious limitations, the evidence was downgraded twice (from high to 'moderate', and from moderate to 'low'). The serious indirectness resulted in an additional downgrading, from low to 'very low'.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
174.	Ferring Pharmaceuticals Ltd	3	Full	311	28–31	Two meta-analyses[1,2]have demonstrated that significantly more live births were achieved in women undergoing IVF or ICSI with hMG than those treated with FSH. The draft guideline acknowledges that significantly more live full-term singleton births were achieved with hMG or hp-hMG thanwith rFSH (page 306, lines 26–27) in the comparison of specific recombinant versus specific urinary gonadotrophins; however, the draft guideline does not reflect this difference in the 'Choice of agent' section. Ferring Pharmaceuticals Ltd would, therefore, like to request that the recommendation on the choice of agent between hp-hMG and rFSH is amended in the final guideline.	Thank you for your comments. As you highlighted, the GDG reviewed the meta-analyses when considering the evidence for urinary and recombinant products. Whilst the GDG acknowledged in their evidence statement that hMG results in higher live birth rates and higher clinical pregnancy rates than rFSH, they explain in the evidence to recommendations section that the evidence does not overwhelming support the use of one product over the other. The GDG was also concerned about the supply and availability of urinary products, as well as the unpredictable future costs of the products, and therefore chose not to recommend a particular product.
175.	Gloucestershire Hospitals NHS Trust / Cotswold fertility Unit	1	Full	10	17	Can maximum recommended dose of clomid be mentioned please	Thank you for your comment. However, NICE clinical guidelines do not usually provide information on maximum dosage as this is determined by outside regulators and is liable to change. You may wish to consider the standard product characteristic values given in the link below: http://www.medicines.org.uk/EMC/medicine/820/SPC/Clomid/
176.	Gloucestershire Hospitals NHS Trust / Cotswold fertility Unit	2	Full	13	52	Can recommended route of luteal support be mentioned please	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							held and the scope was subject to a period of public consultation before it was finalised. The route of luteal support was not selected to be included in the Scope for either the original 2004 Fertility Guideline or the 2012 update of the guideline. Therefore, we cannot take your comments forward or make any substantive reference to the subject in the final version of the updated Guideline.
177.	Greater Manchester Sexual Health Network	23	Full	General		We are pleased that you have included access to sperm washing in these updated guidelines. Access to sperm washing treatment for couples affected by HIV is inequitable across the country. In Greater Manchester (10 PCTs) we found that decision-making was based on inconsistent criteria, occasionally moral judgements and that patients often had to wait several months for a decision to be made on whether they could have funding. During development of our guidelines – and the subsequent paper we wrote on our work – we discovered that clinical research lamented the paucity of commissioning guidelines on access to sperm washing and IVF for couples affected by HIV. With that in mind, this updated guidance is welcomed.	Thank you for your comments.
178.	Greater Manchester Sexual Health Network	1	Full	23	43	Given the small number of centres available to provide ACT and sperm washing treatment (where appropriate) to couples affected by viral infections, it is preferable that infertility investigations are carried out locally and once a treatment plan is agreed (e.g. IUI, IVF) then the couple should be referred on to a unit that has the specialist facilities (i.e. separate lab facilities) to manage patients with viral infection. In Greater Manchester this process is already in	Thank you for your comments. NICE guidance outlines best practice, but does not outline the local implementation of these recommendations. However, the GDG did note that the best quality of care would come from decisions made jointly between fertility and virologist

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						place and couples' fertility is investigated locally and then they are referred for IUI/sperm washing and/or fertility treatment as appropriate. This is better for the couple because it reduces travelling time and is more convenient for them. In addition, if the couple are eligible for travel costs, it reduces the cost of travel to the NHS. We therefore suggest an addition to the existing wording to read: '… hepatitis C or HIV **should have infertility investigations carried out locally by fertility specialists in collaboration with the patient's specialist HIV or hepatitis doctor before being referred for onward treatment to** centres that have appropriate expertise and facilities to provide appropriate safe risk-reduction ~~investigation~~treatment and fertility treatment treatment'.	expertise and have indicated this within the evidence to recommendations. Your comments have been forwarded to the NICE Implementation Team.
179.	Greater Manchester Sexual Health Network	4	Full	26	65	This should be strengthened particularly where there is a transmission risk. We would also recommend the following amendments to make it clear that specialist advice and management for viral infections is unlikely to be provided within the same department that manages infertility investigations and treatment. Our suggested amendment is: 'People **who** test positive for one or more of HIV, hepatitis B, hepatitis C should be ~~offered~~**referred** for specialist advice and counselling and appropriate clinical management'.	Thank you for your comments. Screening was outside of the scope for this chapter and the GDG was unable to change this recommendation. Furthermore, the wording in the original recommendation allows for patient choice to be included within it. The GDG was aware that this choice is important for the implementation of the guidance and therefore offering specialist advice.
180.	Greater Manchester Sexual Health Network	5	Full	26	66	Sperm washing is also recommended in couples who are both HIV+ but who have different resistance profiles. This is to prevent a different resistance profile being transmitted to the female partner. We welcome the recommendation for joint management between a fertility specialist and an HIV specialist. We	Thank you for your comments. Your comments have been considered by the GDG and the relevant recommendation has been amended

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						recommend the following amendment to this paragraph: 'For couples where one or both partners is HIV positive, any decision about fertility management should be the result of discussions between the couple, a fertility specialist and a**n** HIV specialist'.	
181.	Greater Manchester Sexual Health Network	6	Full	26	67	Public health specialists are very concerned about the confusing message given to HIV+ patients in this section and would not recommend unprotected sexual intercourse in serodiscordant couples. This section contradicts infection control guidance and sends the message that condoms should be used at all times except where couples are attempting to conceive. Whilst it may be clinical practice to manage conception in this way, public health specialists are concerned about the public health implications and the legal implications of recommending unprotected intercourse during ovulation provided the man has an undetectable viral load and is compliant with HAART. We would recommend removing this paragraph or if you retain it, to amend it to read, 'Advise couples **affected by HIV that sperm washing is the safest way to reduce the risk of HIV transmission in couples trying to conceive. However, in couples who feel sperm washing is an unacceptable options, HIV clinicians should advise the couple that** where the man is HIV positive **or both partners are HIV positive with different resistance profiles** that transmission of HIV **through unprotected sexual intercourse** i**s reduced**when all of the following criteria are met:	Thank you for your comments. The GDG was aware of the potential public health message that the recommendations may have. It is for this reason that the GDG has been extremely careful in the wording of the recommendations in relation to HIV. Furthermore, the recommendation criterion now includes an additional requirement that a man shows an undetectable viral load for 6 months or more. With this addition, the man must demonstrate an adherence to HAART and therefore more confidence that the viral load and seminal load are equivocal.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						The man (or both partners) are compliant **with treatment provided by their HIV doctor** The man**, or man and woman) have** ….. There are no ….. Unprotected intercourse is limited to the time of ovulation**, in line with guidance provided by their HIV specialist**'.	
182.	Greater Manchester Sexual Health Network	7	Full	26	71	We recommend adding an extra paragraph here to cover infection control in couples trying to conceive where the man is HIV- and the woman is HIV+. Our suggested wording is; '**For couples where the man is HIV negative and the woman is HIV positive who have no documented fertility problems, timed artificial insemination using gallipots at home is recommended and that this is clinically managed by the woman's HIV doctor. Use of condoms is recommended for all sexual contact'**	Thank you for your comments. The scope of guideline was to examine the effectiveness of sperm washing, which is only relevant for a HIV positive male. In order to answer the question sperm washing was compared with viral transmission through unprotected sex and post exposure prophylaxis. The results of this review showed that if certain criteria were met that unprotected intercourse would be a suitable option if the male partner was HIV positive.
183.	Greater Manchester Sexual Health Network	8	Full	26	68	We've seen that you've referenced the Nicoupoullos *et al* 2010 study of 10 years of sperm washing in London but are surprised that other studies (e.g. Bujan *et al* 2007; Mencaglia *et al* 2005; Chrystie *et al* 1998; Al Khan *et al* 2003) were not included. Is there robust evidence that sperm washing may reduce the likelihood of pregnancy and that it may not further reduce the risk of infection when compared to timed unprotected intercourse with an undetectable viral load, given the public health implications of recommending unprotected intercourse? Reading this section after the previous one makes it sound like NICE's preferred recommendation is for HIV+ couples to have unprotected sex rather than	Thank you for your comments. The papers you mention were considered, Khan et al was excluded because it did not meet our inclusion criteria as it presented no primary research. Chrystie et al was not included as it did not report any of our pre-specified outcomes. The opinion of the GDG was that sperm washing would reduce the pregnancy rate. As demonstrated in other parts of the guidance, donor insemination (using IUI) is shown to be inferior to expectant management. The first year of intercourse will produce a pregnancy rate of 82% (within in the 30-34 age range), its

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						offering infection control treatments such as sperm washing, which does not sit comfortably with public health colleagues. Public health colleagues would recommend removing this paragraph as there is evidence (Frodsham *et al* 2003) that couples who conceive through sperm washing demonstrate high levels of safer sex behaviour and that continued safer sex behaviour is necessary to prevent onward transmission of HIV when couples are not trying to conceive.	equivalence (in the same age range) of 6 cycles of IUI has a pregnancy rate of 63%. As donor insemination (through IUI) would be the most common route of administration for washed sperm it was concluded that the pregnancy rate would be reduced. The evidence shows no difference in transmission rates using either sperm washing or unprotected intercourse (within the outlined criteria). Moreover, the evidence does suggest an improved pregnancy rate and significant cost saving with the recommendation for unprotected intercourse. The recommendations made are clear that intercourse should be restricted to coincide with ovulation. The context of this recommendation and the guideline should not be incorrectly extrapolated to safe sex guidance.
184.	Greater Manchester Sexual Health Network	9	Full	26	69	We would recommend that where people are HIV positive and is non-compliant with medication, or their HIV is poorly managed, then the couple is not able to access sperm washing or IVF treatment until this is addressed. Individuals with a high BMI or who smoke are currently denied access to treatment until they address the issue. For equity this should be the same for HIV treatment. We would suggest you amend this paragraph to note that sperm washing is also recommended in couples with HIV where partners have different resistance profiles. Our preferred amendment for this paragraph is, '**For couples where one or both partners** are HIV positive and **one or both partners is** not compliant with HAART or their	Thank you for your comments. The available evidence shows that sperm washing is a valid alternative in situations where, for whatever reason, a male partner does not meet the criterion outlined in the recommendations.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						viral load is 50 copies/ml or greater**, the couple should be advised that they will not be able to access sperm washing or IVF treatments until their HIV is stable and well-managed.'** In Greater Manchester, couples are currently not referred for IVF or sperm washing treatment unless they are compliant with therapy. The rationale for this is that if they are non-compliant with their own therapy then there is a risk that they will not be compliant with monitoring during pregnancy and any therapy for any subsequent children (if the mother is HIV+).	
185.	Greater Manchester Sexual Health Network	10	Full	26	70	We are pleased to see a paragraph outlining that sperm washing is a risk-reduction technique and that you have made it clear that it reduces, but does not remove the risk of HIV transmission.	Thank you for your comments
186.	Greater Manchester Sexual Health Network	11	Full	26	71	Public health specialists are not content that NICE is recommending well-managed HIV and unprotected sex as the first-line treatment before sperm washing. This diminishes the value of sperm washing as an infection control treatment that dramatically reduces the risk and associated financial and human costs of HIV transmission. This could put HIV- women under pressure from their HIV+ partners to have unprotected sex rather than pursue a request for sperm washing treatment. We feel that from a public health point of view it is irresponsible to diminish the value of sperm washing and seemingly recommend a preference for timed un-protected sex. We would recommend that this paragraph is removed.	Thank you for your comments. We agree with the sentiment, and for this reason have retained this recommendation. The recommendation will allow couples to opt for sperm washing if there are apprehensive about unprotected sex, even if the criteria outlined are met. The GDG remained convinced by the evidence that where the outlined criteria are met, unprotected intercourse is the most clinical and cost effective method of conception.Furthermore, the evidence for sperm washing does show a comparative reduction in pregnancy rates and increased cost. Pre and post testing of sperm washing is often inconclusive, while there have been no reported transmissions of HIV it should be

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							noted that not all washed sperm completely removed the virus from the seminal fluid. With all these factors taken into account the GDG opted to recommend unprotected intercourse in place of sperm washing. However as outlined in the first paragraph of this response, the recommendation to offer sperm washing was retained to address the understandable apprehension of some couples.
187.	Greater Manchester Sexual Health Network	12	Full	26	71	We suggest adding an extra paragraph here to specify the number of sperm washing cycles that should be offered to men. In Greater Manchester our guidelines, which were drawn up with the input of Dr. Cheryl Fitzgerald (a fertility specialist from St. Mary's Hospital in Manchester) and GU consultants and we recommend 6 cycles of sperm washing as a pragmatic limit (based on 6 cycles of IUI that were offered in the 2004 NICE guidelines). Our guidelines have been in place for a year and as yet we do not have enough data to determine the optimum number of cycles to achieve a pregnancy through sperm washing. It would seem prudent that as you have recommended a clear number if IVF cycles that the same is done for sperm washing as this would help clear up the inequity of access to this infection control treatment. If you agree with our proposal, we suggest the following wording, '**Eligible men are entitled to a maximum of 6 cycles of NHS-funded sperm washing with unstimulated IUI**'. We suggest referring to 'men' rather than 'couples' because funding for	Thank you for your comments. We have not specified the number of sperm washing cycles that should be offered within this chapter. However, within other parts of guideline we do make a recommendation that 6 cycles of IUI should be offered to those that cannot have intercourse. This population was considered within this recommendation and therefore this recommendation should be used when determining sperm washing and IUI protocol.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						sperm washing is attached to the man's medical records/funding organisation.	
188.	Greater Manchester Sexual Health Network	13	Full	27	72	Public health specialists are pleased to see the inclusion of a paragraph not recommending the use of pre-exposure prophylaxis (PrEP). The evidence base is currently limited but public health specialists and commissioners have concerns about the use of PrEP on ethical and cost grounds and feel that its use would undermine safer sex and condom use messages.	Thank you for your comments. The GDG found that the evidence showed no benefit or harm in the use of PrEP. To clarify their recommendation they have added the following text to the evidence to recommendation section of the chapter: *"The GDG did note that while the evidence for pre-exposure prophylaxis showed no additional benefit for a man with an undetectable viral load, the evidence base was limited. Furthermore, this is an area where the evidence base is new and more research is expected and needed. Currently PrEP is occasionally offered in clinical practice, the cost is relatively low and the perceived extra security it provides is welcomed by some. The GDG concluded that the evidence was not sufficient to make a recommendation for or against the use of PrEP.*
189.	Greater Manchester Sexual Health Network	14	Full	27	73	We would suggest amending this paragraph to make it clear that the uninfected partner's immunity should be tested prior to any attempt at conception. We would recommend adopting wording from the Greater Manchester Sexual Health Network's guidelines to expand this section to read, '**Where couples are serodiscordant (one is hepatitis B+ and the other is hepatitis B-) the recommended action is to vaccinate the uninfected partner. The couple should not attempt to conceive**	Thank you for your comments. The key aim of NICE recommendations is to be concise. The GDG believed that the current wording meets this requirement. Therefore, no change has been made to the wording of the recommendation. The GDG did feel, however, that your additional information is important so has

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						until the vaccinated partner has been tested to ensure adequate surface antibody levels. Until surface antibody levels are determined, a barrier method of contraception (i.e. condoms) should be used for all forms of sexual contact to reduce the risk of transmission.'	adopted the message in the evidence to recommendation section of the text.
190.	Greater Manchester Sexual Health Network	15	Full	27	74	We are pleased that you have outlined that sperm washing is not the recommended treatment for men with hepatitis B. We would recommend expanding this paragraph to read, 'Do not offer sperm washing as part of infertility treatment for men with hepatitis B. **Hepatitis B vaccination of the uninfected partner and any household contacts is the recommended treatment. In the unlikely event that the vaccine fails, sperm washing could be considered, depending on the hepatitis B-positive partner's viral load.**'	Thank you for your comments. The review found no evidence to suggest that sperm washing would be appropriate for reducing the risk of HBV transmission and are therefore unable to recommend its use.
191.	Greater Manchester Sexual Health Network	16	Full	27	75	We would recommend making the following amendment to this paragraph, 'Where one of the parents has hepatitis B, offer them hepatitis B vaccination for their baby **and any existing unvaccinated household contacts** in line with NICE public health guidance …'	Thank you for your comments. The referenced public health guidance does mention other unvaccinated siblings (text below). We agree with you comment, therefore, we have included the words "unvaccinated sibling" in accordance with the terminology outlined in the aforementioned piece of guidance within the evidence to recommendation text in the chapter. *"Health professionals should assess whether or not the baby's siblings need to be immunised against hepatitis B or tested for infection and should offer them vaccinations and blood tests if necessary."*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
192.	Greater Manchester Sexual Health Network	17	Full	27	75	We're surprised that you've not included any paragraphs on hepatitis C infection and sperm washing in this section. We would recommend including a section after the hepatitis B section as we have received queries about couples affected by hepatitis C infection and there is a lot of confusion about appropriate action. We would recommend inserting the following paragraph after the hepatitis B section: 'Do not offer sperm washing as part of infertility treatment for couples affected by hepatitis C.**Where couples are serodiscordant (one is hepatitis C+ and the other is hepatitis C-) the recommended action is to treat the infected partner for their hepatitis C infection. This is because the risk of heterosexual (receptive vaginal intercourse) transmission of hepatitis C in the absence of HIV is extremely low (2%) and the American Association for the Study of Liver Disease guidance does not recommend a need for routine condom usage** [*references for this are listed at the bottom of this comment*]. **The couple should seek advice from their specialist regarding the level of risk of transmission from other forms of sexual intercourse (i.e. anal sex). The couple must refrain from attempting to conceive for 6 months after treatment due to the teratogenic potential (the risk of causing physiological abnormalities or birth defects) of Ribavirin in both men and women.**' Alter M.J. (2002) Prevention of spread of hepatitis C. *Hepatology*; 36(Suppl):S93-	Thank you for your comments. The GDG remained unable to make a recommendation for the use (either for or against) of sperm washing for hep C. They, however, agree that guidance would benefit from recommendations on the management of the condition. The updated recommendations are; that a male with hepatitis C should consult a specialist when considering a pregnancy with a hepatitis C negative partner and that the current understanding within the evidence is that the chance of transmission is low through unprotected intercourse. Furthermore, the GDG recommended that hepatitis C is sought to be eradicated before considering further action. Finally, we would like to bring to your attention the research recommendation below. Once this information is known recommendations akin to the detail offered for hepatitis B and HIV can be made. *"What is the effectiveness of sperm washing in reducing the transmission of hepatitis C from men to their partner?"*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						S98. Workowski K.A., Berman S.M. (2006) Sexually transmitted diseases treatment guidelines, 2006. *MMWR Recomm Rep*, 55:1-94.	
193.	Greater Manchester Sexual Health Network	19	Full	27	79	We would recommend expanding this to make it clear that treatment for Chlamydia should be completed before starting fertility treatment. We suggest amending the paragraph to read, '…with treatment and contact tracing **before starting fertility treatment**'.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Chlamydia trachomatis was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
194.	Greater Manchester Sexual Health Network	21	Full	34	156	Does this paragraph mean that less than 20 minutes bed rest after embryo transfer *is* recommended? If you are not recommending bed rest at all then we would recommend you are more specific here.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
195.	Greater Manchester Sexual Health Network	22	Full	36	179	We would suggest that this paragraph is qualified so that it's clear that the decision to use donor insemination is a decision made by the couple. This would avoid any confusion	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						about which route is preferable out of: donor insemination, sperm washing or timed unprotected intercourse. We would suggest you amend this paragraph to read, ' … severe rhesus isoimmunisation **and is a decision to be made by the couple with advice from clinicians'**.	scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Donor insemination was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
196.	Human Fertilisation Embryology Authority	1	Full	General		• The HFEA licenses and regulates fertility clinics in the UK, both NHS and private. There will be differences in how this guideline is implemented in the clinics we regulate according to whether they are NHS, private or both. • We acknowledge that the guideline is implemented to varying degrees in different areas and different clinics (eg, even though the guideline extends the age range for IVF to be offered in practice it may not necessarily result in more patients having access to treatment) and we hope that this updated version will be implemented more fully than the original.	Thank you for your comments.
197.	Human Fertilisation Embryology Authority	2	Full	18	126	We strongly support this move, specifically for the impact it will have on multiple births, since it will remove any financial incentive of transferring more than one embryo at any one time.	Thank you for your comment.
198.	Human Fertilisation Embryology Authority	3	Full	18	115	IUI only came under our regulatory oversight with the implementation of the EU Tissues and Cells Directive in 2007. Currently there are 28 IUI only centres, many of which are stand alone units carrying out a small number of cycles. This	Thank you for your comments. The GDG was aware that the recommendation on IUI will have an impact on service delivery in the NHS.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						recommendation is likely to change the shape of the sector. The Authority support IUI being an option open to certain patients (eg, patients with PCOS who may be too sensitive to the stimulatory drugs necessary for IVF) and presume that this is the intention of the guideline as indicated by use of the word 'routinely'.	The term 'routine' relates to women who may have social, cultural or religious objections to IVF or where the balance of clinical judgement is that a single cycle of IUI will be as effective as a single cycle of IVF. This has been added to the recommendation. In relation to women with PCOS. It would be not be recommended to use stimulated IUI, for the same reason as not using stimulation in IVF. Furthermore, the evidence shows that IUI without stimulation is no more effective regular unprotected intercourse.
199.	Human Fertilisation Embryology Authority	4	Full	18	128	We welcome this move as it reflects the shifting age of IVF patients. HFEA Register data indicates that since 1991 the average age of women being treated is increasing (from 1991 to 2010 it has increased by 1.5 years for IVF). The live birth rate for IVF patients aged 40-42 (using fresh own eggs) has increased over recent years (12.7% in 2009 compared to 11.1% in 2006). Greater clarity is needed as to whether this applies to same sex couples and single women with fertility problems. To avoid misinterpretation of this guidance 'absolute infertility' needs to be more clearly defined.	Thank you for your comments. Several stakeholders commented that the term 'absolute infertility' was not meaningful or useful in clinical practice. <u>Updated recommendation</u> There was extensive debate and division of opinion within the GDG about whether a recommendation for the provision of IVF could be made for this age group both before and after stakeholder comments. The details of which are described in the full version of the guideline. It was concluded that the uncertainty around the HE model meant that any recommendation for this age-group would have to be based on clinical opinion.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment

							At the end of the meeting the GDG concluded that
							• that the current recommendation including the term 'absolute infertility' should be removed
							• A new recommendation should be drafted based on
							  o ovarian reserve testing
							  o that there was a need for a recommendation highlighting the additional risks associated with pregnancy in women aged 40 to 42 years
							The final version of the reworded recommendation was agreed by the 8 out of 11 members of the GDG:
							In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled:
							• *they have never previously had IVF treatment*
							• *there is no evidence of low ovarian reserve*
							• *there has been a discussion of the additional implications of IVF and pregnancy at this age.*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							•
200.	Human Fertilisation Embryology Authority	7	Full	18	127	In order to avoid differing interpretations it should be clearly spelt out that this point applies to same sex couples and single women (if that is the case). It would also help to clarify whether the guideline is recommending that the 12 cycles of artificial insemination (presumably donor insemination) are funded by the NHS.	Thank you for your comments. 1. The GDG believed that it is explicit that all groups not using vaginal intercourse are covered by this recommendation and did not want to list these and potentially exclude a group. 2. The 12 cycles is split into two parts. The initial 6 cycles are to demonstrate a fertility problem exists. These are paid for by the person. The next six cycles are part of 'expectant management' and are paid for by the NHS as the person has been defined as having a fertility problem. How the first six cycles of AI are provided and funded are outside the Scope of the Guideline.
201.	Human Fertilisation Embryology Authority	8	Full	18	158	The Authority is keeping under review the outcomes and impact of blastocyst transfer. We feel that this guidance is too prescriptive and the option of cleavage stage transfer should be available to patients.	Thank you for your comment. It was not the intention of the GDG to suggest that only blastocyst embryos can be used with SET. The GDG has amended the recommendation to avoid this potential misinterpretation:
202.	Human Fertilisation Embryology Authority	5	Full	33	143	'Natural' cycle IVF contributes to a very small proportion of IVF cycles. Of the 45,227 fresh cycles performed in 2010 using a woman's own eggs, 401 (0.9%) were natural. Although the number of 'natural' cycles increased slightly	Thank you for your comments. The GDG agreed that natural cycle IVF may be an appropriate treatment option in some cases. However, NICE Clinical Guideline recommendations are written for the majority of people, and as it is not an effective

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						from 2009, when 369 cycles were performed with no drugs, the proportion remained the same (0.9%). Although these figures are low 'natural' IVF may be a valuable treatment option for a minority of patients (eg, those suffering from PCOS who may be too sensitive to the stimulatory drugs necessary for IVF). Therefore we suggest that the guidance should be amended to state: "Do not routinely offer women 'natural cycle' IVF treatment."	treatment option, it should not be offered to the majority of women.
203.	Human Fertilisation Embryology Authority	6	Full	33	141	The regulation of OHSS largely falls outside of the HFEA's remit. However, we note that the new guidance on OHSS is prescriptive and may compromise case by case clinical management. For example, it may not be appropriate to prescribe precise numbers relating to estradiol levels and number of follicles.	Thank you for your comments. The recommendation has been and replaced by a more general recommendation about OHSS
204.	Human Fertilisation Embryology Authority	10	Full	34	159	Like our multiple births policy this aims to reduce the number of multiple births through IVF. However the approach proposed by NICE is more prescriptive. The HFEA has been more outcomes-focused, and left more leeway for clinicians to decide how many embryos to transfer on any occasion. We recognise the differences in approach between ourselves and NICE on this issue but don't see any fundamental incompatibility; as a centre complying with ours and NICE's requirements would have no difficulty in doing so.	Thank you for your comments.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						We will keep our position on this issue under review, as with all aspects of our multiple births policy. We welcome the fact that the new NICE guideline takes the issue of multiple births as seriously as we do, in a way which is supportive of our approach.	
205.	Human Fertilisation Embryology Authority	9	Full	35	162	The Authority is keeping under review the outcomes and impact of blastocyst transfer. We feel that this guidance is too prescriptive and the option of cleavage stage transfer should be available to patients.	Thank you for your comment. It was not the intention of the GDG to suggest that only blastocyst embryos can be used with SET. The GDG has amended the recommendation to avoid this potential misinterpretation: "Where a top-quality blastocyst is available single embryo transfer should be used"
206.	Human Fertilisation Embryology Authority	11	Full	35	163	We suggest that this line is amended to ensure that patients are informed about the full range of risks associated with multiple pregnancy and multiple births eg, "When considering double embryo transfer, advise people of the risks of multiple pregnancy associated with this strategy ie,risk of stillbirth, neonatal death and disability in children born and risk of complications to the mother."	Thank you for this comments. The GDG believed that the additional wording will not enhance the recommendation. However, this information will be available in the evidence to recommendation section of the guideline document. Therefore, in this instance no change will be made to the recommendation.
207.	Human Fertilisation Embryology Authority	12	Full	39	199	The Authority has reservations about vitrification being recommended at this point in time as the preferable method to cryopreserve eggs and embryos.	Thank you for your comments. The evidence shows that there was a significantly higher rate of post-thaw survival after vitrification of oocytes compared to controlled rate freezing of oocytes.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						Also, as highlighted in a recent letter sent to all HFEA licenced clinics (Chief Executive's letter CE (12)02) obtaining written consent to the storage and use of gametes and embryos, which reflects the patient's wishes, is imperative.	Furthermore there was an indication that the same to be true in embryo cryopreservation. The GDG was aware that the amount of RCT evidence comparing controlled rate freezing and vitrification is small. They were also aware that there is no long-term data on vitrification use or indeed the primary outcome for the review, live singleton birth. However, the evidence that was available backed their clinical consensus that vitrification should be the preferred technique. The wording of the recommendation only indicates that vitrification should only be offered where the equipment and expertise are available. Controlled rate freezing can still be offered without restriction if this is the only option within a clinic. Furthermore, a research recommendation has been made for further investigating into the long term outcomes of virtrification and the different techniques within vitirification. With regards to your comments about consent, we agree and have made this clear within the evidence to recommendations text
208.	Human Fertilisation Embryology Authority	13	Full	39	203	The Authority has reservations about vitrification being recommended at this point in time as the preferable method to cryopreserve eggs and embryos.	Thank you for your comments. The evidence shows that there was a significantly higher rate of post-thaw survival after vitrification of oocytes compared to

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						Also, as highlighted in a recent letter sent to all HFEA licenced clinics (Chief Executive's letter CE (12)02) obtaining written consent to the storage and use of gametes and embryos, which reflects the patient's wishes, is imperative.	controlled rate freezing of oocytes. Furthermore there was an indication that the same to be true in embryo cryopreservation. The GDG was aware that the amount of RCT evidence comparing controlled rate freezing and vitrification is small. They were also aware that there is no long-term data on vitrification use or indeed the primary outcome for the review, live singleton birth. However, the evidence that was available backed their clinical consensus that vitrification should be the preferred technique. The wording of the recommendation only indicates that vitrification should only be offered where the equipment and expertise are available. Controlled rate freezing can still be offered without restriction if this is the only option within a clinic. Furthermore, a research recommendation has been made for further investigating into the long term outcomes of virtrification and the different techniques within vitirification. With regards to your comments about consent, we agree and have made this clear within the evidence to recommendations text
209.	Human Fertilisation Embryology Authority	14	Full	40	209	The Authority feels that there should be a greater emphasis on clinicians taking account of any new findings on long term health outcomes when informing patients. This could be addressed by adding something along the lines	Thank you for your comments. The GDG agreed that health professionals should be aware of this. This information will

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						of: '"Information given to patients must take account of any new findings on long term health outcomes which may have been published subsequent to the publication of these guidelines."	be added to the evidence to recommendation section, but not to the main recommendation: *"The GDG stated that information given to patients must take account of any new findings on long term health outcomes which may have been published subsequent to the publication of these guidelines."*
210.	Infertility Network UK	1	Full	20	12	Those using donor sperm do not have the option to use fresh sperm and we are concerned that the wording here may encourage some patients to consider other (unlicensed) options with fresh sperm. We would like to see this line reworded to prevent patients using frozen sperm being unduly concerned by reduced success rates.	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
211.	Infertility Network UK	2	Full	23	37	We would recommend the guideline includes a list of definitions including one on the definition of infertility to avoid confusion and commissioners coming up with their own, differing, definition.	Thank you for your comments. As you correctly imply there is more than one definition of infertility. Recommendations 37, 38, 39, 40 and 41 support this view. We have reflected this in an addition to the Glossary together with a definition of 'Reproductive age'
212.	Infertility Network UK	3	Full	23	38	Again, we would recommend that the guideline include a list of definitions including one on the definition of 'reproductive age' to remove any disagreement of exactly what it is, and that this recommendation refers back to this definition so that there is no confusion.	Thank you for your comments. As you correctly imply there is more than one definition of infertility. Recommendations 37, 38, 39, 40 and 41 support this view. We have reflected this in an addition to the Glossary together with a definition of 'Reproductive age'
213.	Infertility Network UK	4	Full	23	40	We would suggest adding 'or psychological therapy' here so that the wording reads 'offer an initial consultation to discuss the options for attempting conception, further assessment and appropriate treatment and/or psychological therapy (for fertility or other conditions)…..'	Thank you for your comments. However, we feel that the phrase *'appropriate treatment'* covers the treatment that would be deemed necessary because of the 'clinically diagnosed physical disability or psychological problem'.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
214.	Infertility Network UK	5	Full	23	41	We would recommend that a time period is given instead of "an earlier referral" for those where it is being considered purely because the woman is aged 36 years or more to avoid confusion. We would recommend 6 months.	Thank you for your comments. The GDG reviewed your suggestion and came to the conclusion that they did not wish to make a specific recommendation regarding what was meant by 'earlier'. In summary, there were two reasons for this: • The Guideline already suggests referral 12 months earlier than was suggested in the original Guideline • There was no evidence upon which to base a figure (eg 6 months). In the text, 6 months is discussed for illustrative purposes only and that could be an interval that is adopted locally but the GDG did not feel that this should be a recommendation.
215.	Infertility Network UK	6	Full	29	93	We would recommend that instead of using the wording "more than 29" the guideline says "30 or more" as we are aware that there has been confusion amongst commissioners on this with some reading it as up to but not including 29.	Thank you for your comments. We have reviewed this wording with the NICE editor and agree with your suggestion. Thus, we have used this approach (*"30 or more"* or whatever age applies) throughout the guideline.
216.	Infertility Network UK	7	Full	29	95	We would recommend adding 'and OHSS' to the end of this recommendation to ensure that women on clomifene citrate are being monitored for the risks of both multiple pregnancy and OHSS.	Thank you for your comments. None of the included studies reported cases of OHSS with the use of clomifene citrate and so the GDG was unable to recommend monitoring specifically for this purpose.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
217.	Infertility Network UK	8	Full	31	113	We are concerned that this recommendation does not allow for women who are 36 and over where the guideline is recommending that they should be referred earlier? Nor does it allow for couples where the female would be over the age limit for NHS funded IVF. We would recommend this be reworded to reflect that women over the age of 36 should be referred earlier, taking into account the upper age limit for accessing IVF treatment on the NHS.	Thank you for your comments. The GDG discussed them following the consultation process. They have recommended that women aged 36 years or more are offered an earlier referral If they are then diagnosed with unexplained infertility, however, the GDG did not agree that these women should be referred for IVF treatment any sooner than younger women. By being referred earlier at the outset they would be able to access discussion of and consideration for IVF more promptly than younger women. Women who are 36y or more with no apparent cause for their infertility after full assessment an investigation still have about a 90% of conceiving after 2 years of expectant management (see Table 5.1 and Figure 5.2, in the full Guideline). It is possible that one or both of those 2 years occur before the women presents with difficulty in conceiving. However, the implication of this and other recommendations in the Guideline is that women should not defer pregnancy until their late 30's as this means that if they do not conceive naturally their therapeutic options are limited
218.	Infertility Network UK	9	Full	31	114	We are concerned that this recommendation does not allow for women who are 36 and over where the guideline is recommending that they should be referred earlier? Nor does it allow for	Thank you for your comments. The GDG discussed them following the consultation process. They have

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						couples where the female would be over the age limit for NHS funded IVF. We would recommend this be reworded to reflect that women over the age of 36 should be referred earlier, taking into account the upper age limit for accessing IVF treatment on the NHS.	recommended that women aged 36 years or more are offered an earlier referral If they are then diagnosed with unexplained infertility, however, the GDG did not agree that these women should be referred for IVF treatment any sooner than younger women. By being referred earlier at the outset they would be able to access discussion of and consideration for IVF more promptly than younger women. Women who are 36y or more with no apparent cause for their infertility after full assessment an investigation still have about a 90% of conceiving after 2 years of expectant management (see Table 5.1 and Figure 5.2, in the full Guideline). It is possible that one or both of those 2 years occur before the women presents with difficulty in conceiving. However, the implication of this and other recommendations in the Guideline is that women should not defer pregnancy until their late 30's as this means that if they do not conceive naturally their therapeutic options are limited
219.	Infertility Network UK	10	Full	32	125	Our comments are as follows: 1. Remove the word "normally" in the first line as a full cycle **always** consists of one episode of ovarian stimulation etc. Change second half of recommendation as follows: "… and the transfer of any resultant fresh embryos followed by the transfer of any frozen embryos resulting from the initial fresh cycle."	Thank you for your comments. After discussion, the GDG felt that the word 'normally' should stay given the variation in practice that exits in reproductive medicine clinics with respect to procedures for transfer of fresh and frozen embryos.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
220.	Infertility Network UK	11	Full	32	126	Given the confusion of exactly what is "absolute infertility" in the recent press coverage of the publication of this consultation and the emails we have received from patients, we recommend that the guideline includes a list of "definitions" which would include a definition of absolute infertility and that the recommendation refers back to this definition. We would like to see the definition of 'absolute infertility' made crystal clear so that patients do not have their hopes raised and, health professionals and commissioners understand exactly who is covered by this definition and therefore eligible for fast tracking. Without a clear definition there is scope for patients in different areas to be treated inequitably depending on the clinician's/commissioners interpretation of 'absolute infertility. We would also like to point out that in view of the ambiguous press coverage when the draft consultation came out, that consideration is given to sending out a clear message on this point when the final guideline is produced as well as in any communications to the media.	Thank you for your comments. Several stakeholders commented that the term 'absolute infertility' was not meaningful or useful in clinical practice. <u>Updated recommendation</u> There was extensive debate and division of opinion within the GDG about whether a recommendation for the provision of IVF could be made for this age group both before and after stakeholder comments. The details of which are described in the full version of the guideline. It was concluded that the uncertainty around the HE model meant that any recommendation for this age-group would have to be based on clinical opinion. At the end of the meeting the GDG concluded that • that the current recommendation including the term 'absolute infertility' should be removed • A new recommendation should be drafted based on o ovarian reserve testing o that there was a need for a recommendation highlighting the additional risks associated

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							with pregnancy in women aged 40 to 42 years The final version of the reworded recommendation was agreed by the 8 out of 11 members of the GDG: *In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled:* • *they have never previously had IVF treatment* • *there is no evidence of low ovarian reserve* • *there has been a discussion of the additional implications of IVF and pregnancy at this age.*
221.	Infertility Network UK	12	Full	32	128	Given the confusion of exactly what is "absolute infertility" in the recent press coverage of the publication of this consultation and the emails we have received from patients, we recommend that the guideline includes a list of "definitions" which would include a definition of absolute infertility and that the recommendation refers back to this definition. We would like to see the definition of 'absolute infertility' made crystal clear so that patients do not have their hopes raised and, health professionals and commissioners understand exactly who is covered by this definition and therefore eligible	Thank you for your comments. Several stakeholders commented that the term 'absolute infertility' was not meaningful or useful in clinical practice. <u>Updated recommendation</u> There was extensive debate and division of opinion within the GDG about whether a recommendation for the provision of IVF could be made for this age group both before and after stakeholder comments. The details of

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						for fast tracking. Without a clear definition there is scope for patients in different areas to be treated inequitably depending on the clinician's/commissioners interpretation of 'absolute infertility. We would also like to point out that in view of the ambiguous press coverage when the draft consultation came out that consideration is given to sending out a clear message on this point when the final guideline is produced as well as in any communications to the media.	which are described in the full version of the guideline. It was concluded that the uncertainty around the HE model meant that any recommendation for this age-group would have to be based on clinical opinion. At the end of the meeting the GDG concluded that • that the current recommendation including the term 'absolute infertility' should be removed • A new recommendation should be drafted based on o ovarian reserve testing o that there was a need for a recommendation highlighting the additional risks associated with pregnancy in women aged 40 to 42 years The final version of the reworded recommendation was agreed by the 8 out of 11 members of the GDG: *In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of*

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							IVF, with or without ICSI, provided the following 3 criteria are fulfilled: • *they have never previously had IVF treatment* • *there is no evidence of low ovarian reserve* • *there has been a discussion of the additional implications of IVF and pregnancy at this age.*
222.	Infertility Network UK	13	Full	32	130	We would like to see further clarity around how previous NHS treatment should be taken into account when considering IVF treatment. If this recommendation is suggesting that the clinical effectiveness of further treatment is to be taken into account, that needs to be made clearer. At the moment some PCTs only offer one cycle of treatment and will refuse to fund further treatment if a patient has already self funded one cycle. Refusing to fund treatment where there is little or no chance of a successful outcome can be justified on clinical effectiveness, but not funding treatment simply because a patient has had one self funded cycle is, we feel, simply a way of rationing treatment.	Thank you for your comments. We have split and changed the recommendation for greater clarity to: • "Any previous full IVF cycle, whether self- or NHS-funded, should count towards the total of 3 cycles that should be offered by the NHS." • "Take into account the outcome of previous IVF treatment when assessing the likely effectiveness and safety of any further IVF treatment." This guideline makes recommendations on the number of cycles that should to be offered, but we are not responsible for whether commissioners will implement this guidance.
223.	Infertility Network UK	14	Full	35	159	Infertility Network UK strongly supports the move to elective single embryo transfer but we do not feel that transferring a single embryo in every patient under 37 undergoing their first cycle will always be the best option for that patient and that the decision needs to be taken	Thank you for your comments. The GDG has outlined criteria based on people receiving 3 full cycles of IVF and furthermore the primary outcome of the guideline is a live full-term singleton birth.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						on an individual basis, after discussion between the clinician and the patient. We would like to see this recommendation amended to allow some scope for double embryo replacement where all the embryos produced are of low quality, there are no previous pregnancies, and after the risks of multiple births have been clearly explained to the patient. We would suggest amending the line to 'in the first and second full IVF cycles use single embryo transfer if one or more top quality embryos are available. Consider using two embryos if no top quality embryos are available.' Despite the fact that the HFEA has written to all PCTs pointing out that it would be inappropriate for all patients to receive single embryo transfer, many are still insisting that all patients have SET even where they are only funding one cycle, or indeed one fresh cycle. We would like to see NICE and the Government doing all they can to ensure PCTs fully implement the new guideline when it is finalised.	Based on the available evidence on effectiveness and safety, it is the conclusion of the GDG that using a single embryo in the first full cycle optimises the chance of a live full-term singleton birth. If this fails then the next 2 full cycles allows more than one embryo to be transferred dependent on embryo quality. Therefore, in this instance no change will be made to the recommendation. The GDG was aware that the implementation of the 2004 guideline has often been varied and limited in many areas of the country'., and one aim of the 2012 update has been to clarify the interpretation of recommendation.
224.	Infertility Network UK	15	Full	35	162	We feel that for some older women, particularly where they are in their last cycle of IVF, and/or where they have had previous unsuccessful cycles, consideration should be given to transferring two good quality blastocysts providing that the risks of multiple birth have been full explained.	Thank you for your comment. Based on the available data the GDG concluded that transferring two top quality blastocyst embryos significantly increased a woman's chances of a multiple pregnancy compared to a single blastocyst or two lower quality embryos. Given that multiple pregnancies are the greatest risk to the health to a mother and unborn children, the GDG concluded that the two blastocysts should not be transferred.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
225.	King's College Hospital - Weston Education Centre	1	Full	General		The hard work of the committee is appreciated in this substantial revision and updating. The new layout style providing tables of evidence, then its interpretation and the follow on recommendations is novel and a huge improvement to understanding and veracity. Although difficult areas were tackled I found nothing personally controversial and the recommendations were reasonable interpretations of the evidence. A few specific comments on a small number of areas follow.	Thank you for your comment.
226.	King's College Hospital - Weston Education Centre	2	Full	98	23	Recommendation 50 re FSH: and the preceding discussion I was unable to find details of when the FSH is advised to be taken and how the result should be related to the estradiol (E2) levels as FSH can vary during the menstrual cycle and its effect on oocyte recruitment strongest during the follicular phase. Interpretation for example a day 7 or 8 FSH 8 in a background E2 of say 300 may functionally be above the 10iu/l, if it had been taken at baseline – i.e. during the menstrual or early follicular phase (days 1-5). Many clinicians do not appreciate this crucial relationship of the feedback between E2 and FSH, especially since request forms generally have a tick box for FSH/LH but require E2 to be requested separately and specifically. It might be recommended that request forms should have either FSH/E2 together or all three, and that it should be taken during the menses or shortly after (day 1-5) for correct interpretation	Thank you for your comments. This is a good point. When drafting the recommendations the GDG assumed that the people using them has the knowledge and skill to apply them, and only a minimum of specified technical application is usually outlined. However, we will add further text to the evidence to recommendation section highlighting the need for specialist knowledge before using these tests.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
227.	King's College Hospital - Weston Education Centre	3	Full	99	10	And recommendation 54: Although acceptable and reasonable to test progesterone even in longer cycles <35 days, many GPs do not appreciate that longer cycles >35 days are likely to indicate poor follicular or luteal function and ovulatory dysfunction; i.e. it is neither appropriate, cost effective nor necessary to measure progesterone in a 40 day cycle even if one were timing it 7 days from this as their will be no effective luteal phase as anovulation is likely. Comment to this effect should be made in recommendations	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
228.	King's College Hospital - Weston Education Centre	4	Full	136	15	Laparoscopic Ovarian Diathermy: In the text here and above I found no comment on risk of LOD in terms of total wattage and number of holes and possible risk to oocyte mass (which reside in the cortex) due to excessive ovarian damage. Perhaps this evidence could be examined and recommendations about caution added.	Thank you for your comment. The GDG believed that it would be too prescriptive to recommend the total wattage and number of holes for LOD. A statement on the risks to oocyte mass can be found in the introduction to WHO Group II disorders, in section 8.3 of the full guideline text, which states: *"Risks of LOD include those associated with surgery and general anaesthesia, and a low risk of causing ovarian damage and/or peri-ovarian adhesions."*
229.	King's College Hospital - Weston Education Centre	5	Full	328	13	Although it is accurate and helpful to give the 2/5 or 16/40 comparator with 1/40 standard, it would be helpful to give also the percentage estimate (40%) -this may increase understanding of just how serious is this level for obstetric and neonatal services when 40% of IVF babies are born in a multiple pregnancy.	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
230.	King's College Hospital - Weston Education Centre	6	Full	335	6	Table 15.22 Woman's is an inappropriate heading for the first column	Thank you for your comment. We have amended the text to match your suggestions.
231.	King's College Hospital - Weston Education Centre	7	Full	335	10	In a similar message to 328, a 36% twin rate for DET equates to over 50% of IVF babies in multiple births – a staggering proportion. The is a typo in 10 – singleton brths	Thank you for your comment. We have amended the text to match your suggestions and correct the typographic error.
232.	King's College Hospital - Weston Education Centre	8	Full	344	40	Table 15.30 gives an admirable vision of consensus of embryo transfer strategies but since it is based on studies that relate to fresh embryos, the leap to application with frozen embryos is less clear. i.e. in a FULL cycle why/how this applies to all the embryos in that cycle – when thawed embryos may have a different / lower implantation potential as shown in table 15.28.	Thank you for your comments. The transfer strategy applies to all embryos (fresh or frozen) collected within that cycle. The GDG was aware that other strategies are used, such as two fresh cycles then using frozen embryos, but the guideline addresses the most common situations. This has been clarified in the evidence to recommendations section: *When considering the number of fresh or frozen embryos to transfer in IVF treatment…"*
233.	Liverpool Women's NHS Foundation Trust	2	Full	335	17 to 29	Same topic – ultrasound guidance for embryo transfer – the text describes a meta-analysis performed by the authors of 8 studies, references 949 to 952, 4 RCT's & 4 quasi-randomised – total 2051 to 3358 procedures. My unit published a RCT in 2008 in Human Reproduction of 2295 embryo transfers randomised to either ultrasound or no ultrasound. We also followed up live birth rate. No difference was observed. This paper has not been included. Please could you inform us why it has been excluded and consider inclusion and then re-do the meta-analysis? Drakeley AJ, Jorgensen A, Sklavounos J,	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						Aust T, Gazvani R, Williamson P and Kingsland CR (2008) A randomized controlled clinical trial of 2295 ultrasound guided embryo transfers. Hum Reprod23(5):1101-06,2008 **(This is one of the largest randomised trials from a single centre in Reproductive Medicine and was cited in Faculty of 1000 medicine F1000 factor 6.0 must read, changes clinical practice)**	
234.	Liverpool Women's NHS Foundation Trust	1	Full	352	20	Recommendation 154 that ultrasound at embryo transfer should be offered as it improved pregnancy rates	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
235.	Merck Serono	3	Full	General		Given the complexity of the guidelines, we would suggest that implementation will be a challenge. We would welcome the opportunity to engage with the implementation unit to understand if there is a role we can play here .	Thank you for your comment.
236.	Merck Serono	2	RR 32	313	2	In regard to this research opportunity, we would refer to the Cochrane Collaboration 2011. A large meta-analysis of RCTs comparing recombinant versus urinary gonadotrophin.Included were 42 trials with a total of 9606 couples. In terms of clinical	Thank you for your comments. The GDG considered the Van Wely (2011) Cochrane review in detail in their own review of urinary and recombinant products. You are correct that 42 trials and 9606 women were

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						evidence, irrespective of the downregulationprotocol used, there was no evidence of a statistically significant difference in live birth rate between recombinant and urinary gonadotrophin. Merck Seronoagrees here with the authors view that, *"Further research on these comparisons is unlikely to identify substantive differences in effectiveness or safety".* Beside, prior to initiate a clinical and cost-effectiveness research the expected value of information of such study should be performed. Currently the procurement process (tender) for the gonadotrophins is indicating that such research may not be needed in the UK. -van Wely,Madelon, Kwan,Irene, Burt,Anna L., Thomas,Jane, Vail,Andy, Van der Veen,Fulco, AlInany,Hesham G., Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles, Cochrane Database of Systematic Reviews, -, 2011	included in the Cochrane review; however, this included comparisons of all recombinant and urinary products. The GDG was of the opinion that the evidence for, specifically, highly purified gonadotrophins is limited. As more of these products are becoming available, the GDG made a research recommendation to encourage studies of their value for future updates of the Guideline.
237.	Merck Serono	1	15.5	321	7-9	With regard to the consideration of high dose recombinant luteinising hormone (rLH) as an alternative to Human chorionic gonadotrophin for inducing final oocyte maturation triggering in IVF and ICSI cycles, Merck Serono agrees with the GDG that the evidence from Youssef et al 2011, "*did not suggest that there is a difference in the clinical benefits or harms*". However, Merck Serono would like to highlight that *Luveris*®, the only recombinant LH product available, is unlicensed for this indication. Also, achieving the dosage required may be impractical in this setting. At present the	Thank you for your comments. Text has been added to the evidence to recommendations section of the chapter to explain this, and this recommendation has been removed from the guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						medication is only available in a 75 international units (IU) vial and in the 3 publications addressed in the Youssef review the high doses delivered were between 5,000-30,000IU. Though the GDG recommends that that the use of rLH may be preferable in women who are at a higher risk of ovarian hyperstimulation syndrome (OHSS), *Luveris*® might not be a viable alternative here. Youssef,AFM Mohamed, Al-Inany,Hesham G., Aboulghar,Mohamed, Mansour,Ragaa, Proctor,Michelle, Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles, Cochrane Database of Systematic Reviews, -, 2011	
238.	Merck Sharp & Dohme UK Ltd	1	NICE Guideline	19	1	We would suggest that the term 'earlier referral for specialist consultation' is more specifically defined in recommendation 1.2.13.7. The full version of the updated guideline states on page 74, lines 38-40 that "if the woman is 36 or over then such assessment should be considered after 6 months of unprotected regular intercourse since her chances of successful conception are lower and the window of opportunity for intervention is less." However, this is not reflected in the recommendation itself, which simply states 'earlier referral' for these women. We would suggest that recommendation 1.2.13.7 is amended to make it clear that women aged 36 years or more should be referred for specialist consultation after 6 months of regular unprotected sexual intercourse.	Thank you for your comments. The GDG reviewed your suggestion and came to the conclusion that they did not wish to make a specific recommendation regarding what was meant by 'earlier'. In summary, there were two reasons for this: • The Guideline already suggests referral 12 months earlier than was suggested in the original Guideline • There was no evidence upon which to base a figure (e.g. 6 months). In the text, 6 months is discussed for illustrative purposes only and that could be an interval that is adopted locally but the GDG did not feel that this should be a recommendation. We have not changed the wording of this recommendation. The current wording allows

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						This is in concordance with guidance produced by the American Society for Reproductive Medicine, which recommends that, "given the anticipated age-related decline in fertility, and the higher risk of pregnancy loss, women older than 35 years should receive expedited evaluation and treatment after 6 months of failed attempts to conceive"[1]. In addition, we would propose that recommendation 1.2.13.7 should clarify that the referral should be to a specialist in fertility, not simply any specialist. Reference 1) The Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists and The Practice of the American Society for Reproductive Medicine. Age-related fertility decline: a committee opinion. Fertil Steril. 2008;90:S154-155.	for referral to an ART unit, whereas referral to a 'specialist in fertility' could suggest a named consultant-level clinician, Therefore, we believe the current wording specifies what expertise is needed but allows flexibility in who provides this reflecting the current variation in the titles of health care professionals who have this expertise.
239.	Merck Sharp & Dohme UK Ltd	2	NICE Guideline	22	12	The third bullet point under recommendation 1.3.3.2 relates to use of the anti-Mullerian hormone (AMH) test to predict the likely ovarian response to gonadotrophin stimulation, and provides the values of less than or equal to 5.4 pmol/l for a low response and greater than or equal to 25.0 pmol/l for a high response. We would suggest that the assay used to generate these values is specified in the recommendation, as use of different assays for AMH can provide different results.	Thank you for your comments. Your comments have been considered by the GDG and the relevant recommendation has been amended

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
240.	Merck Sharp & Dohme UK Ltd	3	NICE Guideline	34	4	Recommendations 1.8.1.3 and 1.8.1.4 advise that women with unexplained fertility should be considered for IVF if they have not conceived after 2 years (including up to 1 year before investigation) of regular unprotected sexual intercourse. We would suggest that women aged 36 or over should be considered for IVF if they have not conceived after 1 year (including up to 6 months before investigation) of regular unprotected sexual intercourse. This would be consistent with recommendation 1.2.13.7, which highlights the need for prompt assessment and discussion of appropriate treatment for women aged 36 or over, and recommends "earlier referral for specialist consultation" for these women. The annual fertility rate among women not using contraception declines with women's age, and declines more rapidly in women older than 35 years, as illustrated in Figure 1 of the NICE version of the updated guideline (page 21). The success of IVF begins to decline from approximately 35 years, with more rapid decline after age 38 years, as discussed on page 82, lines 17-27, of the full version of the updated guideline and shown in Figure 2 of the NICE version of the updated guideline (page 22). This is reflected by guidance produced by the American Society for Reproductive Medicine, which recommends that, "given the anticipated age-related decline in fertility, and the higher risk of pregnancy loss, women older than 35	Thank you for your comments. The GDG has recommended that women that are 36 years or more are offered an earlier referral. If they are then diagnosed with unexplained infertility, however, the GDG did not agree that these women should be referred for IVF treatment any sooner than younger women. By being referred earlier at the outset they would be able to access discussion of and consideration for IVF more promptly than younger women. Women who are 36y or more with no apparent cause for their infertility after full assessment an investigation still have about a 90% of conceiving after 2 years of expectant management (see Table 5.1 and Figure 5.2, in the full Guideline). It is possible that one or both of those 2 years occur before the women presents with difficulty in conceiving. However, the implication of this and other recommendations in the Guideline is that women should not defer pregnancy until their late 30's as this means that if they do not conceive naturally their therapeutic options are limited

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						years should receive expedited evaluation and treatment after 6 months of failed attempts to conceive"[1]. We would suggest that women aged 36 or over are considered for IVF after only 1 year of unprotected sexual intercourse because their chances of conceiving naturally are lower than for younger women, and to allow IVF treatment to begin while their chance success is higher. Reference 1) The Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists and The Practice of the American Society for Reproductive Medicine. Age-related fertility decline: a committee opinion. Fertil Steril. 2008;90:S154-155.	
241.	Merck Sharp & Dohme UK Ltd	4	NICE Guideline	34	18	The second bullet point under recommendation 1.9.1.1 states that women should be advised to try to conceive for a total of 2 years (including up to 1 year before investigation) before IVF will be considered. In line with the comment above (comment number 3) we would suggest that women aged 36 years or over are considered for IVF after trying to conceive for 1 year (including up to 6 months before investigation). This would be consistent with previous recommendations in the NICE guideline, which advise earlier referral to a specialist for women aged 36 years or more (1.2.13.7), and with the American Society for Reproductive Medicine	Thank you for your comments. The relevant recommendation states "Offer an earlier referral for specialist consultation to discuss the options for attempting conception, further assessment and appropriate treatment where: • the woman is 36 years or more • there is a known cause of infertility or a history of predisposing factors for infertility." This was outlined specifically to take women who need early referral outside the main pathway that requires 1 year of failing to

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						guidelines, which recommend expedited assessment and treatment for women aged over 35[1]. Recommending that women aged 36 or over are considered for IVF after trying to conceive for 1 year, rather than 2 years, would allow IVF treatment to begin while their chance success is higher. <u>Reference</u> 1) The Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists and The Practice of the American Society for Reproductive Medicine. Age-related fertility decline: a committee opinion. Fertil Steril. 2008;90:S154-155.	conceive before assessment is considered. Therefore, a woman aged 36 or more would receive early referral for assessment and potential treatment. The treatment plan will be based on the findings of the assessment and this may involve early referral for IVF or a further period of expectant management. However, the implication of this and other recommendations in the Guideline is that women should not defer pregnancy until their late 30's as this means that if they do not conceive naturally their therapeutic options are limited
242.	Merck Sharp & Dohme UK Ltd	5	NICE Guideline	36	23	Recommendation 1.11.1.3 under the section "Access criteria for IVF" states that IVF should be offered to "women aged under 40 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination…". In line with the comments above (comment numbers 3 and 4) we would suggest that women aged between 36 and 39 years are considered for IVF after only 1 year of regular unprotected intercourse to allow IVF treatment to begin while their chance success is higher. This would be consistent with previous recommendations in the NICE guideline, which advise earlier referral to a specialist for women aged 36 years or more (1.2.13.7), and with the	Thank you for your comments. The relevant recommendation states "Offer an earlier referral for specialist consultation to discuss the options for attempting conception, further assessment and appropriate treatment where: • the woman is 36 years or more • there is a known cause of infertility or a history of predisposing factors for infertility." This was outlined specifically to take women who need early referral outside the main pathway that requires 1 year of failing to conceive before assessment is considered. Therefore, a woman aged 36 or more would receive early referral for assessment and

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						American Society for Reproductive Medicine guidelines, which recommend expedited assessment and treatment for women aged over 35[1]. Recommending that women aged 36 or over are considered for IVF after trying to conceive for 1 year, rather than 2 years, would allow IVF treatment to begin while their chance success is higher. Reference 1) The Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists and The Practice of the American Society for Reproductive Medicine. Age-related fertility decline: a committee opinion. Fertil Steril. 2008;90:S154-155.	potential treatment. The treatment plan will be based on the findings of the assessment. This may involve early referral for IVF or a further period of expectant management. However, the GDG did not agree that women aged 36 years or more should be receive early access to IVF purely based on their age. Furthermore, women who are aged 36 years or more with no apparent cause for their infertility after full assessment and investigation still have about a 90% of conceiving after 2 years of expectant management (see Table 5.1 and Figure 5.2, in the full Guideline). It is possible that one or both of those 2 years occur before the women presents with difficulty in conceiving. However, the implication of this and other recommendations in the Guideline is that women should not defer pregnancy until their late 30's as this means that if they do not conceive naturally their therapeutic options are limited.
243.	Merck Sharp & Dohme UK Ltd	6	NICE Guideline	37	19	Section 1.12.2 of the updated guideline is titled 'Down-regulation in IVF'. We believe that this title is incorrect and should be amended because gonadotrophin-releasing hormone (GnRH) antagonists, which are included in this section, do not cause down-regulation[1]. We would suggest that a more appropriate title for section 1.12.2 is "Procedures to avoid premature luteinising hormone surges". Reference	Thank you for your comments. The title of this section has been changed.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						1) Gordon K, Hodgen GD. Basis for differential therapeutic roles of GnRH agonists versus antagonists in clinical practice. Infertility and Reproductive Medicine Clinics of North America. 1993;4(1)201-213.	
244.	Merck Sharp & Dohme UK Ltd	7	NICE Guideline	37	20	We would suggest that recommendation 1.12.2.1 is misleading because GnRH antagonists do not cause down-regulation[1], as is suggested by the recommendation. All other information in recommendation 1.12.2.1 is covered by the subsequent recommendations in Section 1.12.2, therefore this recommendation could be removed from the guideline. Reference 1) Gordon K, Hodgen GD. Basis for differential therapeutic roles of GnRH agonists versus antagonists in clinical practice. Infertility and Reproductive Medicine Clinics of North America. 1993;4(1)201-213.	Thank you for your comments. The GDG believed it is important to have a recommendation stating that regimens to avoid premature luteinising hormone surges should be used prior to stimulation for IVF, before recommending which regimens should be used. The relevant recommendation has been amended:
245.	Merck Sharp & Dohme UK Ltd	8	NICE Guideline	38	1	We would suggest that additional information may be included as part of recommendation 1.12.2.4 to clarify that GnRH antagonists are associated with lower risk of ovarian hyperstimulation syndrome (OHSS), and may be an appropriate treatment option for women at risk of OHSS. A recently published systematic review included 29 randomised trials that reported OHSS incidence among women receiving GnRH agonists or antagonists as part of assisted reproductive technology. The review found that GnRH antagonist protocols were associated	Thank you for your comments The GDG looked in detail at the Al-Inany (2011) Cochrane review when making their recommendations, along with four RCTs that were not included in that Cochrane review . The GDG's view was that clinicians need to be aware of the increased risk of OHSS with the use of GnRH agonists compared with the lower risks with the use of GnRH antagonists. This is stated in the text of the full guideline. The GDG acknowledged that the risk of OHSS is also dependent on which gonadotrophins and ovulation trigger are used during other parts of

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						with 60% lower occurrence of OHSS compared to agonist protocols[1]. We would suggest that it is important that women are informed that GnRH antagonist protocols are associated with a lower risk of OHSS compared to GnRH agonist protocols. Reference 1) Al-Inany HG, Youssef MAFM, Aboulghar M et al. Gonadotrophin-releasing hormone antagonists for assistedreproductive technology (Review). Cochrane Database Syst Rev. 2011;11(5):CD001750.	the IVF treatment cycle, and so it would not be appropriate to recommend against the use of GnRH agonists. This is also stated in the text of the full guideline. However, the GDG acknowledged that there is a need to balance the increased chance of achieving a clinical pregnancy using GnRH agonist with the increased risk of OHSS. Therefore the GDG recommended the use of either GnRH agonist for down regulation or GnRH antagonist, but emphasised that GnRH agonist should only be used in women with a low risk of OHSS. The GDG believed that the evidence for the efficacy of GnRH antagonists is not convincing enough to recommend their use in place of GnRH agonists, but acknowledged that their use is important in women who are at a higher risk of OHSS. The GDG believed the current recommendations and text described the potential benefits and harms of each protocol. The order of recommendations has been swapped to emphasise to clinicians that GnRH agonists should only be used when there is a low risk of OHSS.
246.	Merck Sharp & Dohme UK Ltd	9	NICE guideline	38	4	The current guideline does not mention the potential for reduced gonadotrophin utilisation that is associated with use of GnRHantagonist protocols, compared with the long GnRH agonist protocols.	Thank you for your comments. The GDG looked in detail at the updated version of the Al-Inany Cochrane review (Al-Inany, 2011) in order to make their recommendations. However, the Cochrane

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						A Cochrane review of GnRH antagonist use for assisted reproduction[1] found that more gonadotrophin was used in long agonist protocols compared to antagonist protocols. On average, 300 IU more rFSH was required in the long agonist protocol[1]. We would suggest that, as part of section 1.12.3 of the guideline ("Controlled ovarian stimulation in IVF"), the evidence to demonstrate that, compared to long GnRH agonist protocols, GnRH antagonist protocols require less exogenous gonadotropin utilisation,is considered. <u>Reference</u> 1) Al-Inany H and Aboulghar M. GnRH antagonist in assisted reproduction: a Cochrane review. Hum Reprod. 2002;17:874–885.	review did not explicitly compare the efficacy of different doses of gonadotrophins. However the GDG did not compare the amount of gonadotrophin used in different GnRH agonist and GnRH antagonist protocols and therefore could not makes a recommendation for practice.
247.	Merck Sharp & Dohme UK Ltd	10	NICE Guideline	38	6	We would suggest that the phrase "urinary and recombinant gonadotrophins" in recommendation 1.12.3.2 is updated so that the types of gonadotrophins are listed in alphabetical order (i.e. "recombinant and urinary gonadotrophins").	Thank you for your comment. Although the GDG recommended either urinary or recombinant gonadotrophins could be used, the GDG decided to list urinary products first to reflect that they are the standard product currently in use in UK practice.
248.	Merck Sharp & Dohme UK Ltd	11	NICE Guideline	38	10	Recommendation 1.12.3.3 (under the section "Controlled ovarian stimulation in IVF") states "When using gonadotrophins for ovarian stimulation in IVF treatment: use an individualised starting dose of follicle-stimulating hormone, based on factors that predict success…".	Thank you for your comments. The GDG discussed this and did not agree with your proposal. As you highlighted, the GDG recommended that the lowest effective dose be used in ovarian stimulation, and they recommended a maximum dose of FSH. However, the GDG believed from their clinical

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						We would suggest that the starting dose of gonadotrophins for ovarian stimulation does not need to be individualised and, importantly, the lowest effective dose and duration of use should be used. This is in line with recommendation 1.17.2.4, which states "Limit drugs used for controlled ovarian stimulation in IVF treatment to the lowest effective dose and duration of use."	experience that the lowest effective dose in older women is higher than the lowest effective dose in younger women. They therefore believe that starting doses of gonadotrophins should be individualised, which is reflected in their recommendations.
249.	Merck Sharp & Dohme UK Ltd	15	NICE guideline	38	20	In line with comment 14 above, we would suggest that the evidence for use of a GnRH agonist trigger among women at risk of OHSS when a freeze-all approach being utilised, and when used with modified luteal support, is considered. This may impact recommendation 1.12.3.5 because there is less concern with triggering ovulation in the situations described in the guideline (page 38, lines 22 and 23) if a GnRH agonist trigger is used.	Thank you for your comments. The GDG was aware that the evidence suggests GnRH agonist results in fewer cases of OHSS, but also less pregnancies. The evidence base is not large enough to make a recommendation for their use. The procedures in the IVF procedures chapter are described with the aim of fresh embryo transfer. As outlined on p316 of the full guideline, there is insufficient evidence to support routine cryopreservation in cases with a high risk of OHSS. The GDG therefore did not make recommendations on the use of triggers when the cryopreservation of all embryos is planned.
250.	Merck Sharp & Dohme UK Ltd	14	NICE guideline	39	3	Section 1.12.4 of the updated guideline, regarding triggering ovulation in IVF, does not currently mention the use of GnRH agonists to trigger ovulation in women receiving GnRH antagonist protocols who are at high risk of OHSS. The use of a GnRH agonist trigger is discussed in the full guideline (pages 317-322) however, the distinction between its use in fresh and frozen cycles is not made.	Thank you for your comments. The GDG were aware that the evidence suggests GnRH agonist results in fewer cases of OHSS, but also less pregnancies. The evidence base is not large enough to make a recommendation for their use. The procedures in the IVF procedures chapter are described with the aim of fresh embryo

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						There is evidence to suggest that using a GnRH agonist trigger with a freeze-all approach would provide similar pregnancy and live birth rates to use of an hCG trigger, with the benefit of reduced occurrence of OHSS[1-7]. In addition, a recent meta-analysis of randomised controlled trials in which GnRH agonist trigger was used alongside luteal phase support[2] found no significant difference in delivery rates between GnRH agonist and hCG triggering. It is suggested that modified luteal support will improve outcomes with use of a GnRH agonist trigger, however it is acknowledged that the optimal strategy has yet to be idenitified. We would suggest that the available evidence is considered regarding use of a GnRH agonist trigger during GnRH antagonist protocols for women at risk of OHSS when a freeze-all approach being utilised[1-7], and when used with modified luteal support[2]. References 1. Papanikolaou EG, Humaidan P, Polyzos N et al. New algorithm for OHSS prevention. Repro Biol Endocrinol. 2011;9:147. Available at http://www.rbej.com/content/9/1/147 2. Humaidan P, Kol S, Papanikolaou EG. GnRH agonist for triggering of finaloocyte maturation: time for a changeof practice? Hum Reprod Update. 2011;0:1–15. doi:10.1093/humupd/dmr008	transfer. As outlined on in the full guideline, there is insufficient evidence to support routine cryopreservation in cases with a high risk of OHSS. The GDG therefore did not make any recommendations on the use of triggers when the cryopreservation of all embryos is planned.

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						3. Griesinger G, Schultz L, Bauer T et al. Ovarian hyperstimulation syndrome prevention by gonadotropin-releasing hormone agonist triggering of final oocyte maturation in a gonadotropin-releasing hormone antagonist protocol in combination with a ''freeze-all'' strategy: a prospective multicentric study. Fertil Steril. 2011;95:2029-2033. 4. Eldar-Geva T, Zylber-Haran E, Babayof R, et al. Similar outcome for cryopreserved embryotransfer following GnRH-antagonist/GnRH-agonist, GnRH-antagonist/HCG orlong protocol ovarian stimulation. Reprod Biomed Online 2007;14:148–154. 5. Griesinger G, Kolibianakis EM, Papanikolaou EG, et al. Triggering of final oocytematuration with gonadotropin-releasing hormone agonist or human chorionicgonadotropin. Live birth after frozen-thawed embryo replacement cycles. FertilSteril 2007;88:616–621. 6. Manzanares MA, Gomez-Palomares JL, Ricciarelli E, et al. Triggeringovulation with gonadotropin-releasing hormone agonist in in vitro fertilization patients with polycystic ovaries does not cause ovarian hyperstimulationsyndrome despite very high estradiol levels. Fertil Steril 2010;93:1215–1219.	

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						7. Griesinger G, von Otte S, Schroer A et al. Elective cryopreservationof all pronuclear oocytes after GnRH agonisttriggering of final oocyte maturation in patients atrisk of developing OHSS: a prospective, observationalproof-of-concept study. Hum Reprod 2007;22:1348–52.	
251.	Merck Sharp & Dohme UK Ltd	16	NICE guideline	39	4	We would suggest that the phrase "urinary and recombinant gonadotrophins" in recommendation 1.12.4.1 is updated so that the types of gonadotrophins are listed in alphabetical order (i.e. "recombinant and urinary gonadotrophins").	Thank you for your comment. Although the GDG recommended either urinary or recombinant gonadotrophins could be used, the GDG decided to list urinary products first to reflect that they are the standard product currently in use in UK practice. Recombinant products are also recommended as the future of urinary products in terms of costing and availability is not clear. This is explained in chapter 15 of the full guideline text.
252.	Merck Sharp & Dohme UK Ltd	17	NICE guideline	41	1	Section 1.12.6.6 states: "For women aged under 37 years: • In the first full IVF cycle use single embryo transfer. • In the second full IVF cycle use single embryo transfer if one or more top-quality embryos are available. Consider using two embryos if no top-quality embryos are available. • In the third full IVF cycle transfer no more than two embryos."	Thank you for your comments and taking the time to provide references. The GDG was aware that fertility falls with age. The GDG did consider age groupings of<35y and a 36 - 37y. However, after discussion it was concluded that there was little or no difference in the management of these groups. Therefore, the age groupings were combined. The GDG is aware that DET transfer results in higher live birth rates and that the

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						We would suggest that the evidence for changing this recommendation to apply to women aged <35 years only is considered. It seems that the age group <35 years was not considered separately in the GDG consensus survey (see full NICE guideline, pages 344 – 345). With the current recommendation, women aged 35 and 36 years in their 1st IVF cycle will only be considered for single embryo transfer (SET). Even if these women do not have a top-quality embyo available for transfer they will not be considered for double embryo transfer (DET). However, there is evidence to suggest that women aged 35-36 years have lower live birth rates with SET compared to women aged <35 years. Table 15.21 on page 334-335 of the full NICE guideline presents data reported by Luke et al., 2010[1] and shows significantly higher live birth rates with DET compared to SET in all age groups. Women aged 30-34 were assessed separately in this study and, although statistics are not presented, these women had a higher rate of live births following SET compared to women aged 35-39 years (46.2% vs. 39.9%, respectively). In women aged 35-39 years, the live birth rate following DET increased to 47.8% compared to 39.9% with SET. Table 15.24 on page 336 of the full NICE guideline presents data from Scottish IVF clinics[2]. The live birth rate with SET in women aged 32 years was 50.4%, compared with 40.5% in women aged 36 years. The term live birth rates in these two age groups were 45.4%	recommendation will lead to a fall in pregnancy rates in the first cycle. However, DET is also associated with higher multiple birth rates than SET and that multiple pregnancy is the main risk facing a mother and child. It was for this reason that the GDG pre-specified the primary outcome for the guideline is live full-term singleton birth. For these reasons the GDG recommended that SET should be used in the first of three full IVF cycles in order to maximise the chance of a live full-term singleton birth. Therefore, in this instance no change was made to the recommendation.

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						and 36.4%, respectively. Although statistical analysis between age groups is not presented, these data suggest that there is a difference between ages 32 and 36 years in terms of live births following SET. Women aged 36 years were significantly more likely to have a live birth following SET than DET. This is in line with the American Society for Reproductive Medicine guidelines[3], which state that "Elective SET is most appropriate for those with a good prognosis:age <35 years…". These guidelines also recommend that women aged 35-40 years are considered for SET but only in cases where a top-quality blastocyst stage embryo is available for transfer. <u>References</u> 1. Luke,B., Brown,M.B., Grainger,D.A., et al. Society for Assisted Reproductive Technology Writing Group. Practice patterns and outcomes with the use of single embryo transfer in the United States. Fertil Steril. 2010;93:490-498. 2. Scotland,G. McLernon,D. Kurinczuk,J. et al. Minimising twins in in vitro fertilisation: a modelling study assessing the costs, consequences and cost–utility of elective single versus double embryo transfer over a 20-year time horizon. BJOG. 2011;118:1073–1083. 3. Practice Committee of the Society for Assisted Reproductive Technology and Practice	

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						Committee of the American Society for Reproductive Medicine. Elective single-embryo transfer. Fertil Steril. 2012;97:835–42.	
253.	Merck Sharp & Dohme UK Ltd	18	NICE guideline	50	17	Under the section "Long-term adverse outcome and safety of IVF", recommendation 1.17.2.4 states: "Limit drugs used for controlled ovarian stimulation in IVF treatment to the lowest effective dose and duration of use." We would suggest that, in line with this recommendation, consideration is given to the reduced utilisation of gonadotrophins with use of GnRH antagonist protocols, as discussed in comment 9. In addition, we suggest that recommendation 1.17.2.4 is linked to recommendation 1.12.3.3, which specifically discusses gonadotrophin use for controlled ovarian stimulation. We would propose that it would be appropriate to consider using the lowest effective dose and duration of use as part of recommendation 1.12.3.3.	Thank you for your comments. As you highlight, the relevant recommendation in the full guideline states: *'Limit the use of ovulation induction or ovarian stimulation agents to the lowest effective dose and duration of use.'* The GDG did not agree that this recommendation needed to be repeated in the IVF procedures recommendations. As a general principle, recommendations in NICE Clinical Guidelines are not repeated – they only need to be stated once.
254.	Merck Sharp & Dohme UK Ltd	12	Full Guideline	320	2	The full guideline states on page 320, line 2, "There were significantly more miscarriages per woman with the use of GnRH agonist compared with hCG", however this is contradicted by the data presented in Table 15.16 on page 318, which is intended to support this statement. Table 15.16 states that 6% and 25% women who received a GnRH agonist trigger and 12% and 50% who received hCG experienced pregnancy loss (RR 0.5 (0.1 – 4.7); 0.5 (0.1 – 3.6)). Although not statistically significant these data suggest that fewer women receiving a	Thank you for your comments. This text and the corresponding evidence to recommendations section text have now been amended. Thank you for this comment. This was a referencing error. The reference should read 'Papanikolaou et al., 2011' rather than 'Papanikolaou et al., 2011b'. The full reference is that listed under Papanikolaou et al., 2011:

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						GnRH agonist trigger experienced pregnancy loss compared to those receiving hCG. In addition, the data in Table 15.16 regarding pregnancy loss with GnRH agonists vs hCG trigger (page 318) is referenced to Papanikolaou et al., 2011b. However, we were unable to find the full reference for this in the reference list on pages 479-514, and we were unable to locate the data presented in Table 15.16 regarding pregnancy loss in the reference Papanikolaou et al., 2011. Therefore we could not substantiate the information provided in Table 15.16 regarding pregnancy loss for GnRH agonists vs hCG for triggering ovualtion.	Papanikolaou,E.G., Verpoest,W., Fatemi,H., Tarlatzis,B., Devroey,P., Tournaye,H., A novel method of luteal supplementation with recombinant luteinizing hormone when a gonadotropin-releasing hormone agonist is used instead of human chorionic gonadotropin for ovulation triggering: a randomized prospective proof of concept study, Fertility and Sterility, 95, 1174-1177, 2011 The reference has been amended in the full guideline.
255.	Merck Sharp & Dohme UK Ltd	13	Full Guideline	320	41	The full guideline states "hCG also resulted in less cases of OHSS when compared withGnRH agonist", however this is contradicted by the data presented in Table 15.16 on page 319, which is intended to support this statement. Table 15.16 states that 0% women receiving a GnRH agonist trigger experienced OHSS compared to 3% women receiving hCG (RR 0.1 (0.0 – 0.8)). These data suggest significantly fewer cases of OHSS with use of a GnRH agonist trigger compared to hCG, which is also supported by the statement on lines 14-15 of page 320 "There were significantly more cases of OHSS with the use of hCG when compared with the use of GnRH agonist".	Thank you for your comments. The paragraph has now been amended to say: *'The evidence showed that hCG was associated with more live births and clinical pregnancies than GnRH agonist. Although the evidence showed that hCG resulted in more cases of OHSS when compared to GnRH agonist, the GDG acknowledged that the absolute number of cases was low. Based on the increased the number of clinical pregnancies and live births, the GDG recommended the use of hCG to trigger ovulation.'*
256.	Multiple Births Foundation	1	Full	General		We welcome the revised guideline and recommendations which will be of considerable help with the provision of effective treatment and commissioning of fertility services. We	Thank you for your comment.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						suggest that the final full document would benefit from a review for consistency and clarity (e.g. see following comments on IUI).	
257.	Multiple Births Foundation	2	Full	189	36	**Recommendations 111 and 112** We are pleased support the new recommendations about clomifene citrate. At the Multiple Births Foundation (MBF) we are aware through anecdotal feedback from women that, despite the recommendation in the 2004 guideline that remains unchanged, women who are prescribed clomifene citrate are not always monitored for the first cycle at the minimum when it is prescribed. We are also aware of women obtaining clomifiene from the internet and other sources outside the UK and using it without prior assessment, information about the risks and with no monitoring and cases which have resulted in high order multiple pregnancies. While we fully understand that it is outside the remit of NICE to control this we would ask you to consider how the importance of women understanding the risks of such unsupervised treatment might be emphasised in any supporting documents or other literature that accompanies the guideline. This would also help the other professional bodies and organisations seeking to address this problem.	Thank you for your comments You may wish to contact the NICE implementation team about supporting documents and other literature that will accompany this guideline.
258.	Multiple Births Foundation	4	Full	204	23	It could be more explicit in the Guideline Summary (page 13, section I.(12) bullet point 3) that the recommendations 115 and 116 for artificial insemination (intra cervical and intrauterine) are only recommended for a specifically defined group.	Thank you for your comment. We believe that if the pathway is followed that it is clear that this section relates to couples who are unable to have vaginal intercourse.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
259.	Multiple Births Foundation	5	Full	346	20	**Recommendation 157:** The MBF welcomes and supports the recommendation for the use of the NEQAS grading scheme for embryos. There is an urgent need for consistency in laboratory practice and information given to women and their partners about the quality of their embryos. It is also crucial to support the confidence of patients and practitioners with the implementation of the multiple births minimisation strategies in infertility clinics. **Recommendation 158:** We believe that the NICE guideline will play a significant part in the cultural change which are moving towards, but have not yet reached, for a single baby to be the aim of all fertility treatment and the indicator for the most successful and best outcome for the health of the mother and baby/babies. The MBF would like to see a greater emphasis on the aim of replacing a single embryo for all women as being the ultimate goal with IVF but that exceptions may be made on an individual basis based on female age, embryo number and quality and previous history. There is a growing body of evidence that Late Preterm Infants (babies born between 34 and 36.6 weeks gestation) have more problems such as respiratory distress, hypoglycaemia, jaundice and sepsis resulting in increased mortality and morbidity when compared with term infants. Later there is increased risk of neurodevelopmental delay, learning difficulties and school related problems (Engle 2007, Chyi 2008, Morse 2009,Peacock 2012). At least 50%	Thank you for your complimentary comments about the 2012 update of the Fertility Guideline and the references. The GDG has highlighted throughout the guideline that the primary outcome of IVF should be a live full-term singleton birth. The recommendations that have been outlined are designed to achieve this aim, and this includes use of single embryo transfer in many situations. The GDG was aware of on-going research extended culture and monozygotic twinning, and therefore have not made a research recommendation. Please note that the wording of the recommendations have been amended to clarify the use of single embryo transfer.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						of twins are born before 37 weeks gestation so will fall into this group. We suggest that this should be mentioned in the guideline as it is further evidence for the need to aim for term delivery of single babies. **Recommendations 158 and 162:** There is an emphasis on blastocyst transfer but as identified in the evidence there are concerns about possible risks with extended culture and monozygotic twinning. This is reflected in the Joint RCOG Document- Opinion Paper –Risks of IVF (Human Fertility 2012) We welcome the research recommendations but suggest that there is a specific recommendation to collect data on monozygotic twinning and more follow up studies of multiple birth children born as a result of blastocyst transfer.	
260.	National AIDS Trust (NAT)	1	Full	26-27	66-75	NAT welcomes new guidance relating to viral transmission. If finalised, it represents a crucial step forward in the rights and wellbeing of people living with HIV in the UK. There is now scientific consensus that effective HAART significantly reduces infectiousness and that in this circumstance, the risk of HIV transmission from unprotected heterosexual intercourse is negligible. This is affirmed in the latest guidance from the British HIV Association (BHIVA) on antiretroviral therapy for HIV-1 positive adults. Moreover, not all assisted reproduction techniques are widely available to people living with HIV across the UK, and in many cases will be prohibitively expensive.	Thank you for your comment

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						Sperm washing can also reduce the likelihood of pregnancy. Given these facts, it is important that guidance around fertility keeps pace with scientific knowledge, and gives people with HIV the best possible chance of natural conception while protecting their health and the health of their partner. We are satisfied that this new guidance strikes this balance correctly and appropriately, and urge NICE to maintain the proposed guidance as it stands.	
261.	National AIDS Trust (NAT)	2	Full	26	67	It would be useful to establish that this guidance (unprotected vaginal intercourse presents negligible risk in the event of an undetectable viral load, compliance with HAART, no other infection and during ovulation) is also applicable to unprotected vaginal intercourse where the woman is HIV positive	Thank you for your comments. The scope of the guideline was to examine the effectiveness of sperm washing, which is only relevant for a HIV positive male. In order to answer the question sperm washing was compared with viral transmission through unprotected sex and using pre exposure prophylaxis. The results of this review showed that if certain criteria were met that unprotected intercourse would be a suitable option if the male partner was HIV positive. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised.The scope did not cover areas related to transmission from women to men. Therefore, no review could be undertaken and no recommendations could be made.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
262.	National Infertility Awareness Campaign	1	Full	General		NIAC supports the move to help same-sex couples access fertility treatment, however further clarification is needed throughout the guideline on what services they can access and whether the criteria for accessing these services differs from the criteria of heterosexual couples.	Thank you for your comments. The guideline reflects the fact that there was a legal obligation that it addressed equality of access regardless of sexual orientation.
263.	National Infertility Awareness Campaign	2	Full	20	12	As it is currently worded, this section could be interpreted as a recommendation against the use of thawed sperm. This section may be misleading for those seeking donor sperm insemination, as donor sperm would not have been compared in fresh and frozen cycles due to the nature in which it is procured. (Donor sperm is always frozen to allow thorough screening and quarantine). Those seeking donor sperm cycles only have the option of frozen sperm. As it stands, this statement implies they may be better off seeking fresh alternatives, perhaps from unlicensed means. NIAC recommends the re-wording of this section to prevent patients from being misled.	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
264.	National Infertility Awareness Campaign	3	Full	23	38	This statement appears to conflict with the section on fast-tracking for patients with absolute infertility (Full, 32, 126). For example, what about cases where a patient finds out they are absolutely infertile after undergoing tests for something else such as endometriosis? Could that patient then be fast-tracked or would they need to go through the usual referral process and be subject to the same waiting times? This statement needs clarification in order to minimise the risk of misinterpretation.	Thank you for your comments. The intention of the GDG was very much that once a cause of the infertility was identified then there should be no further delays in the referral of the patient for definitive treatment as stated in the recommendation. We have added text to clarify this important point

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
265.	National Infertility Awareness Campaign	4	Full	23	39	The draft guideline states that for women in same-sex relationships, six self-funded AI cycles are the equivalent to a heterosexual couple failing to conceive after 12 months of unprotected vaginal intercourse. Given that these women will have to self-fund their AI treatment, before they become elgible for further clinical investigation, this seems grossly unfair. At the very least, NIAC recommends that the number of self-funded cycles is reduced to compensate for financial loss.	Thank you for your comments. However, the Scope makes it clear that the Guideline is for people who have a possible pathological problem (physical or psychological) to explain their infertility. Women in same sex relationships can only be considered to be possibly in that category and be considered to be 'infertile' if they have a known cause or a period of unsuccessful artificial insemination (AI). How that AI is provided and funded are outside the Scope of the Guideline. With respect to the specific issue of reducing the number of cycles, the GDG was of the view that they did not feel the figure should be reduced.
266.	National Infertility Awareness Campaign	5	Full	24	49	There is clear evidence to suggest age correlates closely with IVF success rates, however age should not be considered as the best indicator of ovarian response. Recent evidence suggests that AMH is a superior marker for predicting ovarian response (Nelson, S. and Flemming. R, *Prediction of Pregnancy*, 7th May 2010). This evidence should be reflected in the NICE guideline.	Thank you for your comment. This recommendation is that age should be used as an indicator of IVF success during initial consultation as it is rapid, reasonable accurate and cost free. Later recommendations outline further investigations that should be undertaken. The text within the chapter supports this sentiment.
267.	National Infertility Awareness Campaign	6	Full	24	50	This section suggests that antral follicle count alone would be an adequate predictor of ovarian response for IVF. There is data to suggest that AMH is a less variable predictor than AFC and FSH and should always be used, if necessary in conjunction with AFC and FSH. NIAC believes this should be a standard baseline test in all patients considering IVF to optimise success and reduce cancellation due to over or under response.	Thank you for your comments. The GDG did discuss the use of tests in isolation and combination. Based on the available evidence and their own clinical experience, the GDG concluded that it would be best if individual clinical judgement was used in deciding which combination of tests, if any, are required.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
268.	National Infertility Awareness Campaign	7	Full	26	64	Testing for Hepatitis B core anti-body should also be included in this statement to fit in line with recently updated HFEA guidelines.	Thank you for your comment. The GDG was aware of the new legislation for screening of HBV and have made the following statement within the evidence to recommendation text of the chapter: *"The GDG was aware of ongoing developments of the screening of HBV, specially the HFEA consultation on the serological testing for HBsAg and anti-HBc. The GDG was content that the recommendations made within this chapter are complimentary to new screening initiatives and would be adequately supportive to those found positive for hepatitis B."*
269.	National Infertility Awareness Campaign	8	Full	30	111	Some clinics show good results in stimulated IUI with gonadotrophins for unexplained infertility. This statement as it stands, places unnecessary cost on the health service and physical burden on the patient by pushing them towards IVF when IUI can offer a good chance of success. Studies in the draft 2012 NICE guideline mention clomifene citrate, letrozole and anastrozole, but do not mention IUI with gonadotrophins. NIAC recommends NICE collect further evidence on the use of gonadotrophis in stimulated IUI.	Thank you for your comments. IUI with and without gonadotrophins is discussed in chapter 12 of the full guideline However, the evidence in that chapter showed no difference in the number of live births when comparing IUI with or without gonadotrophin stimulation to expectant management. The GDG believed from their clinical experience that several cycles of IUI with stimulation would be required to match the live birth rates achieved by a single IVF cycle. Furthermore, IUI results in higher multiple birth rates as there is less control over the number of embryos produced with ovarian stimulation compared to a single embryo IVF transfer. For these reasons the Guideline

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							• Does not support the use of IUI routinely for the management of unexplained infertility • Recommends that women with unexplained infertility should be referred for IVF if they fail to conceive after a period of expectant management.
270.	National Infertility Awareness Campaign	11	Full	32	126	There is no clear definition of 'absolute infertility'. This may cause considerable confusion amongst health professionals and commissioners. The lack of a clear definition could be used by some commissioners as a means of restricting access.	Thank you for your comments. Several stakeholders commented that the term 'absolute infertility' was not meaningful or useful in clinical practice. <u>Updated recommendation</u> There was extensive debate and division of opinion within the GDG about whether a recommendation for the provision of IVF could be made for this age group both before and after stakeholder comments. The details of which are described in the full version of the guideline. It was concluded that the uncertainty around the HE model meant that any recommendation for this age-group would have to be based on clinical opinion. At the end of the meeting the GDG concluded that • that the current recommendation including the term 'absolute infertility' should be removed

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment

							• A new recommendation should be drafted based on
							  o ovarian reserve testing
							  o that there was a need for a recommendation highlighting the additional risks associated with pregnancy in women aged 40 to 42 years
							The final version of the reworded recommendation was agreed by the 8 out of 11 members of the GDG:
							In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled:
							• *they have never previously had IVF treatment*
							• *there is no evidence of low ovarian reserve*
							• *there has been a discussion of the additional implications of IVF and pregnancy at this age.*
							•

271.	National Infertility Awareness Campaign	12	Full	32	130	Clarification is needed on the term 'take into account the outcome'. As it currently stands, the statement is not clear on how this should effect what the patient is offered.	Thank you for your comments. After discussion we have split and reworded the recommendation for greater clarity to:

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							• *"Any previous full IVF cycle, whether self- or NHS-funded, should count towards the total of 3 cycles that should be offered by the NHS."* • *"Take into account the outcome of previous IVF treatment when assessing the likely effectiveness and safety of any further IVF treatment."*
272.	National Infertility Awareness Campaign	13	Full	33	136	The precise meaning of this statement is unclear and susceptible to misinterpretation. As it currently stands it could mean a) do not offer agonist in those with risk of ovarian hyperstimulation syndrome; or b) In women that have low risk of ovarian hyperstimulation syndrome only offer agonist. NIAC recommends the re-wording of this statement to take into account individual clinic procedures and patients' previous response to either agonist or antagonist.	Thank you for your comment. The relevant recommendation means that GnRH agonists should only be used in women with a low risk of OHSS. It does not preclude the use of GnRH antagonist in these women.
273.	National Infertility Awareness Campaign	14	Full	34	157	Evaluation of embryo quality at both blastocyst and cleavage stages is not always possible in some cases. For example, if a patient produces only three embryos of medium quality it would be inappropriate management to go beyond 3 days of culture as the embryos may likely arrest. NIAC suggests rewording to "Culture embryos to blastocyst where possible and clinically appropriate".	Thank you for your comments. 1) The GDG has recommended that the recently published Association of Clinical Embryologists (ACE/UK) National External Quality Assessment Service (NEQAS) for Reproductive Science embryo and Blastocyst Grading schematic should be used to ensure consistency in the assessment of embryo quality. 2) It was not the intention of the GDG to suggest that all embryos should be cultured to blastocyst stage.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							Based on this comment and other received the wording of the recommendation has been amended for clarity.
274.	National Infertility Awareness Campaign	15	Full	35	159	NIAC supports measures that reduce the risk of multiple pregnancies, however, we feel single embryo transfer should not be recommended for every woman aged under 37 who is undergoing their first cycle of IVF treatment. If the number of embryos are all of low quality this will have a detrimental effect on the patient's chances of success regardless of age. NIAC therefore recommends that two embryos are considered for transfer in instances where all available embryos are of low quality. Similarly in cases where the patient is over 37 years old, NIAC recommends the consideration of three embryo transfers for their third cycle of treatment. Patients within this age bracket already have a reduced chance of success, therefore three embryo transfers should at least be considered as a means of increasing the chance of a successful pregnancy. This should apply in particular to women aged 40-42 who are undergoing IVF treatment. Again, special consideration should be given in instances where all available embryos are of poor quality. Women in this age bracket should of course be informed of the risks associated with double and triple embryo transfers.	Thank you for your comments. The GDG has outlined criteria based on people receiving 3 full cycles of IVF. Based on the available evidence on effectiveness and safety, it is the conclusion of the GDG that using a single embryo in the first full cycle optimises the chance of a live full-term singleton birth. If this fails then the next 2 full cycles allows more than one embryo to be transferred dependent on embryo quality. The GDG was tasked with examining the effectiveness and safety of treatment for the individual woman. Based on the evidence and their clinical experience the GDG concluded that triple embryo transfer in over 40s would put a woman (and any resulting infants) at undue risk of complications and mortality. For example, evidence from Sweden shows the odds of peri/neonatal mortality is 2.42 greater when using DET compared to the general population. For these reasons, for women age 40-42y the recommendation is to consider double embryo transfer (and not triple embryo transfer). Therefore, in this instance no change will be made to the recommendation.
275.	National Infertility Awareness Campaign	16	Full	35	162	"Do not use 2 top quality blastocysts for transfer." In patients under 37 this may be a valid	Thank you for your comment.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						statement, however, In the case of two previous failed cycles and patient nearing or over 40, two top quality blastocysts may be the patients best chance of achieving a healthy singleton. NIAC believes that following this guideline as it stands would result in a decline in pregnancy rates in older patients. NIAC suggestsattaching an age guideline to this statement that also takes into account the number of cycles a patient has had. For example, two top-quality blastocysts could be considered for transfer in the event of two failed cycles (in a patient that is aged 37 or over).	Based on the available data the GDG concluded that transferring two top quality blastocyst embryos significantly increased a woman's chances of a multiple pregnancy compared to a single blastocyst or two lower quality embryos. Given that multiple pregnancies are the greatest risk to the health to a mother and unborn children, the GDG concluded that the two blastocysts should not be transferred. Therefore, in this instance no change will be made to the recommendation. However, the wording has been change to improve clarity: *"Where a top-quality blastocyst is available single embryo transfer should be used."*
276.	National Infertility Awareness Campaign	17	Full	39	196	NIAC welcomes the move to open up fertility services for patients preparing for cancer treatment. However the removal of a lower age limit for cryopreservation raises the issue of child protection. Clinics could potentially get in trouble for providing pornographic material to under 18s. Clear protocols need to be agreed to protect clinics and health professionals from criticism and prosecution.	Thank you for your comments. We agree with your suggestion, and would like to highlight the child protection text within the semen cryopreservation subsection of the chapter. We have also subsequently added additional text to the evidence to recommendations to highlight actions and legislation for the protection of female and males less than 18 years of age.
277.	National Infertility Awareness Campaign	18	Full	39	203	According to the draft guideline, the Guideline Development Group acknowledged the fact that there was a lack of evidence fouvouring vitrification techniques. It also states the following: '*the limited evidence that is available for vitrification shows a benefit and the GDG*	Thank you for your comments. We agree that the originally wording could be misunderstood. The recommendation to offer vitrification was based on evidence showing beneficial post thaw survival rates and

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						were confident that future research would build on early studies to demonstrate the vaibility of its use.' (Page 389). NIAC believes that it would be inappropriate to make a recommendation based on evidence, which may or may not emerge in the future. We would recommend conducting further studies in this area before stating a preference for or against vitrification techniques. NIAC suggests that the original statement is re-worded to reflect the lack of evidence in favour of vitrification techniques. Perhaps along the lines of: *'In cryopreservation of oocytes and embryos, consider the use of vitrification instead of controlled-rate freezing if the necessary equipment and expertise is available'.*	reduced abnormal morphology. The GDG did indicate that new evidence was expected, but made their recommendation based on the evidence they had. We have amended the text within the chapter to provide greater clarity.
278.	National Infertility Awareness Campaign	19	Full	360	168	The draft NICE guideline states that: '*the evidence does not support continuing any form of treatment for luteal phase support beyond 8 weeks'.* Aside from the fact that 8 weeks is commonly cited, there appears to be a lack of evidence to support this claim. Where there is evidence, this appears to be of low quality – this is acknowledged in the draft guideline on page 360. According to the draft guideline, most of the evidence on luteal phase treatments is over twenty years old. Given the limitations of the evidence base, NIAC recommends the re-wording of line 168.	Thank you for your comments. There is some evidence that the use of luteal phase support may be beneficial. However, this evidence is not extensive. As explained in the full guideline, the GDG discussed how offering luteal phase support for an *'extended period of time'* (more than 8 weeks) did not appear to result in more clinical benefits, than a shorter period of luteal phase support. In deciding on the exact recommendation, the GDG argued that it is biologically plausible for luteal phase support to be effective for up to 8 weeks after embryo transfer, after which time the pregnancy is 'self-supporting'. In the light of that the GDG recommended that luteal phase support is often offered for up to 8 weeks after embryo transfer. Based on the evidence of possible benefit, lack of harm and the biological plausibility of the intervention,

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							the GDG recommended that women should be informed that there is no evidence for continuing luteal phase support beyond 8 weeks.
279.	National LGB&T Partnership	1	Full	75	4 - 9	We welcome and support the offer of help with conception being equal for women in same sex or opposite sex relationships, and consequently we strongly support recommendation 39 on pg 77.	Thank you for your comment.
280.	National LGB&T Partnership	2	Full	75	9-10	Couples should not be described as lesbian or gay but as (male or female) opposite sex/same sex. Using terms such as gay couple, lesbian couple or heterosexual/straight couple exclude bisexual people who may be in same or opposite sex relationships.	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
281.	National LGB&T Partnership	3	Full	75	9-10	If male same sex couples are excluded from the Scope of this guidance, their needs must be met considered as quickly as possible in future guidance.	Thank you for this comment. The Scope makes it clear that the Guideline is intended for people who have a possible pathological problem (physical or psychological) to explain their infertility. A man in a same sex relationship who has failed to achieve a pregnancy after an appropriate period of time (12 months with vaginal intercourse or 6 cycles of Artificial Insemination) would be considered to be 'infertile' and he and the surrogate partner would be eligible to be referred for 'further clinical assessment and possible treatment'. We have amended the text to make this clearer.
282.	NHS Direct	1	Full			NHS Direct welcome the update and have no comments on its content as part of the consultation process.	Thank you for your comment.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
283.	NHS Oxfordshire	11	Full		77	Recommendation 37 states that healthcare professionals should define infertility pragmatically. We believe this too be rather loose and would like an addition to this recommendation so that it states; "Healthcare professionals should define infertility pragmatically as the period of time people have been trying to conceive without success after which formal investigation is justified *but should be aware of the potential for harm including overtreatment in initiating investigation too early,"*	Thank you for your comments. We have removed the word 'pragmatically' and replaced it with the phrase 'in practice'. We think this is more precise and clear. The GDG did not add your additional phrase 'but should be aware of the potential for harm including overtreatment in initiating investigation too early'. The GDG did not review any evidence that supported this statement.
284.	NHS Oxfordshire	12	Full		77	Recommendations 37; remove "possible treatment" as this suggests secondary care referral.	Thank you for your comment. The GDG has discussed this wording and do not believe it suggests secondary care referral. Therefore, no change will be made.
285.	NHS Oxfordshire	13	Full		77	Split recommendations 37 and 38 so that primary care advice and clinical inquiry/investigation is separate from offering secondary care investigation and the possible implementation of treatment. This is to prevent overtreatment at an early stage (see previous comments regarding psychological problems) and to make the best use of NHS resources. We believe that primary care clinical enquiry and advice and secondary care investigations are not the same thing. We would thus suggests; Recommendation 37 to read as above in box 11. Recommendation 38*"A woman under the age of 35 who has not conceived after 1 year of unprotected vaginal intercourse, in the absence of any known cause of infertility, should be*	Thank you for your comments. The GDG considered your suggestions and decided to leave the recommendations unchanged for two reasons: • It acknowledged that some areas have excellent models with a clear distinction and effective implementation of the roles of primary and secondary care providers, However, they also recognised that many areas in the country fell below that standard and it was concerned that if a recommendation was made concerning the assessment that should be provided in primary care

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						offered clinical assessment and expectant management in primary care" New recommendation "*A woman under the age of 36 who has not conceived after 2 years of unprotected vaginal intercourse and at least 1 year of expectant managment, in the absence of any known cause of infertility, should be offered a specialist consultation and investigation"*	before people were referred for specialist evaluation it would not be implemented and people would suffer delays in receiving appropriate care – a problem that the guideline is trying to overcome. • Service provision is best worked out at a local level depending on the resources available.
286.	NHS Oxfordshire	14	Full		122	Recommendation 71" If couples who meet all the criteria in recommendation 67 still perceive an unacceptable risk of HIV transmission after discussion with their HIV specialist, consider sperm washing". We disagree and think this recommendation should be removed. We think this recommendation is illogical bearing in mind the evidence quoted within the guideline on pages 117 and following. We also note that it seems to go against the guideline development group (GDG) statements that; "sperm washing only reduced viral load rather than eliminating it, so there would be little or no added benefit "(lines 25-27 page 120) and that; the option of unprotected vaginal intercourse was more cost-effective citing the high cost of sperm washing and the trade off made with lower birth rates (lines 1-3 page 121). No evidence was produced to suggest that the psychological outcomes for the couple or the rate of healthy full-term babies would be improved by considering sperm washing for a perceived risk in a group where sero-conversion of the female par tner or baby has not been seen, as described in the evidence review considered by the GDG.	Thank you for your comments. The recommendation states that couples should be advised that if the male partner meets certain criteria that unprotected intercourse can be considered. However, it would be unethical to force couples to accept this treatment option and sperm washing is an alternative to this. In addition, the GDG did not feel the strength of the evidence was good enough for the complete removal of sperm washing as an alternative.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
287.	NHS Oxfordshire	15	Full		170	Regarding WHO Group II ovulation disorders. Recommendation 93 states that women with a BMI over 29 should be advised to lose weight and informed that this alone may restore ovulation. Improve their response to ovulation induction agents and have a positive impact on pregnancy outcomes. We suggest that this recommendation be strengthened to state that not only should women be advised to lose weight but that they should be referred to weight loss programmes or other active management. The evidence suggests weight loss following a weight-loss programmes is likely to be greater than advice alone.	Thank you for your comments. We have added a cross-reference in this recommendation to recommendation 27, which states that women should be informed that participating in a group programme involving exercise and dietary advice leads to more pregnancies than weight loss advice alone.
288.	NHS Oxfordshire	16	Full		189	Recommendation 114 should be amended from "Offer IVF treatment to women with unexplained infertility who have not conceived after 2 years (including up to 1 year before investigation) of regular unprotected sexual intercourse" to "Offer referral for investigations which may lead to IVF treatment to couples with unexplained infertility who have not conceived after 2 years including at least 1 year of expectant management and regular unprotected sexual intercourse". This will more clearly define a pathway which might proceed from secondary care investigations to a tertiary care referral for IVF and does not imply that IVF will be offered.	Thank you for your comments. The GDG did not agree with your suggested wording. The flow of the recommendations through the guideline chapters, as summarised in the care pathways/algorithms, outline the investigations that have to be done prior to IVF treatment to determine the cause of infertility. The GDG did not agree that further investigations were necessary before IVF treatment is offered to these women. All relevant investigations should be undertaken before people are considered for IVF
289.	NHS Oxfordshire	17	Full		204	Recommendations 115 and 117 replace the wording "before IVF will be considered" with "before referral for consideration of IVF".	Thank you for your comment. The GDG has reviewed the wording of the recommendations, but do not believe it needs to be changed.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
290.	NHS Oxfordshire	18	Full		214	Recommendation 120 "Inform people that the overall chance of a live birth following IVF treatment falls as the number of unsuccessful cycles increases" Change to insert a reference to the table 13.3 or state that the rate of success falls markedly after 3 cycles.	Thank you for your comments. As the text prior to the recommendation explains, the evidence for the recommendation comes from two sources - Tables 13.3 Nelson and Lawlor, 2011) and 13.4 (Roberts et al, 2010). Both show that there are lower chances of success for IVF with failed prior cycles compared to the first attempt. The Nelson and Lawlor data (Table 13.3) whilst showing lower success rates with increasing number of prior failed attempts, does not demonstrate a straightforward inverse relationship between success and number of failed prior cycles. Thus, the multivariate OR for a live birth with IVF is 0.72 with 1 failure, 0.70 with 2 failures. 0.77 with 3 failures. It falls to 0.51 with 4 failures but this rises to 0.68 for 5 or more failures. The Roberts et al data (Table 13.4) shows a more consistent fall in IVF success rates with prior failures. Thus, the unadjusted OR for IVF success compared to the first cycle is 0.81 with the 2nd cycle, 0.78 with the 3rd, 0.73 with the 4th, 0.77 with the 5th and 0.66 with the 6th. Overall, the GDG felt that these two sets data support the statement that *'the overall chance of a live birth following IVF falls as the number of unsuccessful cycles increases'* (as stated in the recommendation). They did not feel there was convincing evidence that it fell 'markedly' after three cycles. The Nelson and Lawlor data suggested that is the case for the 4th cycle but it was higher in the group that had

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							5+ prior cycles, and the Roberts et al data suggested a more stepwise, not precipitate fall in success. Thus, whilst we have amended the text to make the justification for the recommendation clearer we have not changed the recommendation.
291.	NHS Oxfordshire	20	Full		254	The implication of Recommendation 125 "Inform people that normally a full cycle of IVF treatment, with or without intracytoplasmic sperm injection, should comprise one episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s)" is that an incomplete cycle, whether due to patient choice not to proceed or to the lack of production of a viable embryo, does not count as a cycle. Given that the majority of the cost to the NHS and the physical impact on the patient is up to and including harvesting this would appear to permit multiple incomplete cycles. We would like to see more guidance, in this section, to clinicians as to when the number of incomplete cycles contributes to a loss of effectiveness. It is also of concern to NHS commissioners who may be asked to pay for several rounds of incomplete treatment.	Thank you for your comments. We have added a new recommendation which clarifies this point:
292.	NHS Oxfordshire	21	Full		255	Recommendation 128 "In women aged 40 to 42 years, who have not had IVF treatment and where there is no chance of pregnancy with expectant management (absolute infertility) and where IVF is the only effective treatment, offer one full treatment cycle of IVF, with or without intracytoplasmic sperm injection". We have two comments on this recommendation. Cost effectiveness ratio used	Thank you for your comments. **Cost effectiveness ratio used** We agree with your argument and now the Guideline only uses the higher WTP threshold of £30,000 for women of all ages. **The definition of absolute infertility**

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						It does not seem reasonable to us to use the lower Willingness to Pay per QALY of £20,000 (which we see as a reasonable reflection of current NHS cost-effectiveness thresholds as they have developed with NICE) for younger women but to increase this threshold for the women aged 40 to 42 years. Since this guideline is including cost-effectiveness and not only clinical effectiveness we can see no justification for using different limits. It would not be acceptable for commissioners to use the higher willingness to pay threshold for all women so we cannot endorse extending the NICE recommended age limit. The definition of absolute infertility It should be made explicit that this does not include "unexplained fertility"; i.e. that "absolute infertility" is a diagnosis of inclusion, where a reason for infertility is present.	Several stakeholders commented that the term 'absolute infertility' was not meaningful or useful in clinical practice. Updated recommendation There was extensive debate and division of opinion within the GDG about whether a recommendation for the provision of IVF could be made for this age group both before and after stakeholder comments. The details of which are described in the full version of the guideline. It was concluded that the uncertainty around the HE model meant that any recommendation for this age-group would have to be based on clinical opinion. At the end of the meeting the GDG concluded that • that the current recommendation including the term 'absolute infertility' should be removed • A new recommendation should be drafted based on o ovarian reserve testing o that there was a need for a recommendation highlighting the additional risks associated with pregnancy in women aged 40 to 42 years

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							The final version of the reworded recommendation was agreed by the 8 out of 11 members of the GDG: *In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled:* • *they have never previously had IVF treatment* • *there is no evidence of low ovarian reserve* • *there has been a discussion of the additional implications of IVF and pregnancy at this age.*
293.	NHS Oxfordshire	22	Full		255	Recommendation 130 "Take into account the outcome of previous IVF treatment, whether self funded or NHS funded, when considering IVF treatment." We do not find this a helpful statement. Is it suggesting that previous private treatment should not be a reason for excluding women from NHS funding for IVF or is it a reference to the decreased likelihood of a full-term, healthy, singleton birth with an increased number of IVF cycles, whether full or interrupted.	Thank you for your comments. We have added two new recommendations which clarify these points: • "Any previous full IVF cycle, whether self- or NHS-funded, should count towards the total of 3 cycles that should be offered by the NHS." • "Take into account the outcome of previous IVF treatment when assessing the likely effectiveness and safety of any further IVF treatment."
294.	NHS Oxfordshire	23	Full		256	Chapter 15: Procedures used during IVF treatment – We have no comments to make on this chapter	Thank you for your comment.
295.	NHS Oxfordshire	24	Full		363	Chapter 16: Intracytoplasmic sperm injection – We have no comments on this chapter	Thank you for your comment.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
296.	NHS Oxfordshire	25	Full		369	Chapter 17 Donor insemination – We have no comments on this chapter.	Thank you for your comment.
297.	NHS Oxfordshire	26	Full		373	Chapter 18 Oocyte donation – We have no comments on this chapter	Thank you for your comment.
298.	NHS Oxfordshire	27	Full		380	Chapter 19 People with cancer who wish to preserve fertility – This chapter needs to be renamed because the information, evidence and advice includes patients who are receiving treatment with radiotherapy and/or chemotherapy which may impair fertility but not necessarily for cancer. We have no comments on the content of the chapter or the recommendations which reflect the evidence reviewed in Oxfordshire.	Thank you for your comment. The scope of this guideline was to only make specific recommendations for cancer patients. We have, however, added text (below) to make sure that the guideline is explicit on the context of the recommendation the GDG made but does not to preclude their use for other patient groups. *"The scope of this guideline states that recommendations are to be outlined for people undergoing cancer treatment who wish preserve their fertility. The interpretation of the evidence was based on this and recommendations have been written specifically for this population. No recommendations are made for other groups who may prematurely lose their fertility. However, the GDG highlighted that the fact recommendations were not made for other groups should not be used as a justification for not funding cryopreservation in these groups and that the recommendations made in the guideline could be extrapolated to other population who may be at risk of losing their fertility due to treatment."*
299.	NHS Oxfordshire	29	Full		391	Recommendation 199 We would welcome an additional recommendation, or addition to recommendation 199 that cryopreservation of ovarian or testicular tissue should not be offered.	Thank you for your comment. The evidence available for the cryopreservation of ovarian tissue was limited. The GDG felt that it did not show any

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							significant benefit or disadvantage. Therefore, they could not make recommendation. Testicular tissue was not considered within this review and therefore the GDG was unable to make any recommendations about its use. The GDG has highlighted, within the research recommendations, that more work is needed on these areas before guidance is offered.
300.	NHS Oxfordshire	30	Full		392	Chapter 20 Long term safety of assisted reproductive technologies in women with infertility and their children. – We have no comments on this chapter.	Thank you for your comment
301.	NHS Oxfordshire	1	Full	general		We recognise that NICE is not contracted to have regard to the affordability of its clinical guidance however this has to be a consideration for commissioning organisations who have a legal obligation to remain within the financial constraints imposed upon them. The use of health economic evidence within the guideline is helpful. We would encourage a level of cost-effectiveness at no more than £20,000 per QALY. Using a value of £30,000 per QALY is likely to increase the numbers eligible for treatment and thus reduces the affordability for commissioners.	Thank you for your comments. The use of a willingness to pay threshold as an aid to decision making does, albeit imperfectly, have regard to affordability. The rationale and justification for the use of the £30,000 threshold is well argued in the guideline. However, in practice we know that health service commissioners have made their own decisions about affordability which do not relate to the WTP threshold. This is demonstrated by the way in which there has been a wide variation of the implementation of the 2004 IVF recommendations across the country (the 'postcode lottery') when there was a £20,000 WTP threshold and when the financial constraints were not as great as they are now.
302.	NHS Oxfordshire	4	Full	26-37	63	The research quoted here concerning the number of couples who will conceive at 1 year	Thank you for your comments.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						and 2 years (assuming twice weekly intercourse) and informs our comments on page 74.	The GDG discussed at length the issue of 'definitions of infertility' with respect to age. The key issues which formed the basis of the final decision to recommend using 12months of 'trying to conceive using unprotected vaginal intercourse' before referral for assessment were: a) the longer people 'keep trying' the greater their chances of natural conception, b) the chances of natural conception over time was inversely related to the age of the woman c) in the older woman, the longer she waited before referral for assessment and possible treatment the lower the chances of success from various methods of assisted conception especially IVF. The outcome of those discussions was that the GDG chose • 12months for the interval before referral in women less than 36y on the basis that the chances of naturally conceiving in that period would be over 85% • Earlier referral if the woman was 36y or more on the basis that though waiting longer would be increase their chances of natural conception, that was to their disadvantage because assisted reproductive interventions undertaken at a later age would be less successful.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
303.	NHS Oxfordshire	2	Full	24 -34	56	The outcome measure for successful treatment should be "live, full-term singleton birth" and additionally, where relevant, "safe delivery of a healthy child with no adverse consequences to the mother". The outcome measure "Clinical pregnancy" is much less satisfactory, as noted in the guidance.	Thank you for your comment. Live full-term singleton birth was our primary outcome.
304.	NHS Oxfordshire	6	Full	20-27	74	We would agree that the lifestyle advice and general clinical enquiries constitute an evidence based basic level for couples who are anxious about not conceiving however long or short a time they might have been trying. We would separate this from a formal initiation of investigation and assessment of possible infertility.	Thank you for these comments. We think the recommendations make this clear distinction. Separate recommendations consider initial assessment and formal referral for assessment and possible investigations within the defining infertility subchapter.
305.	NHS Oxfordshire	5	Full	12-15	74	Defining infertility – We agree with the suggestion that to define infertility as not having conceived after 1 year will lead to overtreatment. We would also refer to our comments regarding page 29, psychological trauma, and suggest that early definition, particularly in women under the age of 33, is likely to increase anxiety and have a detrimental effect on ability to conceive (evidence quoted within the guideline that anxiety may reduce fertility). We suggest the age of 33 as being an upper limit for requiring 2 years of not conceiving before initiating assessment and investigation because of the evidence that fertility falls at a faster rate after the women has reached the age of 35.	Thank you for your comments. The GDG discussed at length the issue of 'definitions of infertility' with respect to age. The key issues which formed the basis of the final decision to recommend using 12months of 'trying to conceive using unprotected vaginal intercourse' before referral for assessment were: a) the longer people 'keep trying' the greater their chances of natural conception, b) the chances of natural conception over time was inversely related to the age of the woman c) in the older woman, the longer she waited before referral for assessment and possible treatment the lower the chances of success from various methods of assisted conception especially IVF. The outcome of those discussions was that the GDG chose

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							• 12months for the interval before referral in women less than 36y on the basis that the chances of naturally conceiving in that period would be over 85% • Earlier referral if the woman was 36y or more on the basis that though waiting longer would be increase their chances of natural conception, that was to their disadvantage because assisted reproductive interventions undertaken at a later age would be less successful.
306.	NHS Oxfordshire	7	Full	28-30	74	We are unclear as to what a 'pragmatic approach' to defining infertility means.	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
307.	NHS Oxfordshire	3	Full	3-5	29	These lines recognise the psychological and physical trauma which may be associated with investigations and treatment for fertility problems. We would suggest that this should be taken into account within the recommendations when defining infertility and recommending treatment so that the "labelling" of couples as infertile, to whatever degree, should not be made too early. Additionally, invasive investigations and treatment should not be initiated when there is a reasonable chance of pregnancy occurring without interventions.	Thank you for your comments. The guideline outlines the care that an individual and/or couple should receive. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. The management of psychological and physical trauma (which may be associated with investigations and treatment for fertility problems) is outside the remit of the guideline.
308.	NHS Oxfordshire	8	Full	35-37	74	We disagree that couples who have been attempting to conceive for 1 year should be an indication for "further treatment". See our comments at 5 above. We would request	Thank you for your comments. The relevant recommendation actually states that women having regular unprotected

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						explicit separation of clinical assessment/investigation and advice within primary care from referring for further treatment which implies referral to secondary care services.	vaginal sexual intercourse should be *'offered further clinical assessment and investigation'* not *'further treatment'*. The GDG did not wish to make a recommendation as to where this should take place given the variation in primary and second resource provision in the NHS.
309.	NHS Oxfordshire	9	Full	38-40	74	We agree that women who have reached their 36th birthday should be investigated earlier than younger women but are unclear where the evidence is for the cut off of 6 months attempting to conceive.	Thank you for your comments. No recommendation has been made stating a 6 month cut-off should be used. In the supporting text the GDG suggests that 6 months could be considered. This is based on the GDGs clinical experience.
310.	NHS Oxfordshire	28	Full	2	389	We welcome the statement that NHS funding for cryopreservation should not mean that fertility treatment will also be funded.	Thank you for your comment
311.	NHS Oxfordshire	10	Full	3 and following	75 and 76	The section on same-sex couples reflects the requirements for organisations to promote equality of opportunity.	Thank you for this comment. You are correct – it is the introduction of equalities legislation since the original guideline that has made a significant change to the content of this section of the Guideline.
312.	NHS Oxfordshire	19	Full	34	284	It is not clear to us if the definition of a failed cycle means a full cycle of IVF as defined in Recommendation 125 (page 254) which has not produced a pregnancy or includes circumstances where the woman has had a work-up but no eggs have been produced for harvesting.	Thank you for your comments. They have been considered by the GDG and the relevant recommendation has been amended
313.	Nottingham University Hospitals NHS Trust	6				References Aust TR, Brookes S, Troup SA, Fraser WD, Lewis-Jones DI. Development and in vitro	Thank you for providing these references.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						testing of a new method of urine preparation for retrograde ejaculation; the Liverpool solution Fertil Steril.2008 89, 885-91. Hull MG, Glazener CM, Kelly NJ, Conway DI, Foster PA, Hinton RA, et al. Population study of causes, treatment, and outcome of infertility. BMJ 1985;291:1693–7. Steures,P., van der Steeg,J.W., Hompes,P.G., Habbema,J.D., Eijkemans,M.J., Broekmans,F.J., Verhoeve,H.R., Bossuyt,P.M., van,der,V, Mol,B.W., Collaborative Effort on the Clinical Evaluation in Reproductive Medicine, Intrauterine insemination with controlled ovarian hyperstimulation versus expectant management for couples with unexplained subfertility and an intermediate prognosis: a randomised clinical trial, Lancet, 368, 216-221, 2006 Tummon,I.S., Asher,L.J., Martin,J.S., Tulandi,T., Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis, Fertility and Sterility, 68, 8-12, 1997	
314.	Nottingham University Hospitals NHS Trust	7		General		The Trust feels strongly that the guidance given above relating to IUI activity is not only with out sufficient justification but will result in the closure of some NHS based fertility services. Furthermore there is a real risk that without high quality NHS fertility services to act as 'service gatekeeper' effectively managing patients from	Thank you for your comments. The recommendation was based on the best available evidence from RCTs. The GDG concluded that unstimulated IUI was no better than expectant management, and that any benefit from stimulated IUI was outweighed by the increased risk of multiple pregnancies.

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						primary care, through low tec treatments such as IUI and eventually through to an IVF clinic that this 'gatekeeper' role, could end up in the private sector who will have a 'vested interest' in moving patients more rapidly towards IVF. The eventual result could be a fertility industry which disappears entirely from the NHS losing the more impartial checks and balances it provides and resulting in significantly higher cost treatment.	The GDG was aware that the recommendation will change service patterns in the NHS, but believe this change will be beneficial as NHS resources will be used more effectively.
315.	Nottingham University Hospitals NHS Trust	1	FULL	81		Diagnostic semen analysis Recommendation 44. The threshold of 58% vitality is of little or no use and in direct conflict with the threshold of 32 progressive motility. A man may have plenty of progressive sperm e.g. 40% but insufficient vitality e.g. 50%. There is no practical value in testing vitality unless there is <5% motility	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Semen anlysis was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
316.	Nottingham University Hospitals NHS Trust	2	FULL	81		There should be emphasis that the WHO reference ranges are only valid if WHO recommended methods for semen analysis areused.	Thank you for your comments. Your comments have been considered by the GDG and the relevant recommendation has been amended
317.	Nottingham University Hospitals NHS Trust	3	FULL	81		There is no mention of best practice in the extraction of sperm from urine. The Liverpool solution is the only properly documented and (partially) validated method for retrieving sperm after the adjustment of urine pH and osmolarity (Aust et al, 2008).	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
318.	Nottingham University Hospitals NHS Trust	4	FULL	192 199	L15 6	The evidence which compares stimulated IUI with expectant management (EM) is extremely thin and does not truly represent IUI in its best light. Indeed the guidance reads: *"IUI with ovarian stimulation versus expectant management (evidence profile 12.2)* *The evidence quality was very low due to limitations in the study design and wide confidence intervals. P199 L6"* The guidelines recommend that IUI (with ovulation induction) should no longer be used as first treatment for UNEXPLAINED INFERTILITY in favour of expectant management (EM). The major flaw in this assessment is that: 4. Only 2 papers were used to arrive at these conclusions – indeed the guidance suggests that quality evidence is either low or very low 5. One paper Tummon et al 1997 actually suggests that IUI is effective with an LBR of 11% in endometriosis patients 6. The main paper used was: Steures et al 2006 which showed EM to be as effective as IUI in 253 couples. However: a. The IUI pregnancy rate was pitiful at only 6.5% with an	Thank you for your comments. The GDG have considered all your points and reassessed the evidence in light of these. They have concluded that the recommendations should not be changed. However, the GDG wish to highlight that the recommendation states that IUI should not routinely be used, not that it should never be used as a first line treatment. An explanation for this decision is given below. With regards to the methods used, these are outlined in the NICE technical manual and represent current best practice in terms of systematic reviewing. To summarise the process and results: • The comparisons being assessed were: Are IUI (with or without stimulation) more effective than expectant management or one another? • Papers were selected for inclusion based on pre-specified criteria. Data was then extracted and analysis undertaken, again using pre-specified

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						incredible miscarriage rate of 33% and an ongoing PR 4%. In contrast our own centre has an overall 16% PR and 14% LBR. This suggests that this isolated paper 'selected' was operating a 'less than' effective service and should not be used for comparative purposes b. Even in their patients with multifollicular growth the PR is only 5% - in our service this group has an LBR of 23% c. Some patients were shown to have tubal infertility d. Basically the study is weak with a poor quality treatment service and should not be cited to influence national policy Moreover Goverde et al 2000 in the Lancet demonstrated using an RCT that IUI was more cost-effective than IVF in the treatment of unexplained infertility. The papers cited appear to have been carefully selected to portray IUI as ineffective. There is no economic evaluation or accurate costing for IUI with stimulation	and standardised methods. This work was undertaken by an independent technical team. • It is important to remember that GRADE is used to assess the quality of the evidence for answering the specific review question posed by the GDG members. This is contributed to not only by the quality of the study, but also by how useful the evidence is in answering the question posed for the guideline. The quality grading is on the basis of the value of the evidence reported in the study in answering the research question. • The results were then presented to the GDG for discussion. • Based on the available data (IUI with stimulation vs expectant management & IUI with stimulation vs IUI without) and using their primary outcome of achieving live full-term singleton births, the GDG concluded that: IUI with stimulation would result higher pregnancy rates than IUI alone, but a significant proportion of these would be multiple births (relative risks of 10 and many of these would be higher order). The GDG was aware that the regimens used in these studies involved higher drug doses than would be used in current practice. The GDG believed that the Steures et al figures showed the likely outcome if current

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						There is no similar comparison to show the effectiveness of IVF treatment vs EM for unexplained infertility	doses of ovarian stimulants were used, and this showed no difference in pregnancy rates or multiple birth rates compared to expectant management. However, the risk of higher order multiple pregnancies when using stimulated IUI still exists and was a major concern for the GDG. For these reasons the GDG concluded that stimulated IUI should not routinely be used. • No economic evaluation was undertaken on IUI with stimulation compared to expectant management. The reason for this was any such analysis would use the Steures figures showing expectant management is superior to IUI with stimulation, as expectant management has much lower costs it would automatically be more cost-effective. In relation to the Steures paper: • Firstly, the Steures et al paper is an RCT. The GDG agreed that if a population had been selected for IUI then it is likely that pregnancy rates would have been higher than those reported. However, randomised trials are undertaken to avoid this patient selection bias and to provide an estimate of the relative effect between treatments. • Secondly, the Steures et l study was undertaken in 26 units across the

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							Netherlands, so it is unlikely that results are due to poor standards in a single unit. • Finally, Steures et al acknowledge that the pregnancy rate was lower than expected and hypothesised this was due the characteristics of the population not being selected for IUI. However, due to randomisation these women were equally distributed between the groups, so the expectant management arm would be equally affected. Finally, • The Goverde et al (2000) paper compares IUI and IVF, but this was not a comparison included in this review so this paper was not reviewed. • The GDG agreed that data is lacking on IVF compared to expectant management. However, in chapter 14 considerable efforts has been made to compare IVF against expectant management in a health economic model. The GDG has also made a research recommendation that further work is undertaken in this area to confirm the findings of existing RCTs.
319.	Nottingham University Hospitals NHS Trust	5		369		Page 369 Donor Insemination The reference still used today to define the rate of male infertility at 25% (Hull et al, 1985) is almost 30 years out of date. The data is based on WHO reference ranges of the time:	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						sperm concentration 20 millions per ml, 50% progression and 50% normal forms which do not compare well with the recently revised reference range of 2010.	held and the scope was subject to a period of public consultation before it was finalised. Donor insemination was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
320.	Positively UK	1	full	26	64	HIV testing should be opt-out, voluntary and with appropriate pre and post-testing support, in line with the BHIVA HIV testing guidelines for pregnant women	Thank you for your comment. The testing of HIV was outside the scope for this guideline update. The routine testing for HIV during pregnancy is also outside of the remit of this guideline and is covered in the NICE antenatal guideline (http://www.nice.org.uk/CG62).
321.	Positively UK	2	full	26	67	We applaud that the guidelines recognise the role of treatment as prevention for couples who want to conceive	Thank you for your comments
322.	Positively UK	3	full	26	66	At present the guidelines only talk of the scenario of an HIV positive man and HIV negative women. It is necessary to also include the situation when the woman is HIV positive and the man HIV negative; or where both partners are HIV positive. In both cases if the viral load is undetectable and other conditions met (as clearly stated in the guidelines for men living with HIV), couples may opt for unprotected timed intercourse.	Thank you for your comments. The scope of guideline was to examine the effectiveness of sperm washing, which is only relevant for a HIV positive male. In order to answer the question sperm washing was compared with viral transmission through unprotected sex and post exposure prophylaxis. The results of this review showed that if certain criteria were met that unprotected intercourse would be an suitable option if the male partner was HIV positive. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							held and the scope was subject to a period of public consultation before it was finalised. The scope did not cover an areas related to transmission from women to men. Therefore, no review could be undertaken and no recommendations could be made.
323.	Positively UK	4	full	26	66	Before line 66 we would welcome a statement that stresses that couples who have HIV, whether it is the male, female or both people who are HIV positive, should have all the support and care available to overcome infertility problems and achieve their reproductive desires. In the past many people with HIV have been excluded from IVF and other fertility procedures because of the stigma associated with HIV status. We believe it is important to state that they are entitled to the same high quality level of support and care, appropriate to their condition, as the rest of the population.	Thank you for your comments. The GDG believed that the recommendations they have made will make a significant improvement in fertility treatment for people with HIV. It should be noted people with viral disease are also considered throughout the rest of the guidance within the specific equality considerations for each chapter. However, service provision and implementation is outside the remit of the guideline.
324.	Progress Educational Trust	1		6		The reference to 'pelvic conditions' in the introduction to the Guideline seems redundant, because this category is encompassed by that of 'uterine or endometrial factors' already mentioned.	Thank you for your comments. The statement is correct as it stands. The example of a pelvic condition used is endometriosis. Typically it is found away from the uterus and is distinct from "uterine or endometrial factors". In other words "pelvic conditions" are diseases that affect parts of the pelvis apart from the uterus.
325.	Progress Educational Trust	2		7		The introduction to the Guideline refers to 'assisted reproduction techniques'. This terminology is used inconsistently throughout the Guideline, with references to 'assisted reproduction', 'assisted reproduction techniques', 'assisted reproduction procedures',	Thank you for your comments. The GDG agreed that a consistent approach to terminology of assisted reproduction is desirable and useful. Consequently the text and glossary have been amended to achieve

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						'assisted reproduction technology' singular and 'assisted reproduction technologies' plural. Furthermore, 'assisted conception' is a more useful and appropriate term than 'assisted reproduction'. It is a more familiar category in the UK, where hospitals often have 'assisted conception units'. It also refers to all assisted conception regardless of whether or not it results in live birth, which is appropriate to the scope of this Guideline.	greater consistency. Predominantly the terms *'Assisted Reproduction'* or *'Assisted Reproduction Treatments'* have been used depending on the context. However, in some cases the context would require that the type of ART should be specified (for example, donor insemination or IVF or ICSI or IUI). The guideline tried to be consistent where applicable, but there will be some unavoidable variances where the need to for a different phrase is determined by the context described above.
326.	Progress Educational Trust	3		13	1.2.1.2	The reference to 'people who are having artificial insemination to conceive and who are concerned about their fertility' is, insofar as we can tell, a reference to women in same-sex relationships. Presumably the provisions of the Equality Act 2010, and the fact that some people have become pregnant following gender transition and/or sex reassignment therapy, make it difficult or impossible to say as much. The Guideline would, however, be much easier to understand if something could be done to clarify or interpret sections such as this, or at least provide relevant examples.	Thank you for your comments. We think that the text makes it sufficiently clear which women require artificial insemination (AI) to conceive. The use of AI to conceive is not limited to people in same sex relationships. It also covers heterosexual couples where vaginal intercourse is not possible because of some disability. This is highlighted in further recommendations and the details are expanded upon in the equivalent sections of the full version of the Guideline.
327.	Progress Educational Trust	4		13	1.2.1.3	This could be misconstrued as an endorsement of using fresh sperm provided without a license. The ambiguity could be resolved by replacing the words 'inform people who are having artificial insemination to conceive and who are concerned about their fertility' with 'inform those being artificially inseminated with their partner's sperm', to make it clear that this is the relevant scenario.	Thank you for your comments. Your comments have been considered by the GDG and the relevant recommendation has been amended.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
328.	Progress Educational Trust	5		14	1.2.1.5	There is a reference above Table 2 to 'assisted reproduction technology'. This terminology is used inconsistently throughout the Guideline, with references to 'assisted reproduction', 'assisted reproduction techniques', 'assisted reproduction procedures', 'assisted reproduction technology' singular and 'assisted reproduction technologies' plural. Furthermore, 'assisted conception' is a more useful and appropriate term than 'assisted reproduction'. It is a more familiar category in the UK, where hospitals often have 'assisted conception units'. It also refers to all assisted conception regardless of whether or not it results in live birth, which is appropriate to the scope of this Guideline.	Thank you for your comments. The GDG agreed that a consistent approach to terminology of assisted reproduction is desirable and useful. Consequently the text and glossary have been amended to achieve greater consistency. Predominantly the terms *'Assisted Reproduction'* or *'Assisted Reproduction Treatments'* have been used depending on the context. However, in some cases the context would require that the type of ART should be specified (for example, donor insemination or IVF or ICSI or IUI). The guideline tried to be consistent where applicable, but there will be some unavoidable variances where the need to for a different phrase is determined by the context described above.
329.	Progress Educational Trust	6		14	1.2.1.5	The column in Table 2 headed 'ICI using fresh semen' uses figures from van Noord-Zaadstra's 1991 paper 'Delaying childbearing: effect of age on fecundity and outcome of pregnancy'. This was a study of women married to azoospermic husbands who were inseminated with donor sperm. These figures therefore represent the cumulative probability of conceiving a clinical pregnancy among women whose male partners have a known and severe fertility problem, and not (as this table implies) the cumulative probability of conceiving a clinical pregnancy among women *per se*. These figures are almost certainly too high to represent the latter.	Thank you for your comments. The 751 women reported in that study fulfilled the following criteria – they had to • Be married to azoospermic husbands • Be nulliparous • Never received AI before The women had ovulation status confirmed before undertaking the AI but only had tubal patency tested if they failed to conceive after at least 6 cycles of AI. How many women were also receiving ovulation induction because of anovulation is not stated. In theory, if there were many of these cases in the total they might have artificially increased the success rates.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							Another factor that might have contributed to cumulative conception rates being 'too high' – or at least higher than you would have expected - is that fresh semen was used rather than thawed semen. We have amended the text to emphasise the fact that there are very little data to provide guidance on the cumulative success with AI methods. Furthermore, the studies that do exist have limitations.
330.	Progress Educational Trust	7		14	1.2.1.5	The column in Table 2 headed 'IUI using thawed semen' uses figures from the HFEA's website, which are in turn substantiated by a document on that website entitled 'Fertility Facts and Figures 2008'. It is difficult to deduce how the figures in Table 2 were derived from the latter document. Furthermore, it is not clear whether or not the figures in the HFEA's document – which appear to us to be unusually high – represent cumulative probability, and therefore take account of success rates diminishing with numbers of cycles. If these figures do not represent cumulative probability, then they are problematic in three different ways – they are intrinsically misleading, they make for a false juxtaposition with the other figures in Table 2, and they preclude Table 2 being entitled 'Cumulative probability of conceiving a clinical pregnancy'. In short, the derivation of these figures and the type of probability they represent needs to be made clearer. If these figures appear in NICE's Guideline, patients will use them to make decisions about their treatment and commissioners will use them to	Thank you for your comments. You raise two important points of correction: • That it is not possible to discern where the IUI data are gleaned from the reference given (the HFEA website). In fact these were supplemented with more detailed data given to the Guideline developers by the HFEA. This additional data source has now been referenced in both the text and the table. • That the figures presented in this table do not represent 'cumulative probability' but just 'probability'. This has been corrected in the document. We have also acknowledged in the text that the sources of such data are limited.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						decide whether and how to fund treatment. It is therefore imperative that the figures and their provenance are made transparent.	
331.	Progress Educational Trust	8		14	1.2.1.5	There is a hyperlink to the HFEA website contained in the top row of Table 2 whose continued functioningis not assured. When the HFEA relaunched its website in 2009, URLs from the previous iteration of the organisation's website were not preserved and could no longer be used to access information as desired, thereby breaking the majority of 'deep links' to the website that were in use elsewhere. The breaking of links is made more likely in light of the Public Bodies Act 2011 and the Government's consultation on the prospective transfer of the HFEA's functions, which mean that the HFEA may be abolished before NICE next considers updating this Guideline.	Thank you for your comments. You are correct that the 'long term viability' of this website is uncertain. However, it is relevant at the time the Guideline goes to press and the data presented in this section from the HEFA were actually derived from data supplied to the technical team by the HFEA.
332.	Progress Educational Trust	9		18	1.2.13.4	It is unclear whether the fact that a person is single or is in a same-sex relationship qualifies as a 'known cause of infertility', or whether NICE proceeds from an assumption that medical and social causes of infertility can be distinguished. In our view, the distinction is not clear-cut.	Thank you for your comments. Your comments have been considered by the GDG and the relevant recommendation has been amended
333.	Progress Educational Trust	10		18	1.2.13.5	This part of the Guideline specifies what should be offered to 'a woman of reproductive age who is in a heterosexual or a same-sex relationship and is having artificial insemination to conceive (using either partner or donor sperm)', but makes no mention of women who are not in relationships of any kind. This discriminates against single women.	Thank you for your comments. Your comments have been considered by the GDG and the relevant recommendation has been amended
334.	Progress Educational Trust	11		23	1.3.3.3	We very much welcome the acknowledgement that the tests listed have no useful role in clinical practice.	Thank for your comment.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
335.	Progress Educational Trust	12		23	1.3.4.2	The phrase 'in the mid-luteal phase of their cycle (day 21 of a 28-day cycle) to confirm ovulation' seems overly convoluted. A clearer wording would be '7 days prior to menstruation', and this would have the added benefit of properly contextualising the serum progesterone measurement.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Thyroid testing was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
336.	Progress Educational Trust	13		33	1.8.1.1	We very much welcome the recommendation that oral ovarian stimulation agents not be offered to women with unexplained infertility.	Thank you for your comment.
337.	Progress Educational Trust	14		36	1.11.1.2	There is no definition of 'absolute infertility' in the Guideline, beyond there being 'no chance of pregnancy with expectant management'. Providing a more concrete definition is essential, because in the absence of one, commissioners will define the concept in whichever way best suits their interests. It is unclear whether the fact that a person is single or is in a same-sex relationship qualifies as 'absolute infertility'. It is also unclear whether and how the category encompasses male factor infertility. Even men who have a sperm count of zero can occasionally ejaculate sperm, as a consequence of variable sperm production and reabsorptionwithin the testes.	Thank you for your comments. Several stakeholders commented that the term 'absolute infertility' was not meaningful or useful in clinical practice. <u>Updated recommendation</u> There was extensive debate and division of opinion within the GDG about whether a recommendation for the provision of IVF could be made for this age group both before and after stakeholder comments. The details of which are described in the full version of the guideline. It was concluded that the uncertainty around the HE model meant that any recommendation for this age-group would have to be based on clinical opinion.

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							At the end of the meeting the GDG concluded that • that the current recommendation including the term 'absolute infertility' should be removed • A new recommendation should be drafted based on o ovarian reserve testing o that there was a need for a recommendation highlighting the additional risks associated with pregnancy in women aged 40 to 42 years The final version of the reworded recommendation was agreed by the 8 out of 11 members of the GDG: *In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled:* • *they have never previously had IVF treatment* • *there is no evidence of low ovarian reserve*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							• *there has been a discussion of the additional implications of IVF and pregnancy at this age.*
338.	Progress Educational Trust	15		37	1.11.1.5	We very much welcome the setting of an age limit, while also welcoming the fact that this limit has been raised to 43.	Thank you for your comments. Please note that the wording of this recommendation has been amended to read: *In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled:* • *they have never previously had IVF treatment* • *there is no evidence of low ovarian reserve* • *there has been a discussion of the additional implications of IVF and pregnancy at this age.*
339.	Progress Educational Trust	16		37	1.11.1.6	While we welcome the recommendation that the outcome of previous IVF treatment be taken into account when considering IVF treatment, we believe it should be emphasised that what is being referred to here is the outcome of previous treatment and not the fact of previous treatment. We do not believe patients should be penalised for the mere fact of having previously received treatment, and would therefore like the distinction between fact and outcome to be made more explicit.	Thank you for your comments. The GDG has discussed this and split the original recommendation into two new ones which clarify these points:

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
340.	Progress Educational Trust	17		38	1.12.3.5	The recommendation that ovulation should not be triggered with the intention of fresh embryo transfer in women who have a level of estradiol exceeding 15,000 pm/l is not evidence-based. There have been no published randomised studies assessing risk in relation to estradiol levels, and therefore an upper limit has not been defined.	Thank you for your comments. This recommendation has been removed from the guideline.
341.	Progress Educational Trust	18		40	1.12.6.5	The statement 'when performing single embryo transfer in IVF treatment, transfer a single blastocyst if possible' could be misconstrued as tautological. It could be worded more clearly – for example, 'when performing single embryo transfer in IVF treatment, the embryo should be transferred at blastocyst stage if possible'.	Thank you for your comments. Your comments have been considered by the GDG and the relevant recommendation has been amended
342.	Progress Educational Trust	19		41	1.12.6.9	The recommendation that two top-quality blastocysts not be used when performing double embryo transfer is impracticable. The quality of blastocysts is not a measure that can somehow be recalibrated in order to compensate for risks posed by the number of embryos transferred. Rather, the quality of blastocysts is contingent upon many factors over which clinicians have only limited control.Even when standard methods of grading are employed, assessing the quality of blastocysts involves a significant degree of subjective judgment. Knowingly transferring sub-optimal blastocysts is a perverse and counterintuitive exercise that runs counter to established clinical practice.	Thank you for your comments. The reason for not recommending that two blastocysts should be transferred is the clear evidence on the multiple pregnancy rates associated with this approach. The GDG has stated that the recently published NEAC criteria should be used when assessing embryo quality. These criteria are an attempt to overcome the subjectivity that you highlight exists in grading embryos. The GDG has amended the recommendation for clarity but not meaning.
343.	Progress Educational Trust	20		42	1.12.7.3	It could potentially be inferred from the statement that 'the evidence does not support continuing any form of treatment for luteal phase support beyond 8 weeks' gestation' that evidence supports continuing treatment for	Thank you for your comments. There is some evidence that the use of luteal phase support may be beneficial. However, this evidence is not extensive. As explained in

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						luteal phase support up to 8 weeks' gestation. Evidence to date does not appear to support continuing luteal phase support beyond a positive pregnancy test.	the full guideline, the GDG discussed how offering luteal phase support for an 'extended period of time' (more than 8 weeks) did not appear to result in more clinical benefits, than a shorter period of luteal phase support. In deciding on the exact recommendation, the GDG argued that it is biologically plausible for luteal phase support to be effective for up to 8 weeks after embryo transfer, after which time the pregnancy is 'self-supporting'. In the light of that the GDG recommended that luteal phase support is often offered for up to 8 weeks after embryo transfer. Based on the evidence of possible benefit, lack of harm and the biological plausibility of the intervention, the GDG recommended that women should be informed that there is no evidence for continuing luteal phase support beyond 8 weeks.
344.	Progress Educational Trust	21		48	1.16. 1.7	Italy's first live birth following transplantation of ovarian tissue is due to be discussed at the 2012 Annual Meeting of the European Society of Human Reproduction and Embryology (ESHRE), and the relevant paper has been publicised with a press release headed 'Fertility preservation with the cryopreservation of ovarian tissue moves from the experimental to the mainstream'. We are sceptical about the latter claim, and wetherefore agree with NICE's recommendation that only sperm, embryos or oocyctes should be cryopreserved in order to preserve fertility in people diagnosed with cancer. That said, we think it is important to allow for further developments in this area, which could conceivably catch up with the associated hyperbole in the near future.	Thank you for your comments. The GDG agreed with your comment about investing in the development of new techniques of cryopreservation. They have made the research recommendation in line with this action.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
345.	Progress Educational Trust	21		49	1.16. 1.11	We question whether the comparative merits and demerits of vitrification and controlled-rate freezing are sufficiently well established to make such an unambiguous recommendation in favour of vitrification.	Thank you for your comment. The evidence shows that there was a significantly higher rate of post-thaw survival after vitrification of oocytes compared to controlled rate freezing. Furthermore, there was an indication that the same to be true in embryo cryopreservation. The GDG was aware that the amount of RCT evidence comparing controlled rate freezing and vitrification is small. They were also aware that there is no long-term data on vitrification use or indeed the primary outcome for the review, live singleton birth. The GDG did not feel that the evidence is conclusive enough to make a recommendation to only use vitrification. Therefore the current wording allows either technique to be used. Finally, a research recommendation has been made for further investigating into the long term outcomes of virtrification and the different techniques within vitrification.
346.	Progress Educational Trust	22		49	1.17	This heading for the recommendations that follow refers to 'assisted reproduction technologies'. This terminology is used inconsistently throughout the Guideline, with references to 'assisted reproduction', 'assisted reproduction techniques', 'assisted reproduction procedures', 'assisted reproduction technology' singular and 'assisted reproduction technologies' plural. Furthermore, 'assisted conception' is a more useful and appropriate	Thank you for your comments. The GDG agreed that a consistent approach to terminology of assisted reproduction is desirable and useful. Consequently the text and glossary have been amended to achieve greater consistency. Predominantly the terms *'Assisted Reproduction'* or *'Assisted Reproduction Treatments'* have been used depending on the context. However, in some

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						term than 'assisted reproduction'. It is a more familiar category in the UK, where hospitals often have 'assisted conception units'. It also refers to all assisted conception regardless of whether or not it results in live birth, which is appropriate to the scope of this Guideline.	cases the context would require that the type of ART should be specified (for example, donor insemination or IVF or ICSI or IUI). The guideline tried to be consistent where applicable, but there will be some unavoidable variances where the need to for a different phrase is determined by the context described above.
347.	Progress Educational Trust	23		51	4.1	There is a reference above table 2 to 'assisted reproduction technology'. This terminology is used inconsistently throughout the Guideline, with references to 'assisted reproduction', 'assisted reproduction techniques', 'assisted reproduction procedures', 'assisted reproduction technology' singular and 'assisted reproduction technologies' plural. Furthermore, 'assisted conception' is a more useful and appropriate term than 'assisted reproduction'. It is a more familiar category in the UK, where hospitals often have 'assisted conception units'. It also refers to all assisted conception regardless of whether or not it results in live birth, which is appropriate to the scope of this Guideline.	Thank you for your comments. The GDG agreed that a consistent approach to terminology of assisted reproduction is desirable and useful. Consequently the text and glossary have been amended to achieve greater consistency. Predominantly the terms *'Assisted Reproduction'* or *'Assisted Reproduction Treatments'* have been used depending on the context. However, in some cases the context would require that the type of ART should be specified (for example, donor insemination or IVF or ICSI or IUI). The guideline tried to be consistent where applicable, but there will be some unavoidable variances where the need to for a different phrase is determined by the context described above.
348.	Progress Educational Trust	24		53	4.3	There is a reference above table 2 to 'assisted reproduction'. This terminology is used inconsistently throughout the Guideline, with references to 'assisted reproduction', 'assisted reproduction techniques', 'assisted reproduction procedures', 'assisted reproduction technology' singular and 'assisted reproduction technologies' plural. Furthermore, 'assisted	Thank you for your comments. The GDG agreed that a consistent approach to terminology of assisted reproduction is desirable and useful. Consequently the text and glossary have been amended to achieve greater consistency. Predominantly the terms *'Assisted Reproduction'* or *'Assisted*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						conception' is a more useful and appropriate term than 'assisted reproduction'. It is a more familiar category in the UK, where hospitals often have 'assisted conception units'. It also refers to all assisted conception regardless of whether or not it results in live birth, which is appropriate to the scope of this Guideline.	*Reproduction Treatments'* have been used depending on the context. However, in some cases the context would require that the type of ART should be specified (for example, donor insemination or IVF or ICSI or IUI). The guideline tried to be consistent where applicable, but there will be some unavoidable variances where the need to for a different phrase is determined by the context described above.
349.	Progress Educational Trust	25		70		There are three references in the replacement text on this page to 'assisted reproduction procedures'. This terminology is used inconsistently throughout the Guideline, with references to 'assisted reproduction', 'assisted reproduction techniques', 'assisted reproduction procedures', 'assisted reproduction technology' singular and 'assisted reproduction technologies' plural. Furthermore, 'assisted conception' is a more useful and appropriate term than 'assisted reproduction'. It is a more familiar category in the UK, where hospitals often have 'assisted conception units'. It also refers to all assisted conception regardless of whether or not it results in live birth, which is appropriate to the scope of this Guideline.	Thank you for your comments. The GDG agreed that a consistent approach to terminology of assisted reproduction is desirable and useful. Consequently the text and glossary have been amended to achieve greater consistency. Predominantly the terms *'Assisted Reproduction'* or *'Assisted Reproduction Treatments'* have been used depending on the context. However, in some cases the context would require that the type of ART should be specified (for example, donor insemination or IVF or ICSI or IUI). The guideline tried to be consistent where applicable, but there will be some unavoidable variances where the need to for a different phrase is determined by the context described above.
350.	Progress Educational Trust	26		70		The statement that 'the consumption of more than one unit of alcohol per day reduces the effectiveness of assisted reproduction procedures' is much easier to substantiate in relation to women (to whom this statement presumably applies) than it is in relation to men.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						We are guessing that NICE's reference to 'people' rather than 'women' may reflect the fact that some people have become pregnant following gender transition and/or sex reassignment therapy.Nonetheless, the suggestion that alcohol consumption reduces the effectiveness of assisted conception to the same extent in women and men is misleading, and greater clarity is therefore required.	public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
351.	Queen's University Belfast	1	Full. 170 (Section 16.2)	363	14-30	**If couples have non- male subfertility, ICSI should be offered to them only following failed or poor fertilization**. Section 16.2 is misleading. It states that this recommendation is based on ten RCTs comparing ICSI with other types of IVF and that the review showed no difference in fertilization or pregnancy for couples with normal semen. In fact, it is based on a Cochrane review by van Rumste et al, 2003 [1] that actually seems to include results from just one paper ([2]Bhattacharya et al, Lancet 2001 357 2075-79). As such it is not robustly evidence based. I would ask NICE to consider the following points before re-instating this very rigid recommendation. • The numbers of couples included in this ONE study are relatively small (n=224 in IVF group, n=211 in ICSI group) • The study does not give live birth rates or miscarriage rates so further research is needed before this	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. ICSI was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline. However, the GDG did note that clarification of the indications of ICSI within recommendation 170 would be useful for clinicians: In order to do this the following text has been added: *"Although ICSI was not reviewed within the 2012 guideline update, to improve the implementation of the recommendation the GDG have included a note of clarification on the indications of when to use ICSI. ICSI should be offered as part of the first IVF cycle where there is a clear indication for its use (for*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						recommendation should be a NICE guideline. • The semen parameters used to identify couples as having non-male subfertility at time of study (2001) are now viewed as neither predictive of diagnosis of male infertility nor useful in predicting ART outcome[3-6] thus the guideline is based on outdated data. **As a stakeholder and professorial scientist leading a research group in male infertility since 1995, I do not believe the scientific or clinical evidence is sufficient to make this recommendation.** I would suggest in cases of 'failure' should include failure to obtain good embryos, or failure to achieve a pregnancy and NOT be limited to failed or poor fertilization. In any of these cases where clinics should not be prohibited from offering these couples ICSI. As it stands, this NICE recommendation removes clinical judgment by imposing a 'one case fits all' strategy, preventing clinics from making clinical decisions based on individual couples' history and tests and previous IVF outcomes. Furthermore, the current criterion for choosing ICSI over IVF is already a very blunt instrument. It is based simply on pragmatism. If there are enough motile sperm in the ejaculate (<0.5	*example azoospermia) or where there are severe deficits in semen quality, normally determined using WHO semen criteria (WHO, 2010).* Furthermore, the GDG wanted to clarify the wording the 2004 recommendation: this should not be interpreted as ICSI being superior to IVF, the two are equivalent." *"Whilst the evidence for this recommendation has not been updated for the 2012 edition of the guideline, it should be noted for clarification that in the absence of male factors (see recommendation 170), ICSI is not proven to confer a benefit in terms of increased pregnancy rates and should not be offered in the first treatment cycle."*

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						million sperm) IVF is performed, if not, ICSI is recommended. As we know, ICSI is very successful where IVF is impractical. For this reason, we are currently accepting of it clinically although ICSI technique was introduced in 1995 with little research performed before becoming a routine treatment. It is successful with testicular sperm, epididymal sperm, globozoospermia as well as poor quality ejaculated sperm from men with oligostenoteratozoospermia. It is now clear (based on a plethora of publications take7-11 as examples that ICSI also successful even for sperm with damaged DNA. Sperm DNA damage is a major cause of their failure with IVF but since sperm DNA damage does not impact on early ICSI success markers of fertilization, embryo quality or implantation couples with failure with IVF should be offered ICSI where their chances of success would be higher. The scientific rationale for ICSI success with sperm with damaged DNA is again, based on a large number of studies showing • The women who have ICSI are often fertile and their eggs may have more capacity to repair sperm DNA damage[12] • In ICSI, the gametes are not subjected to prolonged culture so the actual gametes used in ICSI may have less damage than those exposed to culture media for hours in IVF procedure[13.] These sperm are placed into optimal	

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						conditions for repair ad future development the same day. This may protect them from lab damage and also allow the eggs to repair their DNA[14] • Poor quality sperm often generate excess ROS. In IVF, oocytes are exposed to oxidative assault from ~half a million such sperm overnight. In ICSI, the oocytes are protected from this ROS attack[15] **References** 1. Van Rumste M M E; Evers J L H; Farquhar C M 2003Intra-cytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in patients with non-male subfertility. Cochrane database of systematic reviews (Online) Issue: 2CD001301 2. Bhattacharya S, Hamilton MP, Shaaban M, Khalaf Y, Seddler M, Ghobara T, Braude P, Kennedy R, Rutherford A, Hartshorne G, Templeton A.Conventional in-vitro fertilisation versus intracytoplasmic sperm injection for the treatment of non-male-factor infertility: a randomised controlled trial Lancet 2001 357 2075-79 3. Lewis S. Is sperm evaluation useful in predicting human fertility? Reproduction	

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						2007;134:1–11. Reproduction 2007 134:31-40 4. Lefièvre L, Bedu-Addo K, Conner SJ, Machado-Oliveira GS, Chen Y, Kirkman-Brown JC, Afnan MA, Publicover SJ, Ford WC, Barratt CL. Counting sperm does not add up any more: time for a new equation? Reproduction.2007 ;133(4):675-84. 5. Guzick DS, Overstreet JW, Factor-Litvak P, Brazil CK, Nakajima ST, Coutifaris C, Carson SA, Cisneros P, Steinkampf MP, Hill JA, Xu D, Vogel DL, National Co-operative Reproductive Medicine Network 2001 Sperm morphology, motility, and concentration in fertile and infertile men. New England Journal of Medicine 345 (19): 1388-1393. 6. Barratt CL, Mansell S, Beaton C, Tardif S, Oxenham SK. Diagnostic tools in male infertility-the question of sperm dysfunction. Asian J Andrology. 2011 Jan;13(1):53-8. Epub 2010 Nov 22. 7. Giwercman, A. et al. Sperm chromatin structure assay as an independent predictor of fertility in vivo: a case-control study. Int J Androl 33, e221-227, doi:IJA995 [pii] 10.1111/j.1365-2605.2009.00995.x. 8. Bungum, M. et al. Sperm DNA integrity assessment in prediction of assisted reproduction technology outcome. Human Reproduction 22, 174-179 (2007). 9. Luke Simon, Deborah Lutton, Joanne McManus, Sheena E. M. Lewis Clinica	

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						significance of sperm DNA damage in reproductive outcome Human Reproduction 2010 25(7):1594-1608 10. Luke Simon Deborah Lutton, Joanne McManus and Sheena E. M. Lewis Sperm DNA damage measured by the alkaline Comet assay as an independent predictor of male infertility and IVF success Fertility and Sterility 2011;95(2):652-657 11. Luke Simon and Sheena E. M. Lewis. Sperm DNA damage or progressive motility: which one is the better predictor of fertilization in vitro? Systems Biology in Reproductive Medicine 2011, 1: 1–6 12. Meseguer M Santiso R Garrido et al, Effect of sperm DNA fragmentation depends on pregnancy outcome quality Fertility and Sterility 2011 95 124-128 13. Dumoulin, JC; Land, JA; Van Montfoort, AP; Nelissen, EC; Coonen, E; Derhaag, JG; Schreurs, IL; Dunselman, GA; Kester, AD; Geraedts, JP and Evers, JL. (2010) Effect of in vitro culture of human embryos on birthweight of newborns. Human Reproduction, 25(3):605-12. 14. Menezo Y, Dale B, Cohen M DNA damage and repair in human ooctyes and embryos- a review Zygote 2010 18 357-365	

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						15. Aitken RJ, De Iuliis GN, Finnie JM, Hedges A, McLachlan RI. Analysis of the relationships between oxidative stress, DNA damage and sperm vitality in a patient population: development of diagnostic criteria. Hum Reproduction 2010; 25: 2415-2426.	
352.	Royal College of Nursing	1	Full	General		The Royal College of Nursing welcomes the reviewed guidance, and fully appreciates the work of the Guideline Development Group. Overall this guidance will be a great help with the provision and commissioning of effective treatment for infertility. However, in light of the aims of NICE guidance being the provision of evidence-based NHS treatment, there still remains inequity of access and provision throughout England, Wales and Northern Ireland (with approx 70% of commissioners prioritising other areas of healthcare). To this end, it appears contentious that the recommendation is to offer one cycle of (NHS funded) treatment to women of 42years of age (presumably up until their 43rd birthday). There has been a vast amount of work invested by the Multiple Births Minimisation Strategy Group, with a move towards elective single embryo transfer (eSET), and acceptance of the associated literature on cumulative success rates - which decrease with advancing maternal age - (Malizia et al., 2009), therefore, to offer one cycle of treatment to women of advancing reproductive age appears to be contrary to the evidence base.	Thank you for your comments. There was extensive debate and division of opinion within the GDG about whether a recommendation for the provision of IVF could be made for this age group both before and after stakeholder comments. The details of which are described in the full version of the guideline. It was concluded that the uncertainty around the HE model meant that any recommendation for this age-group would have to be based on clinical opinion. At the end of the meeting the GDG concluded that • that the current recommendation including the term 'absolute infertility' should be removed • A new recommendation should be drafted based on o ovarian reserve testing o that there was a need for a recommendation highlighting

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						It is also recognised that with increasing societal pressure many women are delaying parenthood therefore, there is support for this recommendation from some of our members.	the additional risks associated with pregnancy in women aged 40 to 42 years The final version of the reworded recommendation was agreed by the 8 out of 11 members of the GDG: *In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled:* • *they have never previously had IVF treatment* • *there is no evidence of low ovarian reserve* • *there has been a discussion of the additional implications of IVF and pregnancy at this age.* We think this reworking of the recommendation now addresses many of the concerns you raise.
353.	Royal College of Nursing	2	Full	General	General	Another concern is the use of the term 'absolute infertility' (this is used severally in the document). Without a clear definition of the terminology, it provides the platform for widespread misinterpretation and possible inappropriate referral.	Thank you for your comments. <u>The definition of absolute infertility</u> Several stakeholders commented that the term 'absolute infertility' was not meaningful or useful in clinical practice.

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							Updated recommendationThere was extensive debate and division of opinion within the GDG about whether a recommendation for the provision of IVF could be made for this age group both before and after stakeholder comments. The details of which are described in the full version of the guideline. It was concluded that the uncertainty around the HE model meant that any recommendation for this age-group would have to be based on clinical opinion. At the end of the meeting the GDG concluded that • that the current recommendation including the term 'absolute infertility' should be removed • A new recommendation should be drafted based on o ovarian reserve testing o that there was a need for a recommendation highlighting the additional risks associated with pregnancy in women aged 40 to 42 years The final version of the reworded recommendation was agreed by the 8 out of 11 members of the GDG: *In women aged 40–42 years who have not conceived after 2 years of regular unprotected*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled: • *they have never previously had IVF treatment* • *there is no evidence of low ovarian reserve* • *there has been a discussion of the additional implications of IVF and pregnancy at this age.* We think this overcomes the problems associated with the original recommendation which included the term 'absolute infertility'.
354.	Royal College of Nursing	3	Full	74	6	**Recommendation 34** It might add to the quality of the revised guideline that an increased dose of Folic Acid (5mg) has been approved by the Scientific Advisory Committee on Nutrition (2009) in the management of obesity in pregnancy (BMI ≥ 30).	Thank you for your comments. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included for review in the 2012 update of the Fertility Guideline. Furthermore, there is not an existing NICE recommendation on this topic to which we can cross refer without undertaking a full review. The evidence on folic acid was considered by the NICE Maternal and Child Nutrition PDG (which published PH11). The PDG considered

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							there was evidence of an association between maternal obesity and poor folate status but not enough evidence to justify a particular recommendation for obese pregnant women. In summary, we cannot take forward your comments or make any substantive changes to the existing topic in the final version of the Guideline. The NICE maternal and child nutrition guidance (PH11) is consistent with the current DH recommendation and the ANC recommendation that women should supplement their diet with 400µg/day of folic acid (5mg/day for women with a previous pregnancy affected by NTD) prior to conception until the 12th week of pregnancy. It also recommends 5mg per day for women with spina bifida or other NTD or whose partner has an NTD - and 5mg per day for women with diabetes but there is no similar recommendation for obese women.
355.	Royal College of Nursing	4	Full	82	16	We are pleased to see section 6.3 on Ovarian reserve testing which includes the new tests to measure AMH and AFC and agree with the recommendations. We are aware that in many private centres AMH is offered routinely to all women on the basis that if the results show that the AMH is very low the likelihood of a live birth is greatly diminished irrespective of age. In these cases it may be appropriate for these women to be fast tracked through the system. Likewise if the AMH is high and other	Thank you for your comments. The GDG has recommended the use of age as an indicator for response to IVF as part of the initial consultation. This is because it is a quick, reasonable accurate and cost free. The results will give the couple and clinician an idea of the likely success of IVF: " *The GDG highlighted that, in their clinical experience, age was a useful initial test for determining ovarian response which was then complemented by other tests which allowed a*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						investigations normal, the women may conceive naturally without further treatment. However, we note that the conclusion of the GDG from the available evidence suggests maternal age as the most reliable predictor of ovarian reserve/response and combined AFC and basal FSH provides an evidence base for prognosis in women who are considering IVF treatment. We would like to ask the GDG to consider whether testing for AMH should be used routinely in first line investigations.	*more individualised estimate of ovarian reserve for each woman. However, they agreed that the accuracy of age as a test in the studies identified was not as good as AMH, AFC or FSH."* The GDG did not believe that a formal test should be used as part of the initial consultation. Once the decision has been made to proceed with fertility treatment then tests, such as AMH, can be used to more accurately predict the response to treatment in any one cycle. However, the GDG did not consider that the evidence was strong enough to support recommending one test over another.
356.	Royal College of Nursing	5	Full	105	5	**Recommendation 64** In the context of Blood Borne Virus Screening, the HFEA have recently sought changes in practice (in accordance with the Cells & Tissue Directive) for all patients to be screened for Hepatitis B Surface Antigen (HBsAG) and anti-HBc (Core antibody), therefore reference to the (minimum) standard should be referred to in this review.	Thank you for your comment. The guideline's update scope was limited only to consider the transmission of viral disease through sperm washing. Therefore, the GDG was unable to review or make recommendations about screening. The GDG was, however, aware of the new legislation for screening of HBV and have made the following statement within the evidence to recommendation text of the chapter: *"The GDG was aware of ongoing developments of the screening of HBV, specially the HFEA consultation on the serological testing for HBsAg and anti-HBc.*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							The GDG was content that the recommendations made within this chapter are complementary to new screening initiatives and would be adequately supportive to those found positive for hepatitis B."
357.	Royal College of Nursing	6	Full	170	98	**Recommendation 98**: We suggest that consideration should be given to screening women with Polycystic Ovary Syndrome (PCOS) who are resistant to clomifene citrate for insulin resistance to predict the risk of later onset Type ll diabetes as a matter of general public health concern. They can then be advised accordingly about health, lifestyle and monitoring which may result in spontaneous pregnancy through modification of diet and subsequent weight loss.	Thank you for your comments. The Fertility guideline offers guidance for the management of people with fertility problems. However, we were not able to go into detail about the management of underlying conditions, such as PCOS. Specifically, it was not included in the Scope for the update in this Guideline. We are therefore unable to add your concerns about screening for insulin resistance in PCOS women to the guideline.
358.	Royal College of Nursing	7	Full	204	23	**IUI:** We support the recommendations in general but would ask the GDG to consider whether in the circumstances where a couple choose not to have IVF for personal religious or ethical reasons and have a male factor problem, IUI may be offered as an exceptional circumstance.	Thank you for your comments. Your comments have been considered by the GDG and the relevant recommendation has been amended
359.	Royal College of Nursing	8	Full	346	15	The RCN are wholeheartedly supportive of elective single embryo transfer (eSET) in accordance with the work of the Multiple Births Minimisation Strategy group and the HFEA recommendation of 10% multiple birth rates for each centre from October 2012. However, it appears somewhat prescriptive to advocate that 'all patients under the age of 37 years should have a SET in their first cycle'. The Association of Clinical Embryologists (ACE) has produced guidance in this regard (Cutting et al., 2008). Female age, embryo number, quality (within the	Thank for your comments. The GDG has outlined criteria based on people receiving 3 full cycles of IVF. Based on the available evidence on effectiveness and safety, it is the conclusion of the GDG that using a single embryo in the first full cycle optimises the chance of a live full-term singleton birth. If this fails then the next 2 full cycles allows more than one embryo to be transferred dependent on embryo quality.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						context of the national grading system) and day of transfer should all be taken into consideration with regards to the number of embryos to transfer, and many centres have invested a great deal of time and effort into developing robust algorithms in an attempt to maximise pregnancy rates whilst reducing overall multiple pregnancy rates. Therefore in carefully selected women, it might be appropriate to consider replacement of two embryos.	In addition, the ACE guidance was used as the basis for the criteria outlined in the guideline, however, these only apply to a single cycle rather than the three outlined in the recommendation. Therefore, in this instance no change will be made to the recommendation.
360.	Royal College of Nursing	9	Full	346	159	**Embryo transfer**: We are concerned about the emphasis given to blastocyst transfer. In practice we are aware that cleavage stage double embryo transfer continues to give rise to high multiple pregnancy rates. We think, therefore that these recommendations lack clarity that in all cases (irrespective of the day of embryo transfer) female age, embryo number, quality (within the context of the national grading system) and previous history should all be taken into consideration with regard to the number of embryos to be transferred.	Thank you for your comments. The GDG believed that the recommendations outlined in this section take into account all the factors mentioned. Furthermore, in the evidence to recommendation section the GDG stated: *"The GDG discussed a number of factors that could influence the success of any embryo transfer strategy and could be included in a decision-making process:* • *The woman's age* • *The woman's obstetric and gynaecological history* • *The number of previous failed IVF attempts* • *The woman's ovarian response or reserve* • *The number of embryos created* • *The quality of the embryos, including blastocysts"*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							Therefore, in this instance no change will be made to the meaning of the recommendation.
361.	Royal College of Nursing	10	Full	390	1	In the context of gamete cryopreservation, the HFEA Gamete Storage (GS) consent form requires patients to consider partner consent for the subsequent use of cryopreserved embryos, which involves conveying complex information at a difficult time, and several qualitative studies have suggestedseparating decisions about storage of sperm from later ethical discussions about their use (Agarwal et al., 2004; Peddie et al, 2012). Estimates suggest that in 2010, one in 715 people in the UK had survived cancer during childhood. Healthcare professionals note a growing emphasis on 'quality of life' after cancer survival (Wallace et al., 2005). Yet, a recent survey of more than 300 health care practitioners conducted by researchers at the Royal Free Hampstead NHS Trust, found that fewer than forty percent considered discussion of future fertility in women diagnosed with breast cancer (NCRI, 2011). Although the guideline development group considered the effects of cancer on fertility in the review process, its remit was 'to examine the effectiveness of different methods of cryopreservation' in the context of preservation of fertility before starting chemo or radiotherapy. It was disappointing that 'quality of life' and associated fertility did not merit discussion and no qualitative studies were included in the review.	Thank you for your comments. Quality of life was not an outcome considered within the review for this topic. The review methodology also stated that RCT studies were the priority, observational studies were only included for the sub-question on cryopreservation of semen. However, we do agree that this is an important consideration to be made. Although we are unable to make a recommendation based on your comments because of the restrictions we placed on our review we have included the following text within the evidence to recommendations section: *"The disparity between the male and female fertility treatment offered at diagnosis is evident in current practice. The implementation of the recommendations should address this pathway of treatment for women and increase the routine information provision for a woman regarding her fertility during oncology consultations."*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
362.	Royal College Of Obstetricians and Gynaecologists	1.	Full	**General**		The RCOG guideline on investigation and management of endometriosis includes two grade A recommendations that I would like the GDG to consider: 1. That tubal flushing improves pregnancy rates in women with endometriosis related infertility and 2. Treatment with GnRH analogues before IVF increases the rates of pregnancy. Would the GDG please consider these recommendations and adopt as appropriate (depending upon the current evidence).	Thank you for your comments. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Tubal flushing was not selected to be included in Scope of the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline. With regards to your second point, that treatment with GnRH analogues before IVF increases the rates of pregnancy, the GDG believed this is already covered in the Fertility guideline with the following recommendation: *"Use either gonadotrophin-releasing hormone agonist down-regulation or gonadotrophin-releasing hormone antagonists as part of gonadotrophin-stimulated IVF treatment cycles."* and the explanatory text: *"The evidence showed higher pregnancy rates in down-regulated IVF cycles compared with non down-regulated cycles. The GDG therefore recommended that down-regulation should be used as part of an IVF cycle. "*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
363.	Royal College Of Obstetricians and Gynaecologists	2.	Full	General		When the GDG state 'take into account the outcome of previous IVF whether it be NHS or private funded', what do they mean by this? Do they mean that women should only be offered three cycles including those self funded, or is that we only offer NHS treatment to women who have responded normally in previous cycles? Clarification would be welcomed.	Thank you for your comments. Your comments have been considered by the GDG and the relevant recommendation has been amended
364.	Royal College Of Obstetricians and Gynaecologists	3.	Full	General		Given the specific criteria for not triggering, guidance on whether a cycle which is cancelled due to excessive response, should be counted as one of the three treatment cycles would be welcomed.	Thank you for your comments. We have added a new recommendation which clarifies this point:
365.	Royal College Of Obstetricians and Gynaecologists	4.	Full	General: male fertility		There is also a substantial body of work assessing the use of other diagnostic tests in the assessment of male fertility such as DNA fragmentation and we feel these should be discussed.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. DNA fragmentation was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
366.	Royal College Of Obstetricians and Gynaecologists	5.	Full	12-15		IVF pathway The provision of IVF for women over the age of 40 is dependent on the definition of absolute infertility. At present the GDG definition is not clear, for example even severe oligospermia has some chance of conception with expectant management although this is very small and ICSI would be the treatment of choice. Do the	Thank you for your comments. Several stakeholders commented that the term 'absolute infertility' was not meaningful or useful in clinical practice. <u>Updated recommendation</u>

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						GDG mean for these to be excluded from treatment as at present only couples with azoospermia or bilateral tubal disease would be those with absolute infertility.	There was extensive debate and division of opinion within the GDG about whether a recommendation for the provision of IVF could be made for this age group both before and after stakeholder comments. The details of which are described in the full version of the guideline. It was concluded that the uncertainty around the HE model meant that any recommendation for this age-group would have to be based on clinical opinion. At the end of the meeting the GDG concluded that • that the current recommendation including the term 'absolute infertility' should be removed • A new recommendation should be drafted based on o ovarian reserve testing o that there was a need for a recommendation highlighting the additional risks associated with pregnancy in women aged 40 to 42 years The final version of the reworded recommendation was agreed by the 8 out of 11 members of the GDG: *In women aged 40–42 years who have not conceived after 2 years of regular unprotected*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled: • *they have never previously had IVF treatment* • *there is no evidence of low ovarian reserve* • *there has been a discussion of the additional implications of IVF and pregnancy at this age.* •
367.	Royal College Of Obstetricians and Gynaecologists	6.	Full	**8**	1	**D – Investigtions of infertility pathway** Ovarian reserve testing – despite later acknowledging in the text that there is no internationally agreed assay for AMH, values for AMH testing are given without stating which assay these are derived from. This will certainly lead to confusion for both clinicians and patients.	Thank you for your comment. Thank you for your comments. Your comments have been considered by the GDG and the relevant recommendation has been amended (these footnotes are not found in the algorithm).
368.	Royal College Of Obstetricians and Gynaecologists	7.	Full	14	1	**J – embryo transfer strategies and recommendation 160** This fails to mention situations whereby a woman's medical condition or previous obstetric history may dictate that single embryo transfer would be prudent. This needs to be made clear as a strategy based on age alone and ignoring other factors is dangerous both for women and their babies.	Thank you for your comment. The GDG agreed that previous obstetric history needs to be taken into account. The GDG has emphasised this in the evidence to recommendation section of the chapter.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
369.	Royal College Of Obstetricians and Gynaecologists	8.	Full	15	1	K special procedures The list of who needs DI fails to mention same sex couples	Thank you for this comment. However, this recommendation is applicable for the clinical requirement of DI. The most common example is severe male factor infertility. These recommendations are not for DI as alternative to intercourse, in those that are unable to have intercourse to conceive. The language used in the initial advice chapter where DI is discussed for the same-sex couple (and similar groups) is deliberately different to separate the two indications. In that context we describe the procedure as artificial insemination (with either partner or donor sperm)
370.	Royal College Of Obstetricians and Gynaecologists	9.	Full	17	2	Pathway M Cancer Therapy. It is very nice to see this clear pathway. I wonder whether at this point it might be acknowledged that this is relevant to other diseases other than just cancer where gonadotoxic therapy is used e.g. some rheumatological conditions, and sickle cell disease where treated with bone marrow transplantation. The application of cryopreservation to other diseases is acknowledged much later in the document but it's rather in the small print and I wonder if this might be highlighted earlier.	Thank you for your comments. The scope of this guideline was to only make specific recommendations for cancer patients. We have, however, added text (below) to make sure that the guideline is explicit on the context of the recommendation the GDG made but does not to preclude their use for other patient groups. *"The scope of this guideline states that recommendations are to be outlined for people undergoing cancer treatment who wish preserve their fertility. The interpretation of the evidence was based on this and recommendations have been written specifically for this population. No recommendations are made for other groups who may prematurely lose their fertility. However, the GDG highlighted that the fact*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							recommendations were not made for other groups should not be used as a justification for not funding cryopreservation in these groups and that the recommendations made in the guideline could be extrapolated to other population who may be at risk of losing their fertility due to treatment."
371.	Royal College Of Obstetricians and Gynaecologists	10.	Full	21	21	Recommendation 16: the timing of artificial insemination is stated to be around ovulation. This seems rather vague and clearer guidance should be provided.	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
372.	Royal College Of Obstetricians and Gynaecologists	11.	Full	28		Page 28 guidelines 90 - 92. It seems surprising that these 3 guidelines are listed first when they don't address the primary treatment modalities in these patients. Some reordering would be appropriate. Thus recommendations 93 and 94 would seem to be the primary ones.	Thank you for your comment. These recommendations have been moved to be presented after the other recommendations related to women who are resistant to clomifene citrate.
373.	Royal College Of Obstetricians and Gynaecologists	12.	Full	29		The manufacturer's view is that cabergoline should be stopped a month before conception and therefore it cannot be used in women attempting to conceive. This seems to be accepted without question despite the finding that it is associated with improved pregnancy rates as well as a rather better side effect profile. This seems to be without any analysis of whether cabergoline does indeed carry a risk of teratogenicity and the guideline group will be aware that it has been widely used for many years in women at the time of conception without apparent clinical risk.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
374.	Royal College Of Obstetricians and Gynaecologists	13.	Full	78		Section 6.2. The guideline appropriately highlights the use of the current WHO recommendations. It would be appropriate however to have some mention that sperm	Thank you for your comments. This recommendation was edited for accuracy as WHO have outlined new standards.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						concentration is a better predictor of fertility than motility or morphology and that there is also debate as to whether concentration or total sperm number is the more appropriate parameter. The text also appears to be written from the point of view that spermatogenesis is either normal or abnormal while of course it is shades of grey, and indeed recognition of this is the basis for the current WHO guidelines based upon 95% confidence intervals rather than distinct diagnostic categories.	Furthermore, it has been clarified that the figures only apply to the tests used by WHO when defining these criteria.
375.	Royal College Of Obstetricians and Gynaecologists	14.	Full	82	16	**6.3 Ovarian reserve testing** The criteria for defining an antral follicle is not given – did all studies use the same criteria ,were studies accepted or rejected if definitions varied. What size of antral follicles is the guideline based on?	Thank you for your comment. The criteria for defining AFC have been added. This was not used as a criterion for including or rejecting studies.
376.	Royal College Of Obstetricians and Gynaecologists	15.	Full	82	16	Section 6, Ovulatory disorders. It is surprising that this section starts with a lengthy discussion of the ovarian reserve which is arguably largely applicable to IVF rather than first line infertility treatment, and indeed this is substantiated by the evidence cited. Assessment of the ovarian reserve is not of primary relevance in the great majority of women presenting with ovulatory disorders, although AMH has been proposed to have good discriminatory ability in the differential diagnosis of oligo/amenorrhoea.	Thank you for your comment. The GDG did look at the overall structure of the guideline. It was felt that keeping investigations together would be more appropriate than separating them.
377.	Royal College Of Obstetricians and Gynaecologists	16.	Full	88		The definition of a low response is not consistent between the AMH and AFC studies: the ESHRE consensus definition for a poor response could be used. (Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L; ESHRE working group on Poor Ovarian Response Definition. ESHRE consensus on the definition of 'poor response' to	Thank you for your comments. These definitions of low response are these reported in the studies and are shown for information only, not as recommendations.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod. 2011 Jul;26(7):1616-24. PubMed PMID: 21505041.)	
378.	Royal College Of Obstetricians and Gynaecologists	17.	Full	99	1	No justification is provided for measuring day 21 progesterone in women with a regular menstrual cycle. Similarly women with irregular menstrual cycles are recommended to have weekly progesterone measurements. For women with profound oligomenorrhoea this does not add any value as a diagnosis of the cause of their irregular periods is required.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
379.	Royal College Of Obstetricians and Gynaecologists	18.	Full	100	1	Recommendation 56. The timing of gonadotrophin assessment should be commented on as measurement outside the early follicular phase will at times detect spontaneous ovulation and these results are frequently misinterpreted.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
380.	Royal College Of Obstetricians and Gynaecologists	19.	Full	104	3	**6.4 assessing uterine abnormalities** There ought to be some mention of 3D ultrasound and 2D and 3D saline hydrosonography here as there is a wealth of literature and it is just ignored!	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
381.	Royal College Of Obstetricians and Gynaecologists	20.	Full	105	16	**6.5 viral transmission** There is no recommendation for management of hepatitis c infected couples. This is needed for completeness	Thank you for your comment. Based on the available evidence the GDG was unable to make a recommendation for the use (either for or against) of sperm washing However, the GDG did make recommendations to make recommendations on information provision. They are that a male with hepatitis C should consult a specialist when considering a pregnancy with a hepatitis C negative partner and that the current understanding within the evidence is that the chance of transmission is low through unprotected intercourse. Furthermore, the GDG recommended that hepatitis C is sought to be eradicated before considering further action. Finally, we would like to bring to your attention the research recommendation below. It is was the GDG's hope that once this information is

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							known recommendations akin to the detail offered for hepatitis B and HIV can be made. *"What is the effectiveness of sperm washing in reducing the transmission of hepatitis C from men to their partner"*
382.	Royal College Of Obstetricians and Gynaecologists	21.	Full	105	4	**6.5 testing viral status** The HFEA and EUTD states that people undergoing IUI/DI also need infection screening. This needs to be made clear.	Thank you for your comment. Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Viral screening was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline. However, there are recommendations made later in the guideline for the routine screening of DI and within oocyte donation – we have added a footnote to this recommendation to direct the reader to these other recommendations.
383.	Royal College Of Obstetricians and Gynaecologists	22.	Full	105	15	Recommendation 64. Viral testing is a requirement of the UK regulatory authority and it seems appropriate for this to be mentioned. It will also be helpful to have a view on the appropriate interval at which these tests should be repeated for couples having IVF.	Thank you for this comment. Screening protocol was not included in the 2012 update scope. Therefore the evidence was not reviewed to allow such a recommendation within this version of the guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
384.	Royal College Of Obstetricians and Gynaecologists	23.	Full	125	1	Surely donor insemination is the only (medical) option for such couples	Thank you for your comment. This section of the Guideline was not updated but we think the statement is satisfactory. It follows a paragraph discussing surgical sperm recovery for use in assisted conception methods in some men with male factor infertility. Thus "*Donor Donor insemination (see Chapter 17) is an alternative treatment option..."* is a valid statement.
385.	Royal College Of Obstetricians and Gynaecologists	24.	Full	127		Section 7.2. hCG alone can be effective in men with post-pubertal onset of hypogonatrophic hypogonadism. The avoidance of the need for FSH in such individuals will be of substantial benefit both from cost effectiveness and patient convenience. An appropriate reference for this is Liu PY et al JCEM 2009, 94, 801.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Medical and surgical management of male factor fertility problems was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
386.	Royal College Of Obstetricians and Gynaecologists	25.	Full	133	28	Section 8.2. Kallmann is miss spelt, it should have 2 n's.	Thank you for pointing out this typographical error. We have made the necessary correction.
387.	Royal College Of Obstetricians and Gynaecologists	26.	Full	135	21	Recommendation 89 et seq. There is frequent recommendation of the use of pulsatile GnRH. The GDG will know that this is unlicensed, and appropriate expertise is rare. Furthermore the current formulation of GnRH available for this therapy makes it extremely expensive. While it is clear that this is an extremely effective therapy in women (and also in men, as	Thank you for your comments. The GDG was aware that the current formulation is expensive, however, the guideline recommends this treatment for a small number of women with WHO Group I disorders and the evidence shows it is effective as you concur. The GDG has added

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						mentioned in the relevant section), in the right hands, it would appear appropriate to mention these caveats rather than the straightforward across the board recommendation as presently phrased.	to the guideline text to highlight that the appropriate expertise is needed for this procedure.
388.	Royal College Of Obstetricians and Gynaecologists	27.	Full	135	22	Ovulation Disorders. This section seems to be missing a clear statement on the efficacy and safety of clomiphene alone as first line therapy in WHOII anovulation.	Thank you for your comment. The section to which you refer is an Introduction to the section on WHO Group II Ovulation Disorders. It is deliberately written in a way that describes existing practice but does not prejudge what the review that is prefaces will conclude. In the Evidence to recommendations section and in the recommendations themselves the GDG believed they have made a clear statement on the efficacy and safety of clomifene citrate alone as first line therapy.
389.	Royal College Of Obstetricians and Gynaecologists	28.	Full	70+73	C3+24	**Factors affecting fertility** Cross reference to the NICE guideline for management of the obese pregnant women who should receive 5mg of folic acid preconceptually would be appropriate.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
390.	Royal College Of Obstetricians and Gynaecologists	29.	Full	83,84		**6. Investigations** AMH is promoted as a marker of the ovarian reserve: this seems appropriate but I wonder	Thank you for your comments.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						how useful the precise numbers given in the NICE guideline actually are. The guideline group will be aware of the differences in AMH results from the assays currently available and with development of the Gen II assay now becoming more widely used these numbers are set to change again. Giving such specific numbers without any discussion as to the assays in which they were derived is therefore potentially misleading and will lead to errors in clinical practice. Details regarding conversion of values from the DSL assay to the Gen II assay is provided in Wallace AM, Faye SA, Fleming R, Nelson SM. A multicentre evaluation of the new Beckman Coulter anti-Mullerian hormone immunoassay (AMH Gen II). Ann Clin Biochem. 2011 Jul;48(Pt 4):370-3. PubMed PMID: 21628625.	We agree with your comment and the assay tests used have been described in footnotes. However, we are unable to add the conversion figures.
391.	Royal College Of Obstetricians and Gynaecologists	30.	Full	169	24	**8. ovulation disorders** Medical management - on what evidence are the statements 'metformin is not used for the management of PCOS' and metformin and clomiphene is not common practice made – I think this statement needs to be referenced or removed.	Thank you for your comments. The sentence stating that metformin is not used for the management of PCOS has been removed. It has been replaced with '*Metformin is currently not licensed for use in the treatment of PCOS (its license is for use in diabetes)'.* The statement about common practice has been edited to state: *"The GDG took into account that gonadotrophins are often used in second line treatment when the woman is resistant to clomifene citrate, and that metformin in combination with clomifene citrate is less common practice in England and Wales."*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
392.	Royal College Of Obstetricians and Gynaecologists	31.	Full	170	1	Recommendation 95. Ultrasound monitoring is recommended in clomiphene treatment. No evidence is presented for this expensive approach.	Thank you for your comment. The GDG believed the potential risks to the mother and babies of a multiple pregnancy are great enough to justify ultrasound scanning.
393.	Royal College Of Obstetricians and Gynaecologists	32.	Full	170	1	Recommendation 96. No evidence is presented for limiting clomiphene treatment to 6 months, This seems to derive from the duration of the licence of this therapy. This also seems at odds with the lengthy discussion and justification of 12 cycles of donor insemination for women who require that therapy. There is also no mention of the management of women who are not clomiphene resistant but who do not conceive on clomiphene therapy despite have regular ovulation.	Thank you for your comments. The GDG acknowledged that there was no evidence addressing the stopping of clomfene citrate after 6 months, however, the main reason the GDG recommended limiting treatment with clomifene citrate to six months is because of the possibility of clomifene citrate resistance. The GDG did not believe that women who are resistant to clomifene citrate should continue to be offered clomifene citrate alone beyond six months. If the woman has not responded to clomifene citrate after six months, other treatment options for these women should be explored. This will also help reduce the costs that result from the additional monitoring needed with the use of clomifene citrate. Text has been added to the full guideline to clarify this. With respect to your comparative statement regarding 12 cycles of DI, please note that the Guideline recommendations that the 12 cycles of donor insemination would include 6 unstimulated cycles and 6 stimulated cycles, and so restricting clomifene citrate treatment to 6 months is not at odds with the donor insemination recommendations.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
394.	Royal College Of Obstetricians and Gynaecologists	33.	Full	171	12	Recommendation 99. In the full discussion of this it would be appropriate to mention current guidelines on echocardiography to assess mitral valve fibrosis in patients taking bromocriptine.	Thank you for your comments. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in Scope of the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
395.	Royal College Of Obstetricians and Gynaecologists	34.	Full	173	8	**9.1 Inntroduction** Bipolar uterus – should this be bicornuate? Also it is mentioned in the introduction and then not referred to again in the text.	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
396.	Royal College Of Obstetricians and Gynaecologists	35.	Full	176	1	Section 9.5. It is surprising to see a recommendation on the value of division of intrauterine adhesions (based upon 1 small case series), but no recommendation regarding the treatment of the fibroid uterus.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Tubal and uterine surgery was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
397.	Royal College Of Obstetricians and Gynaecologists	36.	Full	178	1	Section 10.3. Surgery to an endometrioma is increasingly recognised to reduce the ovarian reserve by removing some normal ovarian tissue. This should be mentioned. It would also	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						be helpful to have guidance on the appropriate treatment of an endometrioma prior to IVF rather than in just spontaneous conception as is currently presented.	scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. Endometrioma was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
398.	Royal College Of Obstetricians and Gynaecologists	37.	Full	192	3+14	**12.1 Evidence profiles1 & 2** The mean and range if the duration of infertility was stated for these studies -this makes no statistical sense – either the data was parametric or non parametric. If it wasn't clear from the studies should they really be included?	Thank you for your comments. Your comments have been considered by the GDG and the relevant text has been amended
399.	Royal College Of Obstetricians and Gynaecologists	38.	Full	200	11	Section 12. There is a very valuable discussion of the health economics of IUI suggesting that it is indeed of some value. This discussion however is not mentioned in the consideration section, which appears primarily driven by individual clinical experience which appears to be at odds to the NICE ethos.	Thank you for your comment. The GDG did consider the health economic analysis in the evaluation. They considered that the absolute resources saved and better use of available time by not routinely providing IUI outweighed the cost-effectiveness. This was one of the reasons that the waiting time for IVF was reduced from 3 years to 2 years. The text in the evidence to recommendation section has been updated to reflect this decision making. *"The GDG highlighted that whilst health economic analysis showed that IUI could be cost effective, that there were no apparent health benefits and potential increased risks associated with IUI (with or without stimulation) when compared with an*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							alternative strategy of expectant management. Therefore, they considered that considerable resources could be saved and used elsewhere."
400.	Royal College Of Obstetricians and Gynaecologists	39.	Full	204	23	Recommendation 117. 12 cycles of DI are recommended without apparent discussion or analysis of the data regarding the health economic benefit of limiting this to 6 cycles of IUI followed by IVF with donor sperm thereafter. As mentioned above, this also seems at odds with the recommendation of limiting ovulation induction therapy to 6 cycles.	Thank you for your comment. This recommendation relates to sex-same couples and other who are unable to have vaginal intercourse. The discussion on equivalence between vaginal intercourse and DI using IUI is outlined below: *"Finally, the GDG discussed what constituted equivalent expectant management for two groups of women (as already shown in chapters 11 and 12):* *For people having unprotected regular vaginal intercourse* *Natural conception rates are shown in Figure 5.1. In summary, over 80% of couples where the women is age 39 years or less will conceive within 12 months. The figure is over 85% where the woman is less than 35 years. If the couple continue to have unprotected regular intercourse for another 12 months, making 24 months in total, cumulative pregnancy success rates rise by about a further 15%.* *The GDG did note that even after two years without a live birth, couples with unexplained infertility, mild endometriosis or mild male factor infertility still had a chance of natural conception. However, the additional*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							cumulative success rates in the third year would be very small. Furthermore they declined with the age of the woman. The GDG felt that this information should be explained early on to women with the diagnosis of unexplained infertility (see Fig 5.1). Thus, the GDG's view was that after two years of unexplained infertility (including the 1 year before testing and diagnosis), IVF should be considered. The cost-effectiveness of IVF under specific circumstances is considered elsewhere (see chapter 13) but the GDG consensus view was that women with a diagnosis of unexplained fertility should be told at the start of their 12 months of expectant management, that they will be considered for IVF after a total of two years without conception. This provides women with unexplained infertility with a clear idea of the period of time they should continue with regular unprotected vaginal intercourse before IVF will be considered(although it will not necessarily be offered). The GDG view was that this would represent a positive approach and lessen the anxiety and depression identified in the expectant management group in the trial reported here. *For people in same-sex relationships where conception was being attempted by DI* *Once, after assessment and investigation, the diagnosis of unexplained infertility, mild endometriosis or mild male factor infertility was made, the GDG felt that further attempts at conception should be made using IUI and donor sperm for a period of time. They*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							highlighted the cumulative success rates with ICI and IUI. Specifically, as reported in Chapter 5, they noted that, whilst after 6 cycles of DI the cumulative chances of successful conception from ICI or IUI in women who are 35 years or less were: • *over 40% for ICI using thawed semen (Federation CECOS et al., 1982)* • *over 50% for ICI using fresh semen (van Noord-Zaadstra et al., 1991)* • *over 60% for IUI using mainly thawed semen (HFEA data http://www.hfea.gov.uk/1270.html#1299)* *After a further 6 months (12 months in total) these figures rose to:* • *over 60% for ICI using thawed semen (Federation CECOS et al., 1982)* • *over 70% for ICI using fresh semen (van Noord-Zaadstra et al., 1991)* • *over 80% for IUI using mainly thawed semen (HFEA data http://www.hfea.gov.uk/1270.html#1299)* *These additional cycles of IUI with donor sperm would be the same as expectant management in couples with unexplained infertility, mild endometriosis or mild male factor infertility having vaginal intercourse. The GDG discussed options for the number of cycles of IUI that should constitute an acceptable period of expectant management.*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							The same issues were raised in this discussion as were covered in the discussion over determining when to refer people for assessment and possible treatment of their infertility (see Chapter 5). The GDG felt that the practical barriers (availability of sperm, cost and time) to undertaking IUI with donor sperm meant, in reality, that same-sex couples with unexplained infertility could not be expected to undergo 12 cycles of IUI in order to achieve numerical equivalence with people having vaginal intercourse with the same diagnosis having 12 months of expectant management. *In conclusion, if as a result of infertility assessment the diagnosis is made of unexplained infertility, mild endometriosis, or mild male factor infertility, the GDG were of the opinion that the women in same-sex relationships should be advised to have a further 6 cycles of IUI with donor sperm (making a total of 12 cycles of DI in total) and that would constitute 'expectant management' for that group*
401.	Royal College Of Obstetricians and Gynaecologists	40.	Full	214		Recommendation 121. This may well be true but is of no value to the couple and indeed is very negative for the majority who have not had a pregnancy.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							the existing topic in the final version of the Guideline.
402.	Royal College Of Obstetricians and Gynaecologists	41.	Full	218		Recommendation 122. In presenting the evidence here it would be very useful to give the odds ratio or similar to show the effect size e.g. by number needed to treat, as this issue is often a criterion for preventing access to NHS treatment. It would perhaps also be appropriate to state the absence of evidence for a beneficial effect of weight loss in women proceeding to IVF, and the time taken to do this needs to be balanced against the inevitable decline in success associated with the increase in aging that will be happening.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
403.	Royal College Of Obstetricians and Gynaecologists	42.	Full	254	36	I don't think this statement is useful – people will therefore assume that this is what they are entitled to regardless of funding available. Perhaps a more useful phrasing would be ' inform commissioners that one full cycle etc'.	Thank you for your comments. The GDG felt that the inclusion of the word 'normally' allows clinical exceptions to this (for example, in some cycles no eggs are available for freezing).
404.	Royal College Of Obstetricians and Gynaecologists	43.	Full	254	36	I don't think this statement is useful – people will therefore assume that this is what they are entitled to regardless of funding available. Perhaps a more useful phrasing would be ' inform commissioners that one full cycle etc'.	Thank you for your comments. The GDG felt that the inclusion of the word *'normally'* allows clinical exceptions to this recommendation (for example, in some cycles no eggs are available for freezing).
405.	Royal College Of Obstetricians and Gynaecologists	44.	Full	313	1	Recommendation 144. We welcome the robust discussion of the absence of value of DHEA treatment. The GDG will be aware that many IVF units are also using low molecular weight heparin and glucocorticoid as adjuvant therapy in IVF and these should also be addressed.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline. However, we would draw your attention to the following text in the Introduction to the Section 15.8 on Luteal Phase Support in the full Guideline: *'A number of other agents have been promoted as being useful in luteal phase support and were mentioned during the scoping phase for the Guideline Update, These include low dose aspirin, heparin, prednisoline, immunoglobulins and/or fat emulsions. The pre-scoping search and review did not identify any RCT evidence suggesting benefit from any of these interventions. Furthermore, it was highlighted that these are not part of conventional care in the UK, and, therefore, they were not included in the final scope for the guideline update.'*
406.	Royal College Of Obstetricians and Gynaecologists	45.	Full	328		**15.7** There is no mention of the increased rate if monchorionic twinning with blastocyst transfers which is associated with increased risks to mother and children. This should at the very least be a research recommendation given this Guidelines very definite push towards blastocyst transfer.	Thank you for your comment. The GDG was aware of this issue when drafting the recommendation, and of on-going research on this. However, this evidence was not reviewed.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
407.	Royal College Of Obstetricians and Gynaecologists	46.	Full	346	20	Recommendation 159. While we applaud the emphasis in reducing the numbers of embryos transferred to minimise the number of multiple pregnancies, the guideline group will be aware that the changes they propose will also have a significant negative effect on overall pregnancy rates. This is not acknowledged or discussed nor is there a clear discussion of why they have arrived at a different result to that presented by the BFS in Cutting et al.'s publication. There is now clear evidence derived from the UK population for limiting the maximal number of embryos to be transferred to two. This should be cited to support the limit (Lawlor DA, Nelson SM. Effect of age on decisions about the numbers of embryos to transfer in assisted conception: a prospective study. Lancet. 2012 Feb 11;379(9815):521-7. PubMed PMID: 22243709).	Thank you for your comments. The GDG was aware that the proposal will reduce overall pregnancy rates in the first cycle. However, the GDG has outlined criteria based on people receiving 3 full cycles of IVF and with the aim of achieving a live full-term singleton birth. Based on the available evidence on effectiveness and safety, it is the conclusion of the GDG that using a single embryo in the first full cycle optimises the chance of a live full-term singleton birth. If this fails then the next 2 full cycles allows more than one embryo to be transferred dependent on embryo quality. The process for developing the algorithm, including the use of the BFS in Cutting et al.'s publication is outlined in section 15.7. However, further text has been added to show the results of this process: *"Initially a table (see table 15.30) was outlined based an algorithm outlined by Cutting et al., 2008. The algorithm included women's age, number of failed IVF cycles, the number and the quality of embryos. In total, there were 27 different clinical scenarios. In addition, the survey contained a number of questions and statements related to embryo transfers, such as the need for information provision to couples about the risks of multiple births.* *Three rounds of voting were then undertaken where GDG members were asked to apply the evidence they had been presented with*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							alongside their own judgement to the clinical scenarios outlined in the table. The survey and voting were all undertaken electronically. Results and comments were combined and anonymised before being returned to the GDG. A detailed description of the methodology used is shown in Chapter 3.The initial table was simplified over the three rounds as consensus allowed clinical scenarios to be combined and the simplified table was used in the final recommendation. Furthermore, as the strategy was based on three full cycles of IVF and the algorithm outlined by Cutting et al, 2008 was based on a single cycle, the GDG varied the embryo transfer strategy used in each cycle in order to maximise the chances of achieving a live full-term singleton birth." The guideline recommends that the number of embryos transferred should be limited to 2:
408.	Royal College Of Obstetricians and Gynaecologists	47.	Full	363		**16.** Line 6 Typo – technique not techniquel	Thank you for pointing out this typographical error. We have made the necessary correction.
409.	Royal College Of Obstetricians and Gynaecologists	48.	Full	365		**Recommendation 170** Very poor fertilisation – this needs to be defined somewhere in the supporting text	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. ICSI was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							the existing topic in the final version of the Guideline. However, the GDG did note that clarification of the indications of ICSI within recommendation 170 would be useful for clinicians: *"Therefore the decision to offer ICSI after IVF failure should involve consideration of the added value that ICSI would have. For example, ICSI could be offered where there the previous IVF cycle demonstrates it may be of value (such as failure of the sperm to bind to the oocyte) or where the fertilisation rate is unexpectedly poor (a common value used is less than a 50% fertilisation rate)."*
410.	Royal College Of Obstetricians and Gynaecologists	49.	Full	365	5-6	Line 5-6 States that chromosome testing should be done for both the couple in the case of azoospermia. This does not appear in the recommendations however.	Thank you for your comment. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. ICSI was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline.
411.	Royal College Of Obstetricians and Gynaecologists	50.	Full	380	1	Section 19. Comment re highlighting that this is of relevance to patients other than those with cancer at an earlier part of this section has been made above.	Thank you for your comment. The scope of this guideline was to only make specific recommendations for cancer patients. We have, however, added text (below) to

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							make sure that the guideline is explicit on the context of the recommendation the GDG made but does not to preclude their use for other patient groups. *"The scope of this guideline states that recommendations are to be outlined for people undergoing cancer treatment who wish preserve their fertility. The interpretation of the evidence was based on this and recommendations have been written specifically for this population. No recommendations are made for other groups who may prematurely lose their fertility. However, the GDG highlighted that the fact recommendations were not made for other groups should not be used as a justification for not funding cryopreservation in these groups and that the recommendations made in the guideline could be extrapolated to other population who may be at risk of losing their fertility due to treatment."*
412.	Royal College Of Obstetricians and Gynaecologists	51.	Full	387	7	Line 7 Kim – main article in Korean – if the information in the main article could not be correlated with the abstract I am unsure as to how the GRADE findings were established	Thank you for your comment. This journal also provides a short report version in English and data was extracted from this.
413.	Royal College Of Obstetricians and Gynaecologists	52.	Full	479		**2012 references** There are multiple errors in the reference list – too many to individually list, with incomplete references and variations in format.	Thank you for your comment. The final version of the guideline will have been copy edited, including a thorough check of the reference list.
414.	Scottish Government	1		General		We read the draft Fertility guideline with interest, and look forward to receiving the final guideline.	Thank you for your comment

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
415.	SPD Swiss Precision Diagnostics GmbH	1	Full	66	17	We welcome the inclusion of a recommendation to advise couples on both frequency and timing of intercourse. As part of the period of 'expectant management' we would recommend advice is given on how to time intercourse to the most fertile period as evidence shows women's accuracy in determining this is variable due to the lack of awareness of their own menstrual cycle characteristics and their own intra-cycle variability. • Zinaman, M. *et al.* Accuracy of perception of ovulation day in women trying to conceive. Curr. Med. Res. & Opin. 2012; 28:1-6	Thank you for your comments. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline. However, we do think that the 2004 text in section 5.3 does implicitly support your statement in that it does not recommend using temperature charts or other clinical non-laboratory predictors of ovulation to time intercourse.
416.	SPD Swiss Precision Diagnostics GmbH	2	Full	67	13	The statement that 'urinary luteinising hormone (LH) kits as indicators of ovulation to time intercourse did not report improvement in the chance of natural conception' has been substantiated by four publications. However these studies did not set out to assess conception rates when using LH tests. (Guida *et al.,* actually assessed the accuracy of LH testing as a method for NFP.) These studies did however all substantiate the accuracy of LH surge as a predictor of ovulation. More recent studies have demonstrated that an awareness of a woman's most fertile days and timing of intercourse can increase the chances of conception.	Thank you for your comments. The topics for the guideline update were considered as part of NICE's standard scoping process. A stakeholder workshop was held and the scope was subject to a period of public consultation before it was finalised. This topic was not selected to be included in the 2012 update of the Fertility Guideline. Therefore, we cannot take your comments forward or make any substantive changes to the existing topic in the final version of the Guideline. However, we do think that there is support of your statement in the existing 2004 text in section 5.3 which states

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						• Gnoth. C *et al.*Time to pregnancy: results of the German prospectivestudy and impact on the management of infertility. Human Reproduction 2003, 18(9), 1959-1966 • Hilgers, TW *et al*. Cumulative pregnancy rates in patients with apparently normal fertility and fertility-focused intercourse. Repro. Med 1992, 37: 864-6: • Stanford, J & Dunson, D. Effects of sexual intercourse patterns in time to pregnancy studies. Am J Epidemiol. 2007, 165:1088-1095 • Robinson, J., Wakelin, M & Ellis, J.E. Increased pregnancy rate with use of the Clearblue Easy Fertility Monitor. Fertil. Steril. 2007, 87(2): 329-34 In addition, a significant proportion of women have been shown to inaccurately identify their fertile days and mistiming of intercourse is a common problem for women failing to conceive • Zinaman, M. *et al.* Accuracy of perception of ovulation day in women trying to conceive. Curr. Med. Res. & Opin. 2012; 28:1-6 • Robinson, J & Ellis, JE. Mistiming of intercourse as a primary cause of failure to conceive: results of a survey on use of a home-use fertility monitor. Curr. Med. Res. Opin. 2007, 23:301-6	*"However, for the minority of couples who find it difficult to have frequent sexual intercourse every two to three days the prediction of ovulation using LH kits can be useful."*
417.	SPD Swiss Precision Diagnostics GmbH	3	Full	67	15	We believe the statement that 'Timed intercourse has been suggested to be an emotionally stressful intervention in the initial	Thank you for your comments.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						evaluation of infertility' has a poor evidence base and new published evidence does not support this. The referenced evidence by Kopitzke, MS *et al*., was a study which used old home ovulation testing products which were difficult for women to use and particularly difficult in interpreting the results. Products have improved substantially since this study and are now both easy to use and the results are very easy to interpret. • Johnson, S. *et al.* Comparison of a digital ovulation test with three popular line ovulation test s to investigate user accuracy and certainty. Expert Opin. Med. Diagn. 2011, 5(6): 467-473 In order to provide level 1 evidence in support of the fact that timing intercourse to the fertile phase of the cycle does not increase stress, SPD has collaborated with the University of Sheffield on a randomised, controlled trial of 210 women trying to conceive naturally. One group were provided with digital ovulation tests and the control group were provided with current NICE guidelines for achieving pregnancy. The study concluded that 'no difference was found in levels of stress between women using digital ovulation tests to time intercourse compared with women who were trying to conceive without any additional aids.' • Ledger, W. *et al*. Impact of use of home ovulation tests on the level of stress in women trying to conceive: a	The evidence was shown to be factually inaccurate and therefore the recommendation was adapted.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						randomised controlled trial. Oral abstract to be presented at ESHRE Congress, Istanbul, July 2nd 2012 • Tiplady, S. *et al*. Attitudes and opinions of women using digital home ovulation tests whilst trying to conceive. Poster abstract to be presented at ESHRE Congress, Istanbul 1-4th July 2012 • Full manuscript in submission	
418.	Stonewall	1	Full	General		Stonewall are Britain's leading lesbian, gay and bisexual equality charity. Stonewall welcome NICE's decision to update current guidance on fertility, recognising some of the issues same-sex couples face. Since the original NICE guidance of 2004, equality legislation has been passed to protect lesbian, gay and bisexual people when accessing services (Sexual Orientation Regulations (2007) – now covered under the Equality Act 2010). In addition, the 2008 Human Fertilisation and Embryology Act removed the 'need for a father' provision which was interpreted by many fertility clinics as an outright ban on lesbians from accessing fertility treatment. Lesbians and bisexual women seeking fertility treatment on the NHS are entitled to exactly the same assessment processes as heterosexual women are, and are protected by the above legislation. However, Stonewall hear from many lesbians looking to start a family of GP's refuse to refer	Thank you for your comment.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						on for fertility treatment and of PCT's who refuse to fund lesbians on the grounds of their sexual orientation. Stonewall therefore welcome the decision to update guidance that reflects the changes in equality legislation and the growing number of same-sex partners seeking fertility treatment.	
419.	Stonewall	2	Full	6	2	Stonewall welcome explicit mention of 'same-sex' relationships	Thank you for your comments
420.	Stonewall	3	Full	12	1	Stonewall welcome explicit reference to 'same-sex' couples and a clear fertility treatment option (intrauterine insemination)	Thank you for your comment.
421.	Stonewall	4	Full	31	116	Stonewall welcome this new update.	Thank you for your comments
422.	Stonewall	5	Full	31	117	Stonewall are concerned that this is unfair - lesbians seeking fertility treatment are expected to pay up to £6,000 (based on average of £1,000 per cycle) before being able to seek NHS treatment – which has been considered the equivalent of heterosexual women attempting to conceive. We are aware that some lesbians try to conceive at home, which does expose them to a number of potential risks. Recommending that lesbian couples fund six cycles of treatment themselves before investigation may dissuade them from accessing safe clinical services.	Thank you for your comments. However, the Scope makes it clear that the Guideline is for people who have a possible pathological problem (physical or psychological) to explain their infertility. Women in same sex relationships can only be considered to be possibly in that category and be considered to be 'infertile' if they have a period of unsuccessful artificial insemination (AI). How that AI is provided and funded are outside the Scope of the Guideline.
423.	Stonewall	6	Full	46	36	Stonewall welcome NICE's consideration of same-sex couples seeking fertility treatment	Thank you for your positive comments about the 2012 update of the Fertility Guideline.
424.	Stonewall	7	Full	75	7	Stonewall agree that lesbians seeking treatment should do so in the safe environment of a clinical setting, and success rates are reasonable.	Thank you for your positive comments about the 2012 update of the Fertility Guideline.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
425.	Stonewall	8	Full	75	38	Stonewall agree that the cost of 6 cycles of IUI is lower than funding 12 cycles of IUI, however the guidance states that this still puts same-sex couples at a disadvantage which Stonewall believe has not been addressed.	Thank you for your comments. However, the Scope makes it clear that the Guideline is for people who have a possible pathological problem (physical or psychological) to explain their infertility. Women in same sex relationships can only be considered to be possibly in that category and be considered to be 'infertile' if they have a known cause or a period of unsuccessful artificial insemination (AI). How that AI is provided and funded are outside the Scope of the Guideline.
426.	Stonewall	9	Full	75	50	Stonewall are concerned that lesbians who have to self-fund six cycles of IUI before being considered for NHS funded cycles, will need undertake 12 cycles within 12 months, ignores the potential for delay in accessing NHS treatment in the month after the sixth cycle of self-funded treatment.	Thank you for your comments. The Guideline makes it clear that if a woman in a same-sex relationship has not conceived after 6 cycles of AI then that is an indication for referral for clinical assessment and investigation before considering further treatment. The further six cycles of AI by IUI would only be undertaken if the investigations confirmed the woman was ovulating and had patent fallopian tubes. There would be a delay whilst the investigations were undertaken just as there would be for people trying to conceive by vaginal intercourse who were unsuccessful after trying to conceive for 12 months.
427.	Stonewall	10	Full	76	35	Stonewall believe this recommendation needs to be strengthened to make sure lesbian couples seeking fertility treatment are given an initial assessment, in line with legislative duties. At present, the guidance is not clear on initial assessments to identify infertility or to	Thank you for your comments. This was a recommendation from the original 2004 Guideline. It applies to all people trying to conceive who *"are concerned about delays in conception"* – both women in same-sex relationships and those people in

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						recommend next steps for those with undefined fertility problems.	heterosexual relationships. We do not think that the two groups need to be specified.
428.	Stonewall	11	Full	203	46	Stonewall believe the recommended six cycles of IUI be funded by the NHS, if they meet criteria on age, weight, and other criterion defined at the beginning of this guidance, in order to remove disadvantage between heterosexual and same-sex couples.	Thank you for your comments. However, the Scope makes it clear that the Guideline is for people who have a possible pathological problem to explain their infertility. Women in same sex relationships can only be considered to be possibly in that category and be considered to be 'infertile' if they have a period of unsuccessful artificial insemination (AI). How that AI is provided and funded are outside the Scope of the Guideline.
429.	Tamba, Twins and Multiple Births Association	1	Full			The views of our members are split on the proposals to further restrict patient choice when it comes to IVF. On the one hand a number feel it is right to reduce the chances of multiple births because of the additional risks these pregnancies may incur. Nevertheless, a considerable proportion still believes that families should be allowed greater input then currently proposed in the draft guidance. Many want more than one child and did not enjoy the experience of fertility treatment and therefore do not feel it fair to force those in this situation to undergo it more then once. Many others feel the proposals do not consider the real world in which these are being present and ignore the fact that the majority of treatments are still paid for privately. A number still question the data presented in support of these proposals taking a similar view to Lord Winston who recently presented at ISTS/World Twin Pregnancy Conference on the situation confirming the risks of not conceiving via fertility treatment are far higher then the risks of having multiples.	Thank you for your comments. The GDG had a similar discussion when weighing up the implications of a multiple birth. We should reiterate that the embryo transfer policy is based on the IVF strategy where women are receiving three full cycles of IVF, and wish to highlight the individual parts should not be viewed in isolation. The evidence considered was of the highest quality available. The GDG has made their recommendations to ensure that the best chance of a live full term singleton birth is reached while minimising the risk to mother and child that come with multiple pregnancy and other reported adverse events.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
430.	Teenage Cancer Trust	1	Full	General		General comment: Teenage Cancer Trust believes young people's lives shouldn't stop because they have cancer, so we treat them as young people first, cancer patients second. We exist to improve the quality of life and chances of survival for the six young people aged between 13 and 24 diagnosed with cancer every day in the UK. We want to make sure every one of them has access to the best possible care and professional support from the point of diagnosis. We fund and develop specialist units within NHS hospitals that bring young people together to be treated by teenage cancer experts in an environment tailored to meet their needs. We welcome the inclusion of a specific section on cancer patients in these guidelines. It is incredibly important that all people with cancer, including teenagers and young adults, are informed of potential fertility problems they may face as a result of treatment for their cancer and have the opportunity to preserve their fertility where possible. We know that young people with cancer currently have very variable experiences of fertility advice and options for treatment and we believe these guidelines will help to address this inequity. At our Find Your Sense of Tumour conference earlier this year we asked 270 young people with cancer about their experiences of fertility	Thank you for your comment.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						advice. 37% were male and 63% were female aged between 12 and 24 when they were diagnosed with cancer. Nearly half of these young cancer patients were not spoken to about their fertility options. Out of those who were spoken to, half were not satisfied with the discussion. These findings clearly demonstrate the scale of the current problems faced by young people with cancer dealing with very difficult decisions about their future fertility. A first step has to be to address the access to information about fertility at diagnosis, which is addressed by new recommendations in these guidelines. It is critical that the recommendations in Chapter 19 are approved and implemented across England, Wales and Northern Ireland, and we hope will be accepted in Scotland.	
431.	Teenage Cancer Trust	2	Full	380	9 – 13	We welcome the context given in the introduction of the need to specifically consider young people's fertility preservation and need for discussion before treatment starts.	Thank you for your comment.
432.	Teenage Cancer Trust	3		381	11 – 14	We support the recommendation that sperm banking must be considered for all males prior to treatment that carries risk of long-term gonadal damage.	Thank you for your comment.
433.	Teenage Cancer Trust	4		381	15 – 17	We welcome the focus on the specific issues facing adolescent boys and the need for specialist advice and counselling to be made available.	Thank you for your comment.
434.	Teenage Cancer Trust	5		381	20 – 22	We support the need for awareness of child protection for anyone under the age of 18.	Thank you for your comment.
435.	Teenage Cancer Trust	6		381	30 – 34	We welcome the recognition of counselling and information as an integral part of the	Thank you for your comment.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						management and need for multi-disciplinary input.	
436.	Teenage Cancer Trust	7		388 389	47 – 49 1-6	We support the need to look at the costs of storing samples and the non-use of stored samples. A 10 year interval is reasonable but in the life of a young person could mean at the time of review they are still only in their mid-20s and truly may not have decided on whether they want to use fertility treatment.	Thank you for your comment. The GDG agreed with your comment. The recommendation implies that 10 years is the minimum amount of time a sample should be stored. To clarify this point the following text has been added to the evidence to recommendations text. *"The statutory 10 years should be considered as a minimum time for storage. If the patient is at significant risk or remains infertile then the material should be stored beyond 10 years. The decision to continue storage should also consider the expected outcome of subsequent fertility treatment, as storing a sample beyond the reproductive age or viability of a patient would be unrealistic."*
437.	Teenage Cancer Trust	8		389	25	We welcome the specific focus on young adults	Thank you for your comment
438.	Teenage Cancer Trust	9		389	29 – 31	We welcome the emphasis on the importance of discussion about fertility with the patient at diagnosis.	Thank you for your comment
439.	Teenage Cancer Trust	10		389	32 – 34	We support the need to also focus on fertility units and their ability to respond urgently in advance of cancer treatment.	Thank you for your comment
440.	Teenage Cancer Trust	11		389	36 – 37	We strongly support the approach of separating policy for cancer patients to the general fertility pathway. This is an important development, and removes any ambiguities there may be in practice about working with cancer patients.	Thank you for your comment
441.	Teenage Cancer Trust	12		389	49 – 52	We welcome the GDG's consideration of the need to remove a set lower age limit for women's access to treatment and believe this is	Thank you for your comment

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						fair and allows young women with cancer to consider appropriate fertility preservation.	
442.	Teenage Cancer Trust	13		390	1 – 8	We support the GDG's position on access to fertility treatment to be in line with individual decisions at the time of use, and we welcome the statement that if there is a reasonable chance of success then it should be offered following successful cancer treatment which may help clarify decisions made in practice.	Thank you for your comment
443.	Teenage Cancer Trust	14		391 – 392		We welcome these new recommendations.	Thank you for your comment
444.	Teenagers and Young Adults with Cancer	1		47		TYAC very much supports the fact that all young people with a cancer diagnosis should be offered fertility preservation when ever that is appropriate. This should be free and the access unhindered. TYAC is supportive of this document.	Thank you for your comments
445.	Terrence Higgins Trust	1	Full	General		As the UK's largest HIV charity, Terrence Higgins Trust warmly welcomes the decision by NICE to consult on an updated version of its Fertility Guidelines. The new approach outlined holds the potential to transform fertility services for men and women living with or affected by HIV in the UK who want to become parents, and goes some way towards demystifying crucial issues around HIV, fertility and conception.	Thank you for your comment.
446.	Terrence Higgins Trust	2	Full	General		We are very concerned however that vaginal sex where the female partner is HIV positive and the male is HIV negative is not considered within the scope of this guideline. We believe that this could result in a serious inequity in access to appropriate conception support for women living with HIV and could result in women having to under go IVF unnecessarily. In cases of vaginal sex among sero discordant	Thank you for your comments. The scope of guideline was to examine the effectiveness of sperm washing, which is only relevant for a HIV positive male. In order to answer the question sperm washing was compared with viral transmission through unprotected sex and post exposure prophylaxis. The results of this review showed

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						couples, the risk is less if the receptive partner is HIV positive than if the insertive partner is HIV positive. We are therefore in the analogous situation whereby NICE will be making a statement with regards to HIV positive men, fertility and the impact of treatment with no similar statement for HIV positive women where the risks may in fact be less. NICE should seek to include HIV positive women in this guideline in order to avoid inequalities in service provision and unnecessary use of IVF. It is not acceptable to fall back on administrative questions of scope where this could exacerbate inequalities in access to care for a vulnerable group.	that if certain criteria were met that unprotected intercourse would be a suitable option if the male partner was HIV positive.
447.	Terrence Higgins Trust	9			116	We would suggest that it would be worth adding a further qualifying statement in the second bullet point which clarifies that this only applies where the viral load/ treatment criteria has not been met. This statement comes from the older version of the guideline and could be potentially misleading if read in isolation. We therefore think that it should be qualified with reference to the new additions to the guideline.	Thank you for your comments. On this occasion, however, the GDG wised to retain the current wording within the recommendation. Although we have recommended unprotected sex (if the man meets our criteria) we still reserve the right for sperm washing to be used if this criteria is not met or the couple are apprehensive. Within this group therefore, the IUI recommendations should be used, regardless of meeting the viral load criteria.
448.	Terrence Higgins Trust	8	Full	26-27	60-72	Terrence Higgins Trust supports all of the statements made in this section of the new guideline.	Thank you for your comment
449.	Terrence Higgins Trust	3	Full	3	30-40	Terrence Higgins Trusts supports the questions posed on HIV and conception. We consider that these are the correct questions to ask when considering risk reduction during vaginal sex	Thank you for your comments. The scope of guideline was to examine the effectiveness of sperm washing, which is only relevant for a HIV positive male. In order to

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						between an HIV negative woman and an HIV positive man. We would argue that HIV positive women and fertility should have been included in these questions.	answer the question sperm washing was compared with viral transmission through unprotected sex and post exposure prophylaxis. The results of this review showed that if certain criteria were met that unprotected intercourse would be a suitable option if the male partner was HIV positive.
450.	Terrence Higgins Trust	4	Full	16	L3	We support the offer of BBV testing to all IVF patients.	Thank you for your comment
451.	Terrence Higgins Trust	5	Full	16	L8	Terrence Higgins Trust fully supports the following statement made in the guidance: 'Advise couples where the man is HIV positive that the risk of HIV transmission to the female partner is negligible through unprotected sexual intercourse when all of the following criteria are met: - the man is complying with highly active antiretroviral therapy (HAART) - the man has a plasma viral load of less than 50 copies/ml - there are no other infections present - unprotected intercourse is limited to the time of ovulation.'	Thank you for your comment
452.	Terrence Higgins Trust	6	Full	16	L9-L10	Terrence Higgins Trust supports the statements made in these boxes in relation to sperm washing.	Thank you for your comment
453.	Terrence Higgins Trust	7	Full	23	43	Terrence Higgins Trust supports the recommendation that people living with HIV who are concerned about their fertility should be referred to providers with appropriate expertise. We agree that it is essential that people are supported by professionals with the appropriate level of knowledge and training.	Thank you for your comment. The guideline sets the best practice, based on clinical and cost effectiveness, for the NHS.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						However, we would welcome inclusion of a statement that underlines the fact that all IVF specialist clinics should have an understanding of the basics with regards to HIV and fertility. Too many of our clients report poor experiences in fertility services due to lack of knowledge and/ or stigma. We would therefore like to see these guidelines act as a lever to improve HIV knowledge levels in all fertility services. We do not want to see a situation whereby people living with HIV are told that they cannot directly access fertility services and subsequently experience unnecessary delays to their treatment.	The recommendations are made to improve treatment for all people included within it. Throughout the guideline, people with HIV are accounted for within the specific equality considerations - not just within this chapter. The GDG did not feel that an additional recommendation is required as the implementation of the entire guideline will make such a recommendation unnecessary.
454.	Terrence Higgins Trust	10	Full	31	116	Terrence Higgins Trust fully supports the inclusion of same sex couples in this guideline.	Thank you for your comments
455.	Terrence Higgins Trust	11	Full	43	RR1-RR12	We welcome the recommendations for further research. However, we would suggest that they need further explanation as to why they could be important or necessary. It would also be worth clarifying that the decision taken by NICE with regards to vaginal sex, viral load and treatment is evidence based and that this research is additional, not essential. As stand alone statements these recommendations could serve to undermine the decision taken by NICE in these guidelines that vaginal sex presents a negligible risk in the right circumstances. Indeed, questions may be raised that this research should have been undertaken in advance of NICE's decision. That said, we are satisfied that NICE's decision is the correct one.	Thank you for your comments. The role of research recommendations is outlined in the methodology chapter. Research recommendations are made on areas where further research is felt to be needed and would improve future versions of the guideline. By outlining these in a NICE guideline it is hoped that they will be given greater priority by researchers and funding bodies. GDG members were asked to rank the research recommendations in terms of importance. From this process the 5 that received the most 'votes' were made the key recommendations. Only those research

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							recommendations that are selected as 'key' are developed in detail. . The research recommendations made within this chapter are to address seminal fluid viral testing, pre-exposure prophylaxis and sperm washing for hepatitis C. These are all are areas where the evidence is not good enough to make comprehensive recommendations. The research recommendations will not affect the implementation of the recommendations.
456.	Terrence Higgins Trust	12	Full	77	43	We would welcome a statement that underlines the fact that all IVF specialist clinics should have an understanding of the basics with regards to HIV and fertility. Too many of our clients report poor experiences in fertility services due to lack of knowledge and/ or stigma. We would therefore like to see these guidelines act as a lever to improve HIV knowledge levels in all fertility services. We would not want to see a situation whereby people are told that they cannot directly access fertility services and subsequently experience unnecessary delays to their treatment	Thank you for your comment. The guideline sets the best practice, based on clinical and cost effectiveness, for the NHS. The recommendations are made to improve service for all people included within it. Throughout the guideline, people with HIV are accounted for within the specific equality considerations - not just within this chapter. The GDG did not feel that an additional recommendation is required as the implementation of the entire guideline will make such a recommendation unnecessary.
457.	Terrence Higgins Trust	13	Full	105	23-24	We would again reiterate our concerns regarding the exclusion of HIV positive women from the scope of this guideline. IN particular we are concerned that the following statement may result in women having to undergo IVF unnecessarily: 'For HIV the standard approach for female to male transmission is use of Assisted reproductive techniques (ART), such as IUI or IVF.'	Thank you for your comments. The scope of guideline was to examine the effectiveness of sperm washing, which is only relevant for a HIV positive male. In order to answer the question sperm washing was compared with viral transmission through unprotected sex and post exposure prophylaxis. The results of this review showed that if certain criteria were met that

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						We find it unacceptable that such an inequality could be created as a result of an administrative decision.	unprotected intercourse would be a suitable option if the male partner was HIV positive.
458.	Terrence Higgins Trust	14		106	8-10	We would strongly urge NICE to address the issue of women living with HIV before this guideline is published.	Thank you for your comment. The scope of guideline was to examine the effectiveness of sperm washing, which is only relevant for a HIV positive male. In order to answer the question sperm washing was compared with viral transmission through unprotected sex and post exposure prophylaxis. The results of this review showed that if certain criteria were met that unprotected intercourse would be a suitable option if the male partner was HIV positive.
459.	University Hospitals Bristol NHS Foundation Trust	1	Full	13	[I2] IVF procedure	it is very hard to think that our PCTs which are currently only willing to fund ONE cycle of IVF/ICSI and three of IUI will agree to finding three cycles of IVF. My fear is that they will cherry pick from this document as it suits them; they will reject this and will accept other proposals like your fairly widespread rejection of IUI.	Thank you for your comments. Our mandate is to produce, clear evidence based guidelines based on clinical and cost-effectiveness. How commissioners implement this guidance is not within our control.
460.	University Hospitals Bristol NHS Foundation Trust	11	Full	General		There is much that is sensible and good in this document; some is a bit bit simplistic (1.12.2.1-3). I think that the over 40 proposals and the three cycles for all is aspirational and potentially destructive, and I cannot express more strongly my unhappiness with the plans to effectively ban IUI.	'Thank you for your comments. **'Over 40 proposals'** & **'Three cycles'** There was considerable debate within the GDG about these recommendations. However, the recommendations are based on the GDGs assessment of the evidence on effectiveness and cost-effectiveness of care.

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							In practice we know that health service commissioners have made their own decisions about affordability which do not relate to the WTP threshold. This is demonstrated by the way in which there has been a wide variation of the implementation of the 2004 IVF recommendations across the country (the 'postcode lottery') and when the financial constraints were not as great as they are now. Please note that the recommendation for women aged 40 to 42 years has been amended to read: *In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled:* • *they have never previously had IVF treatment* • *there is no evidence of low ovarian reserve* • *there has been a discussion of the additional implications of IVF and pregnancy at this age.* **'Banning IUI'** The recommendation that people with unexplained infertility, mild endometriosis or 'mild male factor infertility', who are having regular unprotected sexual intercourse should

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							not be offered IUI routinely is based on evidence that it does not improve the chances of conception. The guideline still recommends the use of IUI in other circumstances as an alternative to vaginal intercourse: • people who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychosexual problem who are using partner or donor sperm • people with conditions that require specific consideration in relation to methods of conception (for example, after sperm washing where the man is HIV positive) • people in same-sex relationships.
461.	University Hospitals Bristol NHS Foundation Trust	2	Full	14	[J1] Embryo transfer strategies	this is a laudable though very loose firm of words, as it is so wide open to varying interpretation.	Thank you for your comment. If you are referring to the title then we think that 'strategies' is correct in that the section deals with a number of clinical recommendations relating to embryo transfer. If you are referring to the content, then we would argue that Section 15.7 of Chapter 15 presents the evidence for and justification of the recommendations very clearly.
462.	University Hospitals Bristol NHS Foundation Trust	3	Full	24	50	this is a very good idea to make explicit what NICE supports and doesn't. These are very clear. You shy away from being any more explicit about AFC and AMG application; trusts and PCTs dance around this. PCTs say we	Thank you for your comment. The GDG highlighted the resource trade-off in the evidence to recommendations section. However, based on the evidence they could not recommend one as being superior to the

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						should do it AMH - trusts say they cannot afford it as it costs x2.5 the cost of an FSH test. P	others and so have left it to clinical judgement and locally available resources.
463.	University Hospitals Bristol NHS Foundation Trust	4	Full	29	94	I was surprised to read this statement about the equivalence of metformin with clomifene. It seems to go against BFS giudelines and all publications presented and published over the last few years. I think it is a right balance myself but am surprised.	Thank you for your comments. It is worth noting that the review of this topic in the Guideline includes the studies presented in the 2010 Cochrane review, with additional studies that were published after the Cochrane review. The cut off date for literature searches for the guideline was prior to the publication of the 2012 Cochrane review, and so it could not be included in the guideline. However, as outlined in table 8.2 in the full guideline, there was no significant difference in the number of live births or clinical pregnancies when studies comparing clomifene citrate to metformin were combined. Based on this, the GDG recommended that metformin or clomifene or a combination of the two could be used in WHO Group II women, taking into account various factors such as the need for monitoring and ease of use. The key point is that for the review all the studies comparing clomiphene with metformin were combined and not subgroup analysed by BMI. The text within Section 8.3, emphasises this point namely that different BMIs were included in the reviewed studies. Although a subgroup analysis by BMI was not undertaken, the GDG noted that the studies that only included women with a BMI of 32 or less (Johnson et al., 2010 [32 or less],

Karimzadeh et al., 2010 [25 to 29.9], Palomba et al., 2005 [30 or less]) showed a trend towards the effectiveness of metformin over clomifene citrate for live birth and clinical pregnancy rates (although this was not significant). Of the two studies that did not apparently restrict BMI, one found a significant advantage of clomifene over metformin for live birth but not clinical pregnancy (Zain et al, 2009) whilst the other found a significant advantage of clomifene over metformin for clinical pregnancy but not live birth (Legro et al., 2007) (both of the non-significant effects were trending towards clomifene). When these five studies were meta-analysed together, no significant difference was found between clomifene citrate and metformin (see the two forest plots below; note Karimzadeh et al., 2010 did not report live birth rates).

Forest plot for live birth

	Metformin		Clomiphene citrate		
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**W**
Johnson 2010	10	35	13	36	
Legro 2007	3	38	6	39	
Palomba 2005	26	50	9	50	
Zain 2009	15	208	47	209	
Total (95% CI)		**331**		**334**	**1**
Total events	54		75		

Heterogeneity: Tau² = 1.03; Chi² = 26.26, df = 3 (P < 0.00001); I²

Test for overall effect: Z = 0.41 (P = 0.68)

Forest plot for clinical pregnancy

Com No.	Stakeholder	Order No	Docu ment	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment

	Metformin		Clomiphene citrate		
Study or Subgroup	Events	Total	Events	Total	W
Johnson 2010	14	35	14	36	
Karimzadeh 2010	13	90	11	90	
Legro 2007	18	208	50	209	
Palomba 2005	31	50	16	50	
Zain 2009	3	38	6	39	
Total (95% CI)		**421**		**424**	1
Total events	79		97		

Heterogeneity: $Tau^2 = 0.54$; $Chi^2 = 25.65$, df = 4 ($P < 0.0001$); $I^2 =$

Test for overall effect: Z = 0.35 (P = 0.73)

The GDG has now clarified in the Guideline text this discussion on the effect of BMI of included women on the results of the studies. They have also added BMI to the list of things to consider when choosing which treatment to use.

The GDG agreed that the order of the bullet points could be misinterpreted as recommending metformin above clomifene citrate. The bullets have been reordered so that clomifene citrate is top of the list, reflecting its status as the current standard treatment for these women.

The recommendation, therefore, now reads:

'*Offer women with WHO Group II anovulatory infertility one of the following treatments, taking into account potential adverse effects, ease and mode of use, BMI, and monitoring needed:*

- *clomifene citrate or*
- *metformin or*

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							a combination of the above. '
464.	University Hospitals Bristol NHS Foundation Trust	5	Full	29	95	It is very disappointing to see this dogma about scans and clomifene being perpetuated. It wastes valuable resources on a treatment approach which has got terrible success rates. In the 8 years since the last guidelines and these, we have not followed this approach in the any of the Bristil clinic treating 100s of wornen each year and not a single multiple pregnancy - not many pregnancies either though. Why are you advocating this and yet effectively banning IUI?	Thank you for your comments. The GDG believed the potential risks to the mother and babies of a multiple pregnancy are great enough to justify ultrasound scanning for at least the first cycle; hence the recommendation. The guideline recommendations do not prevent the use of IUI in all circumstances. We have addressed your more formal criticism of the IUI recommendations in the relevant section. .
465.	University Hospitals Bristol NHS Foundation Trust	6	Full	31	116	In the light of the weight of evidence in support of IUI in just these clinical indications, it is appalling to think you want to remove this option.	Thank you for your comment. The relevant recommendation states that IUI can be offered for the clinical indications below; • people who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychosexual problem who are using partner or donor sperm • people with conditions that require specific consideration in relation to methods of conception (for example, after sperm washing where the man is HIV positive) • people in same-sex relationships.
466.	University Hospitals Bristol NHS Foundation Trust	7	Full	32	131	What about the role of progestogens prior to Gn stimuation demonstraring the reduction in cancelled cycles due to persistent luteal function.	Thank you for your comment. The GDG considered the role of progesterone prior to gonadotrophin stimulation in the pre-

Com No.	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
							treatment section of the guideline (section 15.2). The GDG had a difficult task in specifying the most important outcomes to consider from the studies, and cancelled cycles was not a main outcome specified by the GDG. The GDG therefore did not look at evidence specific to the reduction in cancelled cycles from the use of progesterone prior to gonadotrophin stimulation.
467.	University Hospitals Bristol NHS Foundation Trust	8	Full	33	136	if we knew who was at low risk, our lives would be so much easier	Thank you for your comment. There is a section of the guideline (Chapter 15, section 15.5) that lists several risk factors associated with the development of OHSS. This can be used to ascertain if a woman is at a higher risk of OHSS and therefore in whom down-regulation with GnRH agonist may not be appropriate. The GDG agreed that it is not easy to determine which women are at a low risk of developing OHSS.
468.	University Hospitals Bristol NHS Foundation Trust	9	Full	33	143	I fully agree with this	Thank you for your comment
469.	University Hospitals Bristol NHS Foundation Trust	10	Full	33	144	GH must have a role in women who have post surgical pituitary failure and are GH deficient; I guess the key thing here is the "adjuvant" treatment phrase	Thank you for your comment. You are correct – the use of the word 'adjuvant' is to emphasise that the recommendation is to not use growth hormone (or DHEA) as a standard part of the IVF treatment protocol. This does not prevent its use where clinically indicated, such as in women with post-surgical pituitary failure.

These organisations were approached but did not respond:

A Little Wish

Abbott Laboratories

Association of Anaesthetists of Great Britain and Ireland

Association of British Healthcare Industries

Association of Clinical Pathologists

Association of Radical Midwives

Barnsley Hospital NHS Foundation Trust

Baxter Healthcare

Beckman Coulter

Birmingham Infertility Forum

Bradford District Care Trust

British Association for Counselling and Psychotherapy

British Dietetic Association

British Medical Association

British Medical Journal

British National Formulary

British Psychological Society

British Society for Human Genetics

British Society for Paediatric Endocrinology and Diabetes

BSEC

BUPA Foundation

Cambridge Temperature Concepts Ltd

Cambridge University Hospitals NHS Foundation Trust

Camden Link

Capsulation PPS

Cardiff and Vale University Health Board

Cardiff University

CARE Fertility

Care Quality Commission (CQC)

Central & North West London NHS Foundation Trust

Central London Community Healthcare

Chesterfield Royal Hospital NHS Foundation Trust

Christian Medical Fellowship

CIS' ters

Cleft Lip and Palate Association

Cochrane Menstrual Disorders and Subfertility Group

Commission for Social Care Inspection

Cook Medical Inc.

Daisy Network

Department for Communities and Local Government

Department of Health, Social Services and Public Safety - Northern Ireland

Dorset Primary Care Trust

Downs Syndrome Research Foundation

Equality and Human Rights Commission

Faculty of Public Health

Faculty of Sexual and Reproductive Healthcare

Fertility Friends

Fibroid Network Charity

George Eliot Hospital NHS Trust

Gloucestershire LINk

Great Western Hospitals NHS Foundation Trust

Greater Manchester and Cheshire Cancer Network

Hammersmith and Fulham Primary Care Trust

Hayward Medical Communications

Health Protection Agency

Health Quality Improvement Partnership

Healthcare Improvement Scotland

Hindu Council UK

Hologic Inc.

Independent Healthcare Advisory Services

Innermost Secrets Ltd

Institute for Womens Health

Institute of Biomedical Science

iQudos

IVF Hammersmith

IVF WALES

KCARE

Kent, Surrey and Sussex Health Policy Support Unit

Lambeth Community Health

Lancashire Care NHS Foundation Trust

Leeds Primary Care Trust (aka NHS Leeds)

Lincolnshire Teaching Primary Care Trust

Liverpool Community Health

Liverpool Primary Care Trust

Lothian University Hospitals Trust

Luton and Dunstable Hospital NHS Trust

Maternity Action

Maternity Services Action Group

Medicines and Healthcare products Regulatory Agency

Mid and West Regional Maternity Service Liasion Committee

Midwives Information and Resource Service

Ministry of Defence

MRC Clinical Trials Unit

National Clinical Guideline Centre

National Collaborating Centre for Cancer

National Collaborating Centre for Mental Health

National Collaborating Centre for Women's and Children's Health

National Gamete Donation Trust

National Institute for Health Research Health Technology Assessment Programme

National Obesity Forum

National Patient Safety Agency

National Pharmacy Association

National Public Health Service for Wales

National Treatment Agency for Substance Misuse

NHS Bournemouth and Poole

NHS Clinical Knowledge Summaries

NHS Connecting for Health

NHS Darlington

NHS Fetal Anomaly Screening Programme

NHS Forth Valley

NHS Plus

NHS Sefton

NHS Sheffield

NHS Warwickshire Primary Care Trust

NHS Worcestershire

North Tees and Hartlepool NHS Foundation Trust

North West London Perinatal Network

Nottingham City Hospital

Nuture Antenatal

Obstetric Anaesthetists' Association

Patients Watchdog

Pelvic Pain Support Network

PERIGON Healthcare Ltd

Peterborough City Hospital

Pfizer

Preglem UK

Press for Change

Public Health Wales NHS Trust

Queen Elizabeth Hospital King's Lynn NHS Trust

RAF Families Federation

Randox Laboratories Limited

Royal Berkshire NHS Foundation Trust

Royal College of Anaesthetists

Royal College of General Practitioners

Royal College of General Practitioners in Wales

Royal College of Midwives

Royal College of Paediatrics and Child Health

Royal College of Paediatrics and Child Health , Gastroenetrology, Hepatology and Nutrition

Royal College of Pathologists

Royal College of Physicians

Royal College of Psychiatrists

Royal College of Psychiatrists in Scotland

Royal College of Radiologists

Royal College of Surgeons of England

Royal Cornwall Hospitals NHS Trust

Royal Pharmaceutical Society

Royal Society of Medicine

Royal Surrey County Hospital NHS Trust

Sandwell Primary Care Trust

Schering-Plough Ltd

Scottish Intercollegiate Guidelines Network

Sheffield Teaching Hospitals NHS Foundation Trust

Sickle Cell Society

Social Care Institute for Excellence

Society and College of Radiographers

Society for Endocrinology

Solent Healthcare

South Asian Health Foundation

South Devon Healthcare NHS Foundation Trust

Southampton University Hospitals Trust

Southern Health & Social Care Trust

Stockport Clinical Commissioning Pathfinder

Stockport Primary Care Trust

The Association for Clinical Biochemistry

The British In Vitro Diagnostics Association

The Rotherham NHS Foundation Trust

The University of Glamorgan

UK Clinical Pharmacy Association

UK Thalassaemia Society

United Chiropractic Association

United Lincolnshire Hospitals NHS

VBAC Information and Support

Verity

Welsh Government

Welsh Scientific Advisory Committee

West Hertfordshire Primary Care Trust

Western Cheshire Primary Care Trust

Western Health and Social Care Trust

Wirral University Teaching Hospital NHS Foundation Trust

Women's health partnership

York Hospitals NHS Foundation Trust

Yorkshire &The Humber Specialised Commissioning Group