Fertility (standing committee update)
Consultation on draft guideline - Stakeholder comments table
12 May – 10 June 2016

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1	SH	British Infertility Counselling Association	Short	General	General	BICA were pleased to see that Counselling is integrated throughout the document and has been recognised as an essential part of fertility treatment.	Thank you but this section is strictly outside the scope of this update
2	SH	British Infertility Counselling Association	Short	34	21	Add in Information & counselling section as page 31. Individuals considering fertility preservation should be offered counselling from someone who is specialised in fertility counselling and can discuss the psychological & physical implications of the treatment for themselves, partner and children, if applicable.	Thank you for your comments. This section of the guideline (recommendation 1.16.1.3) was not considered as part of this update and therefore an update to this recommendation cannot be made. However, this has been noted and will be shared with the NICE surveillance team to review as part of the next surveillance review (due in 2017).
3	SH	RCOG	General	General	general	Thank you for asking the RCOG to review the addendum. We feel that it is well written.	Thank you
4	SH	Wirral University Teaching Hospitals NHS Foundation Trust	short	8	1.2.4	Already comply with statements on offering IVF after 2 years in unexplained infertility – this is regionally applied guideline IUI is not routinely offered and is only discussed if; patient requests it or if there is an objection to IVF from the couple	Thank you for your comment.
5	SH	British Andrology Society	general	general	general	*As part of 4 the 2013 update, recommendations on the use of intrauterine insemination were changed. Concerns were raised about the process that was followed when the*	Thank you for your comment. The referral received asked the Clinical Guideline Update Team (CGUT) to review evidence on IUI compared to expectant

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						recommendations about intrauterine insemination were discussed by the Committee during the 2013 update. This update will reconsider the evidence for intrauterine insemination, with or without ovarian stimulation, compared with expectant management for people with unexplained infertility, mild endometriosis and mild male-factor infertility and whether the 2013 recommendations should be updated. **Proposed NICE recommendation following update (2016)** ***For people with unexplained infertility, mild endometriosis or 'mild male factor infertility', who are having regular unprotected sexual intercourse:*** □ *advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered.* □ *do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF). [2016]* The reconsideration appears to be restricted to a	management. Evidence regarding IVF was not reviewed as part of this update. This guideline update focused on IUI versus expectant management. The outcomes of live birth and multiple pregnancies were included in this evidence review. This 2016 update searched for all literature comparing the clinical effectiveness and cost effectiveness of IUI with and without ovarian stimulation compared to expectant management. Evidence was inconclusive in showing that IUI with or without ovarian stimulation is more effective than expectant management and economic evidence suggests that IUI may be considered cost-effective if expectant management were not an option. No changes to recommendations relating to IVF were made as this is outside the scope of this update. However, IVF compared to IUI will be considered in a future update of this guideline. The committee noted HFEA success rates for IUI reported by stakeholders but noted that this data could not be disaggregated by cause of infertility and as such could not inform the committee's deliberations.

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						comparison of IUI with expectant management. We would propose that herein lies the fundamental flaw in this reconsideration. Which is the more appropriate question for NICE to re-consider? What is the efficacy of **IUI versus expectant management** for couples with unexplained infertility, mild endometriosis or 'mild' male factor infertility? Or What is the efficacy of **IUI versus IVF** for couples with unexplained infertility, mild endometriosis or 'mild' male factor infertility? In our Society's expert opinion, the second question is a more relevant one for the speciality. Expectant management is often equated with an absence of treatment and, given the average age of these couples, this delay further reduces their chances of having a family. In addition, given that these couples have presented with infertility following at least a year of unprotected intercourse, why should 'waiting whilst trying to conceive naturally' be a useful comparator.	

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						Pragmatically, once a couple has reached tertiary care, this is an unlikely option to be employed. Even in the primary healthcare sector, as was pointed out at the meeting on 30 March, the female partners of couples offered only expectant management take up a significant number of appointments in the general practitioner's surgery during this expectant management period. Therefore, this approach is not without cost or patient dissatisfaction. It is also clear to members of our Society that IUI success rates vary considerably from clinic to clinic across the UK. This would suggest that when performed with care and attention to every detail of clinical and laboratory management, IUI can be a successful, cost effective and acceptable option for many couples at the beginning of their fertility journey. For these reasons we would request NICE to reconsider, using the comparison of IUI with IVF and thus allow the standing committee to take into consideration a number of new, robust and pertinent studies listed below with summary findings. To make a recommendation on this issue, a number of sub-questions must also be explored.	

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						• Couple selection regimes: which couples should be offered IUI? • Do live births increase with IUI stimulation? • If so, which antagonist regimes are best? • How can multiple pregnancies be prevented? • Is the timing of IUI important in terms of stimulation and time after semen preparation? • If IUI and IVF are equally successful, which is more cost effective? Further, since definite answers cannot yet be made in some areas due to lack of evidence, we would request NICE to keep the recommendation open rather than publishing a blanket recommendation against IUI even in medically appropriate cases and restricting its use to only '*exceptional circumstances of social, cultural or religious objections to IVF.'* Below are our specific responses to this consultation document: Studies included in this update conclude that IUI pregnancy rates are 4-10% per cycle. This is as a result of	

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						'*a systematic search identified 625 articles. The titles and abstracts were screened and 12 articles were identified as potentially relevant. Full-text versions of these articles were obtained and reviewed against the criteria specified in the review protocol. Of these, 12 were excluded as they did not meet the criteria and 7 articles were included from the original guideline. Of these, one article was a secondary publication of other included studies, leaving 6 included studies in total.'* We believe that the inclusion criteria imposed by NICE are flawed and possibly too stringent. In the UK, we are in a situation where treatment is regulated by the Human Fertilisation and Embryology Authority and they compile success rates based across more cycles that are in these publications. The public HFEA database reports pregnancy rates of 12-13% per cycle, this is surely the most relevant data when making decisions about treatment provision in the UK. It is worth noting that the HFEA data, when examined clinic by clinic, does reveal a large variation in success. We would endorse that those clinics not performing to a satisfactory level should not be performing IUI, but that does not mean	

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						that this treatment should not be available to patient; rather that they are entitled to expect treatment by a clinic where the success rates meet the national averages. Clinics with poor results should be encouraged to re-evaluate their protocols and should be monitored until success rates reach the national average.	
6	SH	British Andrology Society	**general**	general	general	Since the consultation in March 2016, two reviews have been published by those working in the field. These reviews include a comprehensive study of all IUI studies. **Bahadur G, Homburg R, Muneer A, Racich P, Alangaden T, Al-Habib A, Okolo S. First line fertility treatment strategies regarding IUI and IVF require clinical evidence. Hum Reprod. 2016 Apr 12. pii: dew075. [Epub ahead of print] Review.** This review by Bahadur concludes 'We reflect on some of the clinical, economic, financial and ethical realities that have been used to selectively promote IVF over IUI, which is less intrusive and more patient friendly, obviates the need for embryo storage and has a global application. The evidence strongly favours IUI over IVF in selected couples and national funding strategies should include IUI treatment options……. These suggestions are an ethically sound basis	Thank you for your comment. Narrative reviews and commentaries (such as in Bahadur 2016 and Woodward 2016) are not routinely included in intervention reviews. In accordance with NICE's methodology, the highest level of evidence was searched, this being systematic reviews of randomised control trials and randomised control trials. This 2016 update searched for all literature comparing the clinical effectiveness and cost effectiveness of IUI with and without ovarian stimulation compared to expectant management as per the review protocol. No new evidence was identified further to that identified in the 2013 evidence review. The evidence available was also inconclusive in showing that IUI with or without ovarian stimulation is more effective than expectant management and the economic evidence suggests that IUI may be considered cost-effective if expectant

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						for constructing the provision of publicly funded fertility treatments.' Another review by **Woodward,B., Tomlinson, M.,and Kirkman-Brown. J., (2016): Replacing IUI with IVF for initial treatment of unexplained infertility: why this NICE recommendation is cause for concern, Human Fertility, DOI: 10.1080/14647273.2016.1182220** is strongly endorsed by the British Andrology Society and the Association of Biomedical Andrologists. It concludes as follows: The latest guidelines from the National Institute for Health and Care Excellence (NICE) for assisted conception (NICE CG156, 2013) recommend that people experiencing unexplained infertility should no longer be offered stimulated intra-uterine insemination (IUI) as a first-line treatment, but rather be directed towards IVF treatment, or alternatively be left to expectant management (EM). NICE has acknowledged that the cited evidence leading to this decision was not sufficiently robust. As such, we are concerned that accordance with these new NICE guidelines may result in people with no identifiable cause of their	management were not an option. Therefore, the committee agreed to retain the original recommendation and no new recommendation favouring IUI with or without ovarian stimulation was made The committee noted the evidence available for the comparison IUI with ovarian stimulation versus IUI without ovarian stimulation was generally inconclusive and various concerns were raised regarding the applicability of one included study (Streures 2006), as 20% of couples in the expectant management group receive IUI prior to the trial completion Additionally, the Committee noted that from the evidence and their clinical experience, IUI with stimulation may increase likelihood of adverse events. Therefore, no changes were made to the 2013 recommendations.

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						infertility being prematurely referred for IVF treatment. IVF constitutes a more invasive and expensive treatment process, which also represents an additional and unnecessary cost pressure to the National Health Service. There is a longstanding need for a robust clinical trial to resolve the uncertainty as to whether one treatment is more appropriate than another. Until such data is available, we suggest that provision of stimulated IUI, in centres achieving a satisfactory live birth rate, represents a significant cost-saving to those commissioning fertility services, with lower risks to people treated.	
7	SH	British Andrology Society	general	general	general	Since IUI success can clearly be influenced by ovarian stimulations protocols and also by timing of insemination, we believe that the additional studies listed below should be included in making this recommendation. **Bakas, P., Konidaris, S., Liapis, A., Gregoriou, O., Tzanakaki, D. and Creatsas, G.** (2011) Role of gonadotropin-releasing hormone antagonist in the management of subfertile couples with intrauterine insemination and controlled ovarian stimulation. *Fertility and Sterility*, 95(6): 2024-2028	Thank you for your comment. The scope of this guideline update was to compare IUI with expectant management. Please see the below for reasons as to why the additional studies listed in your comment were not included in this guideline update: Bakas 2011: The comparison of IUI with ovarian stimulation versus IUI with stimulation and gonadotropin-releasing hormone antagonist was outside of the scope of this update.

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						Summary The use of a GnRH antagonist in conjunction with controlled ovarian stimulation and IUI significantly increases pregnancy rates and reduces the incidence of premature luteinization. **Bensdorp, A.J., Tjon-Kon-Fat, R.I., Bossuyt, P.M.M., Koks, C.A.M., Oosterhuis, G.J.E., Hoek, A., Hompes, P.G.A., Broekmans, F.J.M., Verhoeve, H.R., de Bruin, J.P., van Godle, R., Repping, S., Cohlen, B.J., Lambers, M.D.A., van Bommel, P.F., Slappendel, E., Perquin, D., Smeenk, J.M., Pelinck, M.J., Gianotten, J., Hoozemans, D.A., Maas, J.W.M., Eijkemans, M.J.C., van der Veen, F., Mol, B.W.J., van Wely, M.** (2015) Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation. *British Medical Journal*, 350(g7771). Available at: http://www.bmj.com/content/350/bmj.g7771 [Accessed 4 May 2016]	Bensdorp 2015: The comparisons included IVF compared to IUI which was outside of the scope of this update.. However, evidence regarding IVF compared to IUI will be considered in a future guideline update. Blockeel 2014: Timing of IUI after LH rise was outside of the scope of this guideline update. Hansen 2016: A secondary analysis of an RCT. Predictors of pregnancy and live-birth was outside the scope of this guideline update. Luo 2014: The comparison of IUI with ovarian stimulation combined with GnRH-ant versus IUI with ovarian stimulation alone was outside the scope of this update. Tjon-Kon-Fat 2015: The comparisons included (IVF compared to IUI) was outside the scope of this update. However, evidence regarding IVF compared to IUI will be considered in a future guideline update. . Evidence regarding IVF compared to IUI will be considered in a future guideline update.

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						Summary In vitro fertilisation with single embryo transfer and in vitro fertilisation in a modified natural cycle were non-inferior to intrauterine insemination with controlled ovarian hyperstimulation in terms of the birth of a healthy child and showed comparable, low multiple pregnancy rates. **Blockeel, C., Knez, J., Polyzos, N.P., De Vos, M., Camus, M. and Tournaye, H.** (2014) Should an intrauterine insemination with donor semen be performed 1 or 2 days after the spontaneous LH rise? A prospective RCT. *Human Reproduction*, 29(4): 697-703 **Summary** IUI 1 day after the spontaneous LH rise results in significantly higher clinical pregnancy rates compared with IUI performed 2 days after the LH rise. **Hansen, K.R., He, A.L., Styer, A.K., Wild, R.A., Butts, S., Engmann, L., Diamond, M.P., Legro, r.S., Coutifaris, C., Alvero, R., Robinson, R.D., Casson, P., Christman, G.M., Huang, H., Santoro, N., Eisenberg, E., Zhang, H. and Kennedy, E.** (2016) Predictors of pregnancy and live-birth in couples with unexplained infertility after ovarian stimulation – intrauterine insemination. *Fertility and Sterility*, Mar 3. pii:	Cantineau 2007: The comparisons included were outside the scope of this update. We will share the above references with the NICE surveillance team to consider as part of the next surveillance review.

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						S0015-0282(16)00134-5. doi: 10.1016/j.fertnstert.2016.02.020. [Epub ahead of print] **Summary** Couples in which the female partners drank coffee, tea, or alcoholic beverages in the past had higher pregnancy and live birth rates compared with never or current users. When discontinuing these habits, they might have made other lifestyle changes to improve the pregnancy outcome. **Luo, S., Li, S., Jin, S., Li, Y. and Zhang, Y.** (2014) Effectiveness of GnRH Antagonist in the Management of Subfertile Undergoing Controlled Ovarian Stimulation and Intrauterine Insemination: A Meta-Analysis. *Plos One* [online], Volume 9(10). Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4192303/ [Accessed 4 May 2016] **Summary** This meta-analysis suggested that GnRH-ant can reduce the incidence of premature luteinisation and increase the clinical pregnancy rate when used in COS/IUI cycles, and it was especially useful for non-PCOS patients. However, evidence to support its use in PCOS patients is still insufficient.	

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						Tjon-Kon-Fat, R.I., Bensdorp, A.J., Bossuyt, P.M.M., Koks, C., Oosterhuis, G.J.E., Hoek, A., Hompes, P., Broekmans, F.J., Verhoeve, H.R., de Bruin, J.P., van Golde, R., Repping, S., Cohlen, B.J., Lambers, M.D.A., van Bommel, P.F., Slappendel, E., Perquin, D., Smeenk, j., Pelinck, M.J., Gianotten, J., Hoozemans, D.A., Maas, J.W.M., Groen, H., Eijkemans, M.J.C., van der Veen, F., Mol, B.W.J. and van Wely, M. (2015) Is IVF – served two different ways – more cost-effective than IUI with controlled ovarian hyperstimulation? *Human Reproduction*, 30(10): 2331-2339 **Summary** Both IVF strategies are significantly more expensive when compared with IUI-COH, without being significantly more effective. In the comparison between IVF-MNC and IUI-COH, the latter is the dominant strategy. Whether IVF-SET is cost-effective depends on society's willingness to pay for an additional healthy child. **Cantineau AE, Cohlen BJ, Heineman MJ.** (2007) Ovarian stimulation protocols (anti-oestrogens, gonadotrophins with and without GnRH agonists/antagonists) for intrauterine	

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						insemination (IUI) in women with subfertility. *Cochrane Database Syst Rev.* 2007 Apr 18;(2):CD005356. **Summary** Robust evidence is lacking but based on the available results gonadotrophins might be the most effective drugs when IUI is combined with ovarian hyperstimulation. When gonadotrophins are applied it might be done on a daily basis. When gonadotrophins are used for ovarian stimulation low dose protocols are advised since pregnancy rates do not differ from pregnancy rates which result from high dose regimen, whereas the chances to encounter negative effects from ovarian stimulation such as multiples and OHSS are limited with low dose gonadotrophins. Further research is needed for each comparison made.	
8	SH	British Andrology Society	general	general	general	**Cost-effectiveness criteria 1** NICE's report *Social value judgements: principles for the development of NICE guidance* 2 sets out the principles that GDGs should consider when judging whether an intervention offers good value for money. In order to ascertain the cost -effectiveness of IUI compared with expectant management would require a further	Thank you for your comment. The clinical evidence review for this update focussed on IUI vs expectant management only. Because the review did not identify robust evidence that IUI was more effective than expectant management, the committee did not prioritise new economic analyses for this review question.

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						exploration of the costs of expectant management. This is not a nil cost to the NHS since women seek repeated appointments in primary care during this period. To ascertain the cost- effectiveness of IUI versus IVF also requires an in depth study. This is not available from current literature and would require retrieval of data from primary sources as to the numbers of couples who could be treated by IUI for initial treatment of unexplained infertility rather than IVF. The cost effectiveness should be calculated on the range of success rates in the recent reviews instead of the smaller number included in the current update. **In summary, if IUI were practiced more effectively (by implementation of most appropriate staffing, stimulation protocols and insemination timing), there would be three potential benefits to patents:** • **Funds will be released for additional IVF cycles for couples with more complicated causes of infertility** • **Couples presenting with idiopathic infertility, who account for 20-30% of IVF cycles nationally,**	

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						would be less likely to be over-treated by bypassing lower risk IUI to high tech IVF or ICSI without a scientific rationale. • **Patient acceptability and religious tolerance would be greater as IUI can be performed with no 'down' ovarian regulation, fewer internal scans, no general anaesthetics and less time off work.**	
9	SH	Clinical Effectiveness Unit. Faculty of Sexual and Reproductive Healthcare	Addendum	8	general	We concur with the evidence base behind the recommendation not to offer intra-uterine insemination unless there is a specific indication to offer this.	Thank you for your comment.
10	SH	North Middlesex University Hospital NHS Trust	Addendum	7	6 9	Concerns were raised about the process that was followed when the recommendations about intrauterine insemination were discussed by the Committee during the 2013 update This relates to the management of interests during the 2013 CG156 meeting. The construction of the question ` the evidence for intrauterine insemination, with or without ovarian stimulation, compared with expectant management	Thank you for your comment. Narrative reviews and commentaries (such as in Bahadur 2016 or Woodward 2016 respectively) are not routinely included in intervention reviews. In accordance with NICE'S methodology, the highest level of evidence was searched, this being systematic reviews of randomised control trials and randomised control trials

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						for people with unexplained infertility, mild endometriosis and mild male-factor infertility' is unusual and constructed by GDG members around one of the lowest IUI pregnancy rates in the UK, while apparently attempting to justify utilising IVF with weak economic studies. This experience contrasts with UK experience (HFEA grey database for the period in consideration and not used by NICE). The low grade (Appendix H) provided by NICE already suggest repeating the same question is fraught with biases. The question transposed in its trueness reads; `***If a clinic had the worst possible IUI outcome would this procedure be better off than non-treatment'*** The answer to this question is invariably biased and built into the question and precludes new GDG members to contribute meaningfully. Equally, would practices with the worst possible IVF results be economically viable against non-treatment? The second major fault line was in allowing GDG members to speak freely of `**their experience in clinics'** which already dovetailed into accepting verbal views as evidence.	as per the review protocol. The lack of high quality evidence available and included in this evidence review is noted in the addendum, section 2.6 pg 18. No new evidence was identified further to that identified in the 2013 evidence review. The evidence available was also inconclusive in showing that IUI with or without ovarian stimulation is more effective than expectant management and the economic evidence suggests that IUI may be considered cost-effective if expectant management were not an option. Therefore, the committee agreed to retain the original recommendation and no new recommendation favouring IUI with or without ovarian stimulation was made The referral received asked the Clinical Guideline Update Team (CGUT) to review evidence on IUI compared to expectant management. Therefore, the guideline committee did not formulate this evidence review question. Evidence regarding IVF was not reviewed as part of this update and will be considered in a future update of this guideline. The guideline committee are independent of NICE and

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						This is not evidence based decision making and therefore the objective of showing the process was without fault does not hold. Most of the concerns against IUI were not evidence based and Cochrane reviews did not support any of the concerns within the CG156 document. The same question opened up and thoroughly peer reviewed demonstrated that expectant management may be comparable to treatment with clomiphene and timed intercourse or IUI**, BUT the data also shows IVF, with or without ICSI, is no more effective than gonadotropins with IUI for unexplained infertility.** However, adequately powered, randomized controlled trials that compare all of the available treatments for unexplained infertility were needed (Evidence-based approach to unexplained infertility: a systematic review, Gunn D, and Wright Bates G. Fertility and Sterility, Vol. 105, No. 6, June 2016}. A French prospective study indicated that the use of GnRH antagonists has a positive effect on the delivery rate, especially in the multifollicular stimulations The overall live birth rate was 11.4% per cycle, varying from 8.4% to 17.6% between centers. The main differences in practice that had a statistically significant impact on the delivery rate were the	do not represent their organisations. They are involved in independently interpreting the evidence recommendations. For further information regarding NICE's process and methods and the role of the guideline committee, please section 3 of the NICE guidelines manual 2014. For information on how the committee interprets the evidence in making recommendations, please see section 9.1 of the manual. The committee members are invited to discuss their clinical experience at committee meetings but base all recommendations on the evidence included in the guideline addendum. This is in line with NICE's methods of developing evidence based guidelines. The review by Gunn et al 2016 was not included in this evidence review as the comparisons included IVF compared to IUI which was outside of the scope of this update. However, IVF compared to IUI will be considered in a future update of this guideline. Monraisin 2016: is an observational study and the comparison included GnRH antagonists versus IUI which is outside of the scope of this guideline update.

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						use of GnRH antagonists (15.2% with versus 9.4% without) and the number of mature recruited follicles (9.4% for one versus 15.2% for two). (Evaluation of intrauterine insemination practices: a 1-year prospective study in seven French assisted reproduction technology centres Monraisin O et al., Fertil Steril June 2016Volume 105, Issue 6, Pages 1589–1593) Now asking the question if mainstream IUI practice was economically viable then this question is also answered through peer review evidence. IVF-SET compared with IUI-COH was €43,375 reflecting the additional costs necessary to achieve one additional healthy child in the IVF-SET group, compared with IUI-COH (Tjon-Kon-Fat et al., 2015). The CCGs deserve better and wholesome guidance about the cost effectiveness of IUI against unnecessary and costly IVF treatment and NICE have a duty of care to ensure the full picture is provided to the public. CCGs are currently paying over the odds for unnecessary IVF treatments and the public estimate of fertility expenditure including the private sector (who are increasingly granted CCG contracts despite their non-legal adherence or compliances to FOI) is £550million	We will share this reference with the NICE surveillance team to consider as part of the next surveillance review. Tjon-Kon-Fat 2015: The comparisons included (IVF compared to IUI) was outside the scope of this update. However, evidence regarding IVF compared to IUI will be considered in a future guideline update. Bensdorp 2015: The comparisons included IVF compared to IUI which was outside of the scope of this update. However, evidence regarding IVF compared to IUI will be considered in a future guideline update. Because the clinical evidence review did not find conclusive evidence that IUI was effective compared to expectant management, no health economic model was constructed for this review question.

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						http://www.managementtoday.co.uk/go/news/article/1050516/ivf-business-making-babies/. World report on fertility treatments reveals high use of ICSI and the Chief Editor of Human Reproduction journal attacks the over-use of ICSI as 'ineffective and costly care'. We are arguing the same. https://www.sciencedaily.com/releases/2016/05/160521071201.htm http://www.telegraph.co.uk/wellbeing/health-advice/doctors-diary-fertility-clinicstricks-of-the-trade/ http://www.telegraph.co.uk/women/family/the-great-fertility-scam-are-older-women-being-fleeced-in-their/ Patients are interested in IUI and this is shown by the most number of webpage hits on the HFEA website were for IUI procedures (HFEA Annual conference, 2016). Therefore, NICE have a moral duty to patients, the public and the funding bodies to ensure evidence is watertight and beyond doubt, but this has been very weak with the specific question asked.	

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						Answering a narrow question and then making broadbrush assumptions leads to non-evidence based guidance. NICEs own surveillance group in June 2015 rightly identified a more open question and suggests there was an urgency to consider new information which could alter the recommendation. That would constitute an update rather than a review. Two papers need to be read in its entirety in response to this consultation to understand the problem with IUI, IVF and the NICE guidelines (Bahadur et al 2016 and Woodward et al., 2016). Bahadur G, Homburg R, Muneer A, Racich P, Alangaden T, Al-Habib A, Okolo S. First line fertility treatment strategies regarding IUI and IVF require clinical evidence. Hum Reprod. 2016 Apr 12. pii: dew075. [Epub ahead of print] Review. Woodward,B., Tomlinson, M.,and Kirkman-Brown. J., (2016): Replacing IUI with IVF for initial treatment of unexplained infertility: why this NICE recommendation is	

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						cause for concern, Human Fertility, DOI: 10.1080/14647273.2016.1182220 Tjon-Kon-Fat RI, Bensdorp AJ, Bossuyt PM, Koks C, Oosterhuis GJ, Hoek A, Hompes P, Broekmans FJ, Verhoeve HR, de Bruin JP et al. Is IVF-served two different ways-more cost-effective than IUI with controlled ovarian hyperstimulation? Hum Reprod 2015;30:2331–2339. Bensdorp AJ, Tjon-Kon-Fat RI, Bossuyt PMM, Koks CAM, Oosterhuis GJE, Hoek A, Hompes PGA, Broekmans FJM, Verhoeve HR, de Bruin JP et al. Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation. Br Med J 2015;350: 2015 doi:http://dx.doi.org/10.1136/bmj.g7771 (Published 09 January 2015) Cite this as: Br Med J 2015;350:g7771.	
11	SH	North Middlesex University Hospital NHS	Addend	6 56 35	general	*This update will reconsider the* ***evidence for intrauterine insemination, with or without ovarian stimulation, compared with expectant management for people with***	Thank you for your comment. The lack of high quality evidence available and included in this evidence review is noted in the addendum, section 2.6 pg 18. No new

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		Trust	um			***unexplained infertility, mild endometriosis and mild male-factor infertility*** *and whether the 2013 recommendations should be updated.* We were concerned that this recommendation implied that IUI was ineffective and this was based on *very weak to weak grade evidence* as shown in Appendix H (pages 56 onwards) and appendix G. This recommendation was widely flawed and a recommendation could not be justified on the grade of evidence and the availability of literature (see references within Bahadur et al., 2016; Woodward et al., 2016); HFEA database (grey data). NICE describes the evidence as **Very Low Grade information** (Appendix H). The comparisons of poorly performing IUI with expectant management serves no useful purpose other than introduce an `interest bias for profitable IVF procedures'. NICE as an independent body must dissociate its recommendations which fuel monetary interests derived from non-evidenced foundation. The wider concerns relate to the effectiveness of IUI and IVF procedures, and this has not been properly addressed and	evidence was identified further to that identified in the 2013 evidence review. The evidence available was also inconclusive in showing that IUI with or without ovarian stimulation is more effective than expectant management and the economic evidence suggests that IUI may be considered cost-effective if expectant management were not an option. Therefore, the committee agreed to retain the original recommendation and no new recommendation favouring IUI with or without ovarian stimulation was made. The referral received asked the Clinical Guideline Update Team (CGUT) to review evidence on IUI compared to expectant management. Evidence regarding IVF was not reviewed as this was not part of the scope of this update. Evidence regarding IVF compared to IUI will be considered in a future guideline update. The guideline committee are independent of NICE and do not represent their organisations. They are involved in independently interpreting the evidence recommendations. For further information regarding NICE's process and methods and the role of the

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						new data exists (see references in Bahadur et al., 2016; Woodward et al., 2016; Gunn 2016; Monraisin 2016). The available data from the UK HFEA when the recommendation was made suggests UK practice exceeded almost twice the low level of pregnancy outcomes used in the evidence consideration. New data has since some about (identified by the NICE surveillance team in June 2015). Therefore, the NMUH-RMC cannot support the repeated use of non-evidence based facts to `construct a guideline/recommendation' which impacts on patient choices and against the backdrop of good practices with IUI within the UK (HFEA database). IUI is the least intrusive procedure and least expensive procedure. The highest number of webpage visits by potential patients on the HFEA website was for IUI (HFEA conference slides 2016). The NMUH-RMC recommends against using non-evidence based guidelines which comes about by using a `closed question. This exercise is of doubtful value to the normal clinic practices.	guideline committee, please section 3 of the NICE guidelines manual 2014. For information on how the committee interprets the evidence in making recommendations, please see section 9.1 of the manual. Please also note the committee's interests are declared at each committee meetings and these are available in the Declarations of Interest table. The referral received asked the Clinical Guideline Update Team (CGUT) to review evidence on IUI compared to expectant management. Evidence regarding IVF was not reviewed as this was not part of the scope of this update.. Monraisin 2016: is an observational study and the comparison included GnRH antagonists versus IUI which is outside of the scope of this guideline update. We will share this reference with the NICE surveillance team to consider as part of the next surveillance review. Tjon-Kon-Fat 2015: The comparisons included (IVF compared to IUI) was outside the scope of this update. However, evidence regarding IVF compared to IUI will be considered in a future guideline update.

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							Bensdorp 2015: The comparisons included IVF compared to IUI which was outside of the scope of this update. However, evidence regarding IVF compared to IUI will be considered in a future guideline update. Narrative reviews and commentaries (such as in Bahadur 2016 and Woodward 2016) are not routinely included in intervention reviews. In accordance with NICE'S methodology, the highest level of study design is sought for intervention reviews: this is systematic reviews of randomised control trials and randomised control trials.
12	SH	North Middlesex University Hospital NHS Trust	Addendum	6	4	Suitable topics for update are identified through the surveillance programme In June 2015 NICE surveillance reported; ***Clinical question: What is the effectiveness of intrauterine insemination (IUI) in people with unexplained infertility, mild endometriosis or 'mild' male factor infertility?*** 5. NICE received a query about the formulation of the recommendations on IUI. Additionally, a further RCT[4] on IUI was highlighted by the Chair of the Evidence Update	Thank you for your comments. The referral received asked the Clinical Guideline Update Team (CGUT) to review evidence on IUI compared to expectant management. Bensdorp 2015: The comparisons included IVF compared to IUI which was outside of the scope of this update. However, evidence regarding IVF compared to IUI will be considered in a future guideline update. Evidence was inconclusive in showing that IUI with or without ovarian stimulation is more effective than

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						Advisory Group during sign-off of the completed Evidence Update. This study suggested that IUI is non-inferior to in-vitro fertilisation (IVF). The panel felt that the **new study provided new evidence that should be considered in an update and felt that this question should be updated with more urgency than the other questions under consideration.** **Decision:** NICE to update this clinical question using Standing Committee for Updates via the Clinical Guidelines Update Team. [4]Bensdorp AJ, Tjon-Kon-Fat RI, Bossuyt PM et al. (2015) Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation. BMJ 350: g7771 The NMUH-RMC fully support and agree with the NICE surveillance team to have identified this question (which is also an open question) and for this to be followed through. The NMUH-RMC is concerned that NICE acknowledged the importance and urgency to update the guidelines for IUI, but	expectant management and economic evidence suggests that IUI may be considered cost-effective if expectant management were not an option. Therefore, further to the 2013 recommendations, a recommendation favouring IUI with or without ovarian stimulation was not made

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						somehow disengages this finding in a meaningful way to construct and update the recommendation for IUI. As it stands the current exercise is seen as review of the old data and **cannot strictly be classified as an `update'**.  The **NMUH-RMC** wish to see IUI efficiently practised in the UK, just like in the European countries where effective IUI programmes for first line treatment is well established. **NMUH-RMC** supports the use of reliable evidence to issue `guidance's'. IUI is a low cost and lesser intrusive treatment. The economic evidence did not support the removal of IUI.	
13	SH	North Middlesex University Hospital NHS Trust	General	1	General	The NMUH-RMC feels the recommendation gives a false portrayal of IUI to UK CCGs when in fact money saving strategies could be possible. The NMUH-RMC is mindful of the efficient use of public monies.	Thank you for your comment. In accordance with NICE's methodology, the highest level of evidence was searched, this being systematic reviews of randomised control trials and randomised control trials.
14	SH	North Middlesex University Hospital NHS Trust	General	1	General	The NMUH-RMC believes the current recommendations give a false portrayal of IUI as a procedure to patients as the evidence is very weak and new evidence is persuasive. It is psychologically important for patients to undergo treatment without doubtful labels.	Thank you for your comment. The committee also discussed the current "do not routinely offer" IUI recommendation (1.9.1.3) and noted that the current wording could be considered restrictive in light of the weak evidence base. However, the committee

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							acknowledged that the current wording of the recommendation encouraged consideration of IUI as a treatment option in some circumstances, for example when people have social, cultural or religious objections to IVF). The committee agreed that a recommendation with a 'do not routinely offer' wording provides some flexibility, whereas a 'do not offer' recommendation provided definitive guidance against the use of an intervention
15	SH	North Middlesex University Hospital NHS Trust	General	1	General	The recommendation is inadequately derived based on very low level evidence. It gives a false portrayal of the technique universally utilised, and to potentially 75 million subfertile couples worldwide	Thank you for your comment. The committee also discussed the current "do not routinely offer" IUI recommendation (1.9.1.3) and noted that the current wording could be considered strong in light of the weak evidence base. However, the committee acknowledged that the current wording of the recommendation encouraged consideration of IUI as a treatment option in some circumstances, for example when people have social, cultural or religious objections to IVF). The committee agreed that a recommendation with a 'do not routinely offer' wording provides some flexibility, whereas a 'do not offer' recommendation provide definitive guidance against the use of an intervention
16	SH	North Middlesex University	Gene	1	4/6	**Significant papers and reviews are already at hand for NICE panel to consider. The evidence within these paper**	Thank you for your comment. The scope of this guideline update was to compare IUI with expectant

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		Hospital NHS Trust	ral			**to recommend the routine use of IUI;** Bahadur G, Homburg R, Muneer A, Racich P, Alangaden T, Al-Habib A, Okolo S. First line fertility treatment strategies regarding IUI and IVF require clinical evidence. Hum Reprod. 2016 Apr 12. pii: dew075. [Epub ahead of print] Review. Woodward,B., Tomlinson, M.,and Kirkman-Brown. J., (2016): Replacing IUI with IVF for initial treatment of unexplained infertility: why this NICE recommendation is cause for concern, Human Fertility, DOI: 10.1080/14647273.2016.1182220 Tjon-Kon-Fat RI, Bensdorp AJ, Bossuyt PM, Koks C, Oosterhuis GJ, Hoek A, Hompes P, Broekmans FJ, Verhoeve HR, de Bruin JP et al. Is IVF-served two different ways-more cost-effective than IUI with controlled ovarian hyperstimulation? Hum Reprod 2015;30:2331–2339. Bensdorp AJ, Tjon-Kon-Fat RI, Bossuyt PMM, Koks CAM, Oosterhuis GJE, Hoek A, Hompes PGA, Broekmans FJM, Verhoeve HR, de Bruin JP et al. Prevention of multiple pregnancies in couples with unexplained or mild male	management. Please see the below for reasons as to why the additional studies listed in your comment were not included in this guideline update: Bensdorp 2015: The comparisons included IVF compared to IUI which was outside of the scope of this update. However, evidence regarding IVF compared to IUI will be considered in a future guideline update. Tjon-Kon-Fat 2015: The comparisons included (IVF compared to IUI) was outside the scope of this update. However, evidence regarding IVF compared to IUI will be considered in a future guideline update. Gunn et al 2015: The comparisons included (IVF compared to IUI) was outside the scope of this update. However, evidence regarding IVF compared to IUI will be considered in a future guideline update.. Monraisin 2016: is an observational study and the comparison included GnRH antagonists versus IUI which is outside of the scope of this guideline update. We will share this reference with the NICE surveillance

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						subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation. Br Med J 2015;350: 2015 doi:http://dx.doi.org/10.1136/bmj.g7771 (Published 09 January 2015) Cite this as: Br Med J 2015;350:g7771. Plus Gunn et al and Monraisin et al (above)	team to consider as part of the next surveillance review. Narrative reviews and commentaries (such as in Bahadur 2016 and Woodward 2016) are not routinely included in intervention reviews. In accordance with NICE'S methodology, the highest level of study design is sought for intervention reviews: this is systematic reviews of randomised control trials and randomised control trials.
17	SH	North Middlesex University Hospital NHS Trust	General	1	4	**The studies considered within the NICE guidelines have an unfair and often misleading representation of the IUI procedure.** 1. Most studies analysed within NICE have pregnancy rates (around (4-10%) well below the national average. 2. HFEA database (grey data) shows national averages of around 12-13 % per cycle, suggesting better practice in number clinics. 3. Much depends on risks and properly informed choices for patients and their safety and having a strict cancellation policy (Peeraer et al., 2015). Reports with pregnancy rates of 13-20 % per cycle (Karlstrom, 1993, Karande 1995, Manganiello, 1997; Karlstrom, 1998) had in common the	Thank you for your comment. The pregnancy rates are taken from the highest quality evidence available to the committee, in accordance with NICE'S methodology, the highest level of evidence was searched, this being systematic reviews of randomised control trials and randomised control trials. The committee noted HFEA success rates for IUI reported by stakeholders but noted that this data could not be disaggregated by cause of infertility and as such could not inform the committee's deliberations. Information on benefits and risks associated with IUI and

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						usage of 75-150 iui hMG, while 2 studies reported pregnancy rates of 13% per cycle had utilised uFSH (Balash 1994 and Matorras 2002). The reasons for the treatment were; unexplained, male factor, endometriosis, female factor, cervical factor, mixed. Common to all these was the use of ovulation triggering dose of 10,000 iu hCG, while 2 studies (Manganiello, 1997, Matorras 2002) used 5,000iu. In contrast the same studies reported pregnancy outcomes of 4-7% per cycle for the CC stimulated cycles. Plus Gunn et al and Monraisin et al (above) Our clinic is getting a pregnancy rate of around 15-20% per cycle and which translates as around 25-34% of the cohort of women undergoing IUI. Many UK IUI clinics are achieving this therefore it was so unusual for NICE to have to have allocated so much public resources in analysing the worst possible IUI scenario and to justify IVF usage. The evidence consideration cannot be extended to current normal UK IUI practice.	decisions on cancellation policies were both outside the scope of this update. However, this has been noted and will be shared with the NICE surveillance team to review as part of the next surveillance review (due in 2017).
18	SH	North Middlesex University Hospital NHS Trust	General	1	General	The NMUH-RMC is mindful of the public perception of `infertility' and that fair and balanced consideration are made. Importantly, we wish to ensure evidence based practices are conducted and where possible to ensure savings can be made.	Thank you for your comment. With regards to the specific costs mentioned in your final paragraph, we have not presented any unit costs and have conducted no original health economic work for

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						The expected national projection of fertility treatment costs to the NHS is around £550 million. http://www.managementtoday.co.uk/go/news/article/1050516/ivf-business-making-babies/. http://www.dailymail.co.uk/health/article-193870/Can-NHS-afford-400m-IVF-bill.html http://www.independent.co.uk/life-style/health-and-families/health-news/fertility-watchdog-hfea-concerned-private-clinics-ivf-treatment-a7028751.html Costings are presented with a false sense of economy throughout the debate. Although gonadotrophin is more expensive than clomid, the cost differences become insignificant once the cost of the whole procedure, including scans and consultations are taken into account. Similarly, there is a cost to expectant management.	this update so are unable to comment.
19	SH	North Middlesex University Hospital NHS Trust	General	1 77	General	• Answers to a narrow question cannot be extended to wider aspects of IUI practice as this would not satisfy scientific or clinical scrutiny nor withstand a peer review. • Legally its unsafe to continue with this	Thank you for your comment. The scope of this guideline update was to compare IUI with expectant management. It is important to note that the current recommendation regarding IUI is a "do not routinely offer" recommendation, which provides some degree of

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						recommendation • Morally its incorrect to continue with this recommendation • IUI must be returned for clinical use with immediate effect since evidence was never against this procedure	flexibility in offering IUI. No evidence was identified to change the recommendations.
20	SH	British Association of Urological Surgeons	Addendum	6 56 35	general	*This update will reconsider the* ***evidence for intrauterine insemination, with or without ovarian stimulation, compared with expectant management for people with unexplained infertility, mild endometriosis and mild male-factor infertility*** *and whether the 2013 recommendations should be updated.* Comparing IUI with expectant management is questionable and appears to have no useful purpose in subfertility patients. IUI is the least invasive and least expensive procedure undertaken in patients with subfertility. The recommendation that IUI being ineffective is based on *very weak to weak grade evidence* as indicated in Appendix H (pages 56 onwards) and appendix G, however this can not be justified on the level of evidence and the availability of current literature (Bahadur et al 2016 and Woodward et al	Thank you for your comment. Evidence was inconclusive in showing that IUI with or without ovarian stimulation is more effective than expectant management and economic evidence suggests that IUI may be considered cost-effective if EM were not an option. Therefore, a recommendation favouring IUI with or without ovarian stimulation was not made as the review identified no studies that would support this. The lack of high quality evidence available and included in this evidence review is noted in the addendum, section 2.6 pg 18. The referral received asked the Clinical Guideline Update Team (CGUT) to review evidence on IUI compared to expectant management. Evidence regarding IVF was not reviewed as part of this update.

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						2016) The effectiveness of IUI and IVF procedures, does not appear to have been addressed in light of recent data (see references in Bahadur et al., 2016; Woodward et al., 2016). The UK data on IUI available from the HFEA when the initial recommendation was proposed suggests that UK practice exceeded almost twice the low level of pregnancy outcomes used in the evidence consideration. Therefore, BAUS cannot support a recommendation based on inaccurate data when there are clearly areas of good practice using IUI within high volume units in the UK.	In accordance with NICE'S methodology, the highest level of study design is sought for intervention reviews: this is systematic reviews of randomised control trials and randomised control trials. Therefore, the highest level of evidence was included in this evidence review. The committee noted HFEA success rates for IUI reported by stakeholders but noted that this data could not be disaggregated by cause of infertility and as such could not inform the committee's deliberations.
21	SH	British Association of Urological Surgeons	Addendum	6	4	Suitable topics for update are identified through the surveillance programme In June 2015 NICE surveillance reported; ***Clinical question: What is the effectiveness of intrauterine insemination (IUI) in people with unexplained infertility, mild endometriosis or 'mild' male factor infertility?*** 5. NICE received a query about the formulation of the	Thank you for your comments. The referral received asked the Clinical Guideline Update Team (CGUT) to review evidence on IUI compared to expectant management. The trial Bensdorp et al 2015 was identified by the NICE surveillance team but was not included in this evidence review as the comparison IVF compared to IUI) was not included. However, IVF compared to IUI will be considered in a future update of this guideline.

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						recommendations on IUI. Additionally, a further RCT[4] on IUI was highlighted by the Chair of the Evidence Update Advisory Group during sign-off of the completed Evidence Update. This study suggested that IUI is non-inferior to in-vitro fertilisation (IVF). The panel felt that the **new study provided new evidence that should be considered in an update and felt that this question should be updated with more urgency than the other questions under consideration.** **Decision:** NICE to update this clinical question using Standing Committee for Updates via the Clinical Guidelines Update Team. [4]Bensdorp AJ, Tjon-Kon-Fat RI, Bossuyt PM et al. (2015) Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation. BMJ 350: g7771 BAUS fully support and agree with the NICE surveillance team to have identified this question. BAUS is concerned that NICE acknowledged the importance	No new evidence was identified further to that identified in the 2013 evidence review. The evidence available was also inconclusive in showing that IUI with or without ovarian stimulation is more effective than expectant management and the economic evidence suggests that IUI may be considered cost-effective if expectant management were not an option. Therefore, the committee agreed to retain the original recommendation and no new recommendation favouring IUI with or without ovarian stimulation was made

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						and urgency to update the guidelines for IUI. However the current update is merely a review of the old data and cannot strictly be classified as an `update'. If IUI is practised efficiently in the UK (similar to Europe) where effective IUI programmes for first line treatment are well established then there is scope to obtain better levels of evidence.	
22	SH	British Association of Urological Surgeons	General	general	General	The recommendation is based on poor levels of evidence which does not reflect the outcomes of a technique used in over 70 million subfertile couples worldwide and deemed less invasive and more cost effective.	Thank you for your comment. The lack of high quality evidence available and included in this evidence review is noted in the addendum, section 2.6 pg 18. In accordance with NICE'S methodology, the highest level of study design was sought for intervention reviews: this is being systematic reviews of randomised control trials and randomised control trials. No new evidence was identified further to that identified in the 2013 evidence review. The evidence available was also inconclusive in showing that IUI with or without ovarian stimulation is more effective than expectant management and the economic evidence suggests that IUI may be considered cost-effective if expectant management were not an option. Therefore, the committee agreed to retain the original recommendation

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							and no new recommendation favouring IUI with or without ovarian stimulation was made
23	SH	British Association of Urological Surgeons	general	1/1	4/6	**Papers suggested for further review include:** Bahadur G, Homburg R, Muneer A, Racich P, Alangaden T, Al-Habib A, Okolo S. First line fertility treatment strategies regarding IUI and IVF require clinical evidence. Hum Reprod. 2016 Apr 12. pii: dew075. [Epub ahead of print] Review. Woodward,B., Tomlinson, M.,and Kirkman-Brown. J., (2016): Replacing IUI with IVF for initial treatment of unexplained infertility: why this NICE recommendation is cause for concern, Human Fertility, DOI: 10.1080/14647273.2016.1182220 Bensdorp AJ, Tjon-Kon-Fat RI, Bossuyt PMM, Koks CAM, Oosterhuis GJE, Hoek A, Hompes PGA, Broekmans FJM, Verhoeve HR, de Bruin JP et al. Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with	Thank you for your comment. The referral received asked the Clinical Guideline Update Team (CGUT) to review evidence on IUI compared to expectant management. Evidence regarding IVF was not reviewed as part of this update. Bensdorp 2015: The comparisons included IVF compared to IUI which was outside of the scope of this update. However, evidence regarding IVF compared to IUI will be considered in a future guideline update. Evidence regarding IVF compared to IUI will be considered in a future guideline update. Narrative reviews and commentaries (such as in Bahadur 2016 and Woodward 2016) are not routinely included in intervention reviews. In accordance with NICE'S methodology, the highest level of study design is sought for intervention reviews, this is systematic reviews of randomised control trials and randomised control trials.

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						controlled ovarian hyperstimulation. Br Med J 2015;350: 2015 doi:http://dx.doi.org/10.1136/bmj.g7771 (Published 09 January 2015) Cite this as: Br Med J 2015;350:g7771.	
24	SH	British Association of Urological Surgeons	General	1/1	4/6	**The studies used in the document are open to further criticism:** 1. Most studies analysed within NICE have pregnancy rates below the national average : (around (4-10%) 2. HFEA database (grey data) shows national averages of around 12-13 % per cycle, suggesting better practice in a number of clinics.	Thank you for your comment. The committee noted HFEA success rates for stimulated IUI reported by stakeholders but noted that this data could not be dis-by cause of infertility and as such could not inform the committee's deliberations. The pregnancy rates are taken from the highest quality evidence available to the committee, in accordance with NICE'S methodology, the highest level of evidence was searched, this being systematic reviews of randomised control trials and randomised control trials.
25	SH	Association of Biomedical Andrologists	general	general	General	A commentary summarising our concerns about the decision to replace IUI (intrauterine insemination) with IVF (in vitro fertilisation) for unexplained infertility has now been published in the journal Human Fertility. Please see: Woodward et al (2016): Replacing IUI with IVF for initial treatment of unexplained infertility: why this NICE	Thank you for your comment. Please note that narrative reviews and commentaries (such as Woodward 2016) are not routinely included in intervention reviews. In accordance with NICE'S methodology, the highest level of evidence was searched for intervention evidence reviews, this being systematic reviews of randomised control trials and randomised control trials. Therefore,

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						recommendation is cause for concern. Human Fertility, DOI: 10.1080/14647273.2016.1182220 This commentary was produced due to the Association of Biomedical Androligsts (ABA) and British Andrology Society (BAS) being contacted by members of our respective professional bodies expressing concern about this specific area of the NICE guidance. The authorship of the commentary includes ABA and BAS Executive Committee members. The commentary was made available to all members of the ABA to ensure that the points of view of members were captured. We chose Human Fertility as the journal for publication, since this journal is affiliated to all of the national professional bodies involved in clinical assisted conception. As such, all the professional bodies hold NICE in high regard. This commentary was therefore subject to extensive peer review, due to the content which questions the decision to replace IUI with IVF as a first-line therapy for people with unexplained infertility. Due to the length of the peer review process, the acceptance and subsequent publication was	the highest level of evidence was included in this evidence. No new evidence was identified further to that identified in the 2013 evidence review. The evidence available was also inconclusive in showing that IUI with or without ovarian stimulation is more effective than expectant management and the economic evidence suggests that IUI may be considered cost-effective if expectant management were not an option. Therefore, the committee agreed to retain the original recommendation and no new recommendation favouring IUI with or without ovarian stimulation was made. Evidence regarding IVF compared to IUI will be considered in a future guideline update. Please note that NICE guidance cannot be amended during guideline updates without evidence to support this with the exception of editorial amendments to reflect NICE style and language.

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						delayed, despite the original commentary being written within 6 months of publication of CG156 in 2013. To summarise our commentary, NICE has acknowledged that the cited evidence leading to the decision to replace IUI with IVF as a first-line therapy for people with unexplained infertility was not sufficiently robust. The ABA is concerned that accordance with these new NICE guidelines may result in people with no identifiable cause of their infertility being prematurely referred for IVF treatment. IVF constitutes a more invasive and expensive treatment process, which also represents an additional and unnecessary cost pressure to the National Health Service (NHS). There is a longstanding need for a robust clinical trial to resolve the uncertainty as to whether one treatment is more appropriate than another. Until such data is available, the ABA suggest the NICE guidance is changed to allow provision of stimulated IUI, in centres achieving a satisfactory live birth rate. Where centres are not achieving a satisfactory live birth rate, the ABA are keen to offer training, possibly in collaboration with other professional	

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						bodies, to improve the services offered. Correct provision of stimulated IUI will represent a significant cost-saving to those commissioning fertility services, with lower risks to people treated.	
26	SH	Association of Biomedical Andrologists	general	general	General	The proposed NICE recommendation following update (2016) states that for people with unexplained infertility, mild endometriosis or 'mild male factor infertility', who are having regular unprotected sexual intercourse: □ *do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF). [2016]* The ABA is concerned that this decision has been made based on the wrong question being asked. Instead of a comparison with expectant management, the ABA believes it would have been more appropriate to ask: "What is the efficacy of IUI versus IVF for couples with unexplained infertility, mild endometriosis or 'mild' male factor infertility?"	Thank you for your comment. The referral received asked the Clinical Guideline Update Team (CGUT) to review evidence on IUI compared to expectant management. Evidence regarding IVF was not reviewed as this was outside the scope of this guideline update. Evidence regarding IVF compared to IUI will be considered in a future guideline update.
27	SH	Association of Biomedical	gene	general	Appendi	NICE acknowledges the definitions used in Appendix C are limited. Correct male reproductive health pathological	Thank you for your comment. The WHO 2010 criteria for defining mild male factor infertility was used and the

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		Andrologists	ral		x C	diagnosis and treatment requires robust investigation and accurate semen analysis. On 3rd June 2016, only 3 andrology laboratories were accredited by UKAS to ISO15189. This call in to question the accuracy of the semen analyses in the evidence assessed by NICE.	studies included did not define mild male factor infertility in accordance to any another criteria.
28	SH	Association of Biomedical Andrologists	general	general	General	The ABA are keen to see age-adjustments added to future decisions relating to IUI.	Thank you for your comment. Age was included as a subgroup in the evidence review protocol. However, no evidence regarding age subgroups were found.
29	SH	Association of Biomedical Andrologists	general	general	General	Please see the following manuscript that reflects on some of the clinical, economic, financial and ethical realities that have been used to selectively promote IVF over IUI and provides evidence that favours IUI over IVF in selected couples: Bahadur et al (2016). First line fertility treatment strategies regarding IUI and IVF require clinical evidence. Hum.Reprod. 2016 Apr 12. pii: dew075.	Thank you for your comment. The reference provided was reviewed. Please note that narrative reviews and commentaries (such as in Bahadur 2016) are not routinely included in intervention reviews.
30	SH	Association of Biomedical Andrologists	general	general	General	Please see the following manuscript that highlights the need for adequately powered, randomized controlled trials that compare all of the available treatments for unexplained infertility before an acceptable decision can be made for people with unexplained infertility:	Thank you for your comment. This review was not included in our evidence review and we have double-checked the reference list to ensure we have not missed any studies that would meet the inclusion criteria for this review. We will share this reference with the NICE surveillance team to consider as part of the next

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						Gunn et al (2016) Evidence-based approach to unexplained infertility: a systematic review. Fert.Steril.; 105(6):1566-1574.	surveillance review.
31	SH	Association of Biomedical Andrologists	general	general	General	Please see the following manuscript that highlights that GnRH antagonists significantly improve the success rate of IUI, and also provides evidence for 7 fertility clinics: Monraisin et al (2016) Evaluation of intrauterine insemination practices: a 1-year prospective study in seven French assisted reproduction technology centers. Fert. Steril.:105(6): 1589–1593.	Thank you for your comment. Monraisin 2016: is an observational study and the comparison included GnRH antagonists versus IUI which is outside of the scope of this guideline update. We will share this reference with the NICE surveillance team to consider as part of the next surveillance review.
32	SH	Association of Biomedical Andrologists	general	general	general	Please see the following manuscripts by the same team that highlight that: 1) in terms of healthy offspring (with similar multiple birth rates) IVF with elective single embryo transfer (eSET) in a modified natural cycle was non-inferior to stimulated IUI. 2) IVF strategies are significantly more expensive when compared with stimulated IUI, without being significantly more effective.	Thank you for your comment. This update focused on IUI compared with expectant management. Please see the below for reasons as to why the studies listed in your comment were not included in this guideline update: Bensdorp 2015: The comparisons included IVF compared to IUI which was outside of the scope of this update. However, evidence regarding IVF compared to IUI will be considered in a future guideline update.

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						Bendsorp et al (2015) Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation. BMJ, 350(g7771). Tjon-Kon-Fat et al (2015) Is IVF – served two different ways – more cost-effective than IUI with controlled ovarian hyperstimulation? Hum.Rep., 30(10): 2331-2339	Tjon-Kon-Fat 2015: The comparisons included IVF compared to IUI which was outside of the scope of this update. However, evidence regarding IVF compared to IUI will be considered in a future guideline update.
33	SH	Association of Clinical Embryologists	Addendum	7	6 7	"*Concerns were raised about the process that was followed when the recommendations about intrauterine insemination were discussed by the Committee during the 2013 update*" The original question asked, "What is the effectiveness of intrauterine insemination (IUI) in people with unexplained infertility, mild endometriosis or 'mild' male factor infertility?" The outcome, that "the GDG recommends that IUI (with or without stimulation) should not be routinely offered" was based on very few papers, all over 10 years old and of low or very low quality.	Thank you for your comment. This 2016 update searched for all literature comparing the clinical effectiveness and cost effectiveness of IUI with and without ovarian stimulation compared to expectant management. Evidence was inconclusive in showing that IUI with or without ovarian stimulation is more effective than expectant management and economic evidence suggests that IUI may be considered cost-effective if expectant management were not an option. Therefore, no changes to the 2013 recommendations were made. The lack of available high quality evidence is noted in the addendum, section 2.6 pg 18.

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						We would argue that mainstream IUI practice **is** economically viable, based on other more recent studies and opinion: [1] A multicentre, open label, three arm, parallel group, randomised controlled non-inferiority trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation. The study demonstrated no difference in live birth rates or multiple pregnancy rates between IVF and IUI. The authors concluded that, "there seems no reason to abandon intrauterine insemination with controlled ovarian hyperstimulation as a first line treatment of couples with unexplained or mild male subfertility and an unfavourable prognosis for natural conception" [2] The incremental cost effectiveness ratio for IVF-SET compared with IUI with controlled ovarian hyperstimulation (COH) was found to be €43 375 for the birth of an additional healthy child. IUI-COH was also found to be significantly more effective at lower costs compared to IVF in a modified natural cycle. No evidence was found to support IVF as a	

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						first-line strategy in couples with unexplained and mild subfertility. [3] [4] In addition these papers give a comprehensive overview of the failings of the 2013 NICE guidelines with regard to this issue and provide evidence that IUI should continue as a financially viable first line treatment for couples with unexplained, mild endometriosis and mild male factor infertility.	
34	SH	Association of Clinical Embryologists	Addendum	7 35 55 56 62	8 11	*"This update will reconsider the evidence for intrauterine insemination, with or without ovarian stimulation, compared with expectant management for people with unexplained infertility, mild endometriosis and mild male-factor infertility and whether the 2013 recommendations should be updated"* We are concerned that this statement implies that IUI was ineffective, based on *very weak to weak grade evidence* as shown in Appendices G and H. The 2013 recommendation was widely flawed and could not be justified on the grade of evidence and the availability of literature at the time. The comparison of poorly performing IUI with expectant management serves no useful purpose.	Thank you for your comment. This 2016 update searched for all literature comparing the clinical effectiveness and cost effectiveness of IUI with and without ovarian stimulation compared to expectant management. Evidence was inconclusive in showing that IUI with or without ovarian stimulation is more effective than expectant management and economic evidence suggests that IUI may be considered cost-effective if expectant management were not an option. Therefore, no changes to the 2013 recommendations were made. . The lack of available high quality evidence is noted in the addendum, section 2.6 pg 18. Quality appraisal of the evidence, using the GRADE

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						A large number of UK clinics continue to offer IUI, with little change to protocol or patient suitability criteria, since issue of the 2013 guidelines [5]. This indicates reluctance by this sector to accept recommendations not grounded in evidence based medicine.	methodology, was conducted. This grades the quality of the evidence from very low to high quality. Evidence was not excluded on the basis of quality as this introduces selection bias into the evidence review.
35	SH	Association of Clinical Embryologists	Addendum	6	4	"*Suitable topics for update are identified through the surveillance programme*" In June 2015 NICE surveillance reported; *Clinical question: What is the effectiveness of intrauterine insemination (IUI) in people with unexplained infertility, mild endometriosis or 'mild' male factor infertility?* 5. NICE received a query about the formulation of the recommendations on IUI. Additionally, a further RCT [1] on IUI was highlighted by the Chair of the Evidence Update Advisory Group during sign-off of the completed Evidence Update. This study suggested that IUI is non-inferior to in-vitro fertilisation (IVF). The panel felt that the *new study provided new evidence that should be considered in an update and felt that this question should be updated with*	Thank you for your comment. The referral received asked the Clinical Guideline Update Team (CGUT) to review evidence on IUI compared to expectant management. However, IVF compared to IUI will be considered in a future update of this guideline.

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						more urgency than the other questions under consideration. Decision: NICE to update this clinical question using Standing Committee for Updates via the Clinical Guidelines Update Team. We fully support and agree with the NICE surveillance team, that this question has been identified and for it to be purposefully followed through.	
36	SH	Association of Clinical Embryologists	Addendum	9	12 15	The review question is, "*What is the effectiveness of intrauterine insemination (IUI) compared with expectant management in people with unexplained infertility, mild endometriosis or 'mild' male factor infertility?"* However, the second recommendation then states, "*do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural or religious objections to IVF). [2016]"* The recommendation does not correspond to the question asked. We suggest that the question should have been, "what is the effectiveness of intrauterine insemination (IUI) compared with **IVF** in people with unexplained infertility, mild	Thank you for your comment. The referral received asked the Clinical Guideline Update Team (CGUT) to review evidence on IUI compared to expectant management. Evidence regarding IVF was not reviewed as part of this update. However, IVF compared to IUI will be considered in a future update of this guideline. This 2016 update searched for all literature comparing the clinical effectiveness and cost effectiveness of IUI with and without ovarian stimulation compared to expectant management. Evidence was inconclusive in showing that IUI with or without ovarian stimulation is more effective than expectant management and economic evidence suggests that IUI may be considered cost-effective if expectant management were not an

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						endometriosis or 'mild' male factor infertility?" Expectant management for potential IUI candidates may be inappropriate, especially for those women whose fertility is already in age-related decline. We would suggest that NICE at this time do not issue a blanket recommendation of not offering IUI treatment (except in exceptional circumstances) for patients with unexplained infertility, mild endometriosis or 'mild male factor infertility' We would like to propose that the option of using IUI as a first line treatment for selected patients is an appropriate, cost effective, safer and less invasive approach compared with IVF.	option. Therefore, no changes to the 2013 recommendations were made.
37	SH	Association of Clinical Embryologists	Addendum	15	1 4	Regarding the results of the economic literature review which included only one study [6]: "*This study was partially applicable with very serious limitations, which included no use of QALYs, a short time horizon, statistically insignificant effect size on the primary outcome and use of potentially inappropriate costs*" The Association of Clinical Embryologists feels that to base recommendations on the cost effectiveness IUI treatment on	Thank you for your comment. The recommendations made by the committee in 2013, and retained by the committee in 2016, stemmed largely from the lack of clinical evidence of effectiveness of IUI over expectant management. While this study supported this conclusion, the committee agreed that its quality was not sufficiently high to be an important factor in decision making. .

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						such low quality data is inappropriate and would hope that NICE reconsider their position in this instance.	
38	SH	Association of Clinical Embryologists	general	General	general	Success rates: The HFEA holds the largest database of IUI results which shows that overall the pregnancy rates are approx. 13% per cycle. However, success rates do vary enormously across clinics and accept that the poorer performing clinics would not necessarily offer the patient a cost-effective chance at pregnancy. We would like to suggest that patients with a good IUI prognosis should be offered the option of IUI treatment (safer and less invasive than IVF) at a high performing clinic.	Thank you for your comment. The committee noted HFEA success rates for IUI reported by stakeholders but noted that this data could not be disaggregated by cause of infertility and as such could not inform the committee's deliberations.
39	SH	Association of Clinical Embryologists	Short/full	general	general	The Association of Clinical Embryologists feels the recommendation gives a false portrayal of the effectiveness of IUI to UK CCGs and to patients. IUI strategies can be, and are, implemented for a selected group of patients, which save money and involve less risky and less invasive medical procedures.	Thank you for your comment. This 2016 update searched for all literature comparing the clinical effectiveness and cost effectiveness of IUI with and without ovarian stimulation compared to expectant management. No new evidence was identified further to that identified in the 2013 evidence review. The evidence available was also inconclusive in showing that IUI with or without ovarian stimulation is more effective than expectant management and the economic

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							evidence suggests that IUI may be considered cost-effective if expectant management were not an option. Therefore, the committee agreed to retain the original recommendation and no new recommendation favouring IUI with or without ovarian stimulation was made
40	SH	Association of Clinical Embryologists	general	general	general	We are concerned that these recommendations may be reviewed by CCGs and interpreted incorrectly as applicable to all patients. IUI is likely to be more effective in couples where expectant management is not possible (e.g. same sex couples or couples where there exist psychological or physiological barriers to vaginal intercourse). However, the recommendation, without expressly acknowledging the potential for increased cost effectiveness in such groups, may lead to CCGs implementing a blanket block on all IUI treatments. A possible subsequent effect may be that IUI expertise could be lost in the NHS and patients may be "forced" into IVF when a cheaper less invasive treatment would have been their best first line treatment.	Thank you for your comment. Recommendation 1.9.1.1 "Consider unstimulated intrauterine insemination as a treatment option in the following groups as an alternative to vaginal sexual 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. **[new 2013]**"
4	S	Association of	ge	gen	4	Recent significant papers and reviews are already at hand	Thank you for your comment. The scope of this

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1	H	Clinical Embryologists	neral	eral	6	for NICE panel to consider. The evidence and opinion within these papers recommend the routine use of IUI and the Association of Clinical Embryologists would like to strongly suggest their review by the panel: [1] Bensdorp AJ et al (2015). Br Med J;350:7771. doi:http://dx.doi.org/10.1136/bmj.g7771 [2] Tjon-Kon-Fat RI et al (2015). Hum Reprod;30:2331. doi: 10.1093/humrep/dev193 [3] Bahadur G et al (2016). Hum Reprod. doi:10.1093/humrep/dew075. [Epub ahead of print]. [4] Woodward,B et al (2016): Hum Fertil, doi: 10.1080/14647273.2016.1182220 [5] Kim D et al (2015). BMJ Open, 5, e007588. doi: 10.1136/bmjopen-2015-007588. [6] Wordsworth S et al (2011). Hum Reprod; 26(369 doi: 10.1093/humrep/deq315	guideline update was to compare IUI with expectant management. Please see the below for reasons as to why the additional studies listed in your comment were not included in this guideline update: Bensdorp 2015: The comparisons included (IVF compared to IUI) was outside of the scope of this update. Evidence regarding IVF compared to IUI will be considered in future guideline updates. Tjon-Kon-Fat 2015: The comparisons included (IVF compared to IUI) was outside of the scope of this update. Evidence regarding IVF compared to IUI will be considered in future guideline updates. Wordsworth 2011: The comparisons included (clomifene citrate compared to IUI) was not included in this evidence review. Please note that narrative reviews and commentaries (such as in Bahadur 2016 and Woodward 2016) are not routinely included in intervention reviews. In accordance with NICE'S methodology, the highest level of study design is sought for intervention reviews: this is

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							systematic reviews of randomised control trials and randomised control trials. Therefore, the highest level of evidence was included in this evidence review.
42	SH	Department of Health	general	general	general	No comments	Thank you.
43	SH	British Fertility Society	Addendum	general	general	The responses from our membership cover the complete range of views – from acceptance of the guideline as it stands to rejection of the change made in 2008. We believe that this reflects significant division of expert professional opinion on the subject of the role of intrauterine insemination in unexplained subfertility and where there is mild male factor or mild endometriosis. This reflects both the history of the guideline and also the lack of useful literature.	Thank you for your comment.
44	SH	British Fertility Society	Addendum	general	General	There is a concern, since IUI continues to be undertaken in some centres as a first line treatment rather than IVF, that the question of IUI against expectant management in couples in those groups who have had a genuine 2 years subfertility, whilst valid, is not the only comparison to make and that a comparison with IVF would also be useful. It is recommended that NICE consider that evidence alongside current included evidence. It is recognised however that the quality of that data is not high either. The most recent paper by Bensdorp et al (2015) uses a definition of unexplained	Thank you for your comment. The trial referenced (Bensdorp et al 2015) was identified by the searches but was not considered for inclusion for this evidence review as the comparisons examined (IVF compared to IUI) is outside of the scope of this update. Evidence regarding IVF compared to IUI will be considered in a future guideline update.

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						subfertility at one year of trying and therefore is excluded from the current discussion. The argument is made that centres undertaking IUI regularly have superior results. Two opinion papers have been published recently in relation to this. *Bensdorp, A.J., Tjon-Kon-Fat, R.I., Bossuyt, et al (2015) Prevention of multiple pregnancies in couples with unexplained or mild male subfertility: randomised controlled trial of in vitro fertilisation with single embryo transfer or in vitro fertilisation in modified natural cycle compared with intrauterine insemination with controlled ovarian hyperstimulation. British Medical Journal, 350(g7771). Available at: http://www.bmj.com/content/350/bmj.g7771*	
45	SH	British Fertility Society	addendum	general	general	There is concern that that it may be detrimental to patients in some regions to be firm on the guideline since commissioning is not equitable and in nearly all regions not NICE compliant with respect to IVF. The removal of that support may significantly reduce access to treatment for many couples. NICE are encouraged to be sympathetic to the complex commissioning issues which remain in this specialist area.	Thank you for your comment. The committee recognises that there are geographical variances in the availability of treatments and this is noted as an equalities issue (Section 2.6, Evidence to recommendations, pg 21). However, no changes to recommendations relating to IVF were made as this is outside the scope of this update. Evidence regarding IVF compared to IUI will be considered in a future guideline update.
46	SH	British Fertility Society	adde	general	general	It is recognised that the literature is not helpful and although the Bhattacharya paper (2008) describes the best structured	Thank you for your comment. The committee reviewed the research recommendations (number 22 and 23)

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			ndum			trial to date it does not fully address the dilemmas. The BFS supports the call for good quality studies to resolve this issue which should be prioritised in any national research strategy for the subspecialty.	made in the 2013 guideline update and noted that research to examine the effectiveness of IUI (with and without stimulation) compared to expectant management in couples with endometriosis and mild male factor infertility had been recommended. The committee considered these research recommendations to be still valid and did not make any new research recommendations.
56	SH	RCN	General	General	General	The Royal College of Nursing welcomes proposals to update these guidelines. The RCN invited members of its Fertility Nursing Forum to review the document on its behalf. Comments below reflect the views of our members.	Thank you for your comment.
57	SH	RCN	General	General	General	Some of the comments here relate to other sections of the guideline apart for the Addendum as we consider that these points should be reviewed as soon as possible.	Thank you for your comment. We have made a note of this and will pass this onto the NICE surveillance team.
58	SH	RCN	Full	21	General	We support the proposal that the evidence review does not indicate a change to the recommendations. We also support the recommendation that an up to date trial to assess the efficacy of IUI is needed. We welcome the fact that the committee discussed and noted the inequity in the provision of fertility services	Thank you for your comment. The committee reviewed the research recommendations (number 22 and 23) made in the 2013 guideline update and noted that up to date research to examine the effectiveness of IUI (with and without stimulation) compared to expectant management in couples with endometriosis and mild male factor infertility had been recommended. The

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						with variations geographically and in the types of treatments offered. We hope this will help to reinforce the need for commissioners and service providers to address these unacceptable differences.	committee felt that the research recommendations in the outlined in the 2013 guideline update covered the research that what they would like to recommend and therefore did not make any new research recommendations.
59	SH	RCN	Full	General	General	We support the recommendation for an up to date trial of IUI procedures and success rates. This will give us a better standing for providing patients with up to date evidence and aid professionals when calculating individual success rates.	Thank you for your comment. The committee have noted the lack of up to date evidence in this area in section 2.6 of the addendum.
60	SH	RCN	CG156	1.3.6	l	We acknowledge that the comments below are not part of the addendum draft as they relate to the CG156 recommendations 1.3.6 and 1.3.7 – thyroid function tests and endometrial biopsy. The recommendations are over 12 years old and have not been updated since 2004. There are new innovations that might suggest the evidence needs to be reviewed by NICE and possibly new recommendations put in place, hence the inclusion in this consultation. **Thyroid function tests:** We are concerned that this recommendation may imply that	Thank you for your comment. These areas of the guideline were not reviewed as part of this update. However, this has been noted and will be shared with the NICE surveillance team to consider as part of the next surveillance review.

Fertility (standing committee update)
Consultation on draft guideline - Stakeholder comments table
12 May – 10 June 2016

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						thyroid testing should only be undertaken after a fertility problem has been diagnosed. If detected sooner it could allow a patient to commence medication to ease the problem and help the patient's hormonal problems regulate. New studies have shown this could be recommended as a blood test as part of the fertility work up profile. **Question 1:** It will be challenging to implement change in practice however it should not significantly increase the cost of treatment for patients or the NHS.	
61	SH	RCN	CG156	1.3.7		**Endometrial Biopsy**: We are concerned that this recommendation would not help women with repeated implantation failure of embryos. There is evidence to suggest that the new ERA test, which is a personalized genetic test to diagnose the state of endometrial receptivity in the window of implantation helps. This molecular diagnostic tool is used to analyse the expression levels of 238 genes related to the status of endometrial receptivity. **Question 1**: It would present a challenge cost wise but would give hope for the woman who repeatedly has implantation failure despite no obvious problem, such as unexplained infertility not related to age etc.	Thank you for your comment. These areas of the guideline were not reviewed as part of this update. However, this has been noted and will be shared with the NICE surveillance team to consider as part of the next surveillance review.

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						Research and time has moved on since this was recommended in 2004, so important that the guideline is updated to reflect current evidence.	
62	SH	RCN	General	General	General	New studies also indicate that women and men with low levels of Vitamin D can suffer with fertility problems. We suggest that NICE should look at the evidence into this and see if this is something it should be recommending to get patients tested as part of a work up before embarking on expensive IVF treatments.	Thank you for your comment. Low levels of Vitamin D as a possible cause of Fertility was excluded from the scope of this update. Your comment has been noted and this will be shared with the NICE surveillance team to consider as part of the next surveillance review (due in 2017).