National Institute for Health and Care Excellence

4-year surveillance (2017) – Ectopic pregnancy and miscarriage (2012) NICE guideline CG154

Appendix B: stakeholder consultation comments table

Consultation dates: 10 to 30 August 2016

Do you agree with the proposal not to update the guideline?

Stakeholder	Overall response	Comments	NICE response
King's College Hospital NHS Trust	Disagree	There were some questions that were not considered in the original guidance and if the guidance is not revised, then these questions will not be asked. We believe that the provisional decisions to disregard pertinent evidence are flawed in some instances and we have some specific comments on the consultation document: 1) Potential query that was not addressed: 'which biochemical tests are useful in the management of women with PUL'? This question does not focus on diagnostic accuracy, but on determining appropriate follow up regimens 2) Pages 15& 16 – Fertility outcomes and success rates – the evidence is jumbled up in these sections – some relates to ectopic pregnancy, not miscarriage and this should be in the section on the treatment of ectopic pregnancy 3) page 16 – the review of the evidence regarding expectant management of miscarriage shows that there are increases in duration of bleeding and unplanned admission. In the safety section you state: 'Impact statement Expectant management is associated with more risks than surgical management but the evidence base does not indicate superiority for either treatment. The study is in line with current recommendations which offer the choice of both to the woman.' This is not true – the current guidance recommends expectant treatment as the first line management, not that women are offered a choice. 4) page 18 – Etonogestrel implants – this was a study looking at whether using contraceptive implants at the time of medical terminations reduced the success rate of the procedure (because giving a progestogen alongside an antiprogesterone, mifepristone, could counteract its effect). This is why also looked at number of subsequent pregnancies. We do not believe that this study is of any real relevance to this guideline as it was not evaluating a different regimen for medical treatment that could be potentially be extrapolated to miscarriage.	Thank you for your comment. No published evidence was identified during the surveillance review on which biochemical tests are useful in the management of women with pregnancy of unknown location, therefore this question was not proposed for inclusion. Thank you for highlighting that some studies on ectopic pregnancy had been included under miscarriage these have been moved to the correct section. The impact statement on page 16 has also been amended to reflect the recommendations. Thank you for your comments on etonogestrel implants, this study was reviewed and considered not to be relevant to NICE guideline CG154. Therefore, it has been excluded from Appendix A: summary of evidence from surveillance. For methotrexate (MTX) no evidence was identified that would impact on current recommendations. This surveillance review searched for systematic reviews and RCTs published between 8 July 2014 to 2 May 2016. The decision to update guideline recommendations is based on published evidence as well as topic expert feedback. Therefore it was

		5) We do not believe that MTX should be offered to stable women with the diagnosis of an ectopic pregnancy on USS and hCG <1500 as a firstline treatment. This is because of the risk of a) misdiagnosis and b) over-treatment. We accept that in the absence of an RCT considering expectant management, you cannot draw an evidence based conclusion, but we believe that a repeat hCG should be mandatory to exclude an ongoing pregnancy with a repeat ultrasound before MTX treatment if the hCG is rising to try to ensure an IUP has not been missed. 6) NQ-02 – This question does not really make sense. Maybe it should have been 'What is diagnostic accuracy of serum biomarkers for determining a viable intrauterine pregnancy in women with threatened miscarriage or a PUL'? We disagree with the impact statement – a follow up visit will not always be necessary to determine the location of a pregnancy – not if the patient has a clinical history typical of a miscarriage and a very low progesterone or a rapidly falling hCG.	proposed not to update recommendations related to methotrexate treatment (recommendations 1.6.3, 1.6.5-1.6.6, 1.6.12) at this time. For NQ-02, this question has been amended to reflect your suggested change in wording. The impact statement has also been amended.
British Society of Gynaecological Endoscopy	Disagree	**NQ_03 How effective is expectant management compared to medical management for ectopic pregnancy?** Expectant management for selected patients should be added to the guideline Evidence 1: Data from University College Hospital 2013 evaluation a protocol for expectant management in women with HCG less than 1500 demonstrated a 70% success rate, no major complications and that this strategy was suitable for 30 % women with an ectopic pregnancy. 'Efficacy and safety of a clinical protocol for expectant managent of selected women diagnosed with a tubal ectopic pregnancy. D Mavrelos, H Nicks, A Jamil, E Jauniaux and D Jurkovic. *Ultrasound Obstet Gynaecol 2013; 42: 102-107* Evidence 2: METEX study randomized medical and expectant management in women with ectopic preganacies and pregnancies of unknown location, and low HCG. Expectant management was successful with uneventful disease resolution in 60% women and no less successful that treatment with methotrexate. Benefit demonstrated in reduced side effects and there was cost saving. 'Methotrexate or expectant management in women with an ectopic pregnancy or pregnancy of unknown location and low hCg concentrations.' *N.M.Van Mello et al. Human reproduction, vol28, No1, pp. 60-67, 2103* **154 – 16 Recommendation 'Offer systemic Methotrexate as a first line treatment to women……..a HCG level less than 1500'**. Evidence 1 & 2 (above) demonstrate that Methotrexate has no additional treatment benefit over expectant management, and incurs greater cost and higher risk of side effects. Expectant management should be offered first line in this situation.	Thank you for your comment. The two studies you refer to by Mavrelos et al. (2013) and Van Mello et al. (2013) were found and included during the Evidence Update (2014). This evidence has been added to Appendix A: summary of evidence from surveillance under a new review question NQ-04. Due to the increased evidence on expectant management for ectopic pregnancy, the impact statement has been changed to 'New evidence identified that may impact on the guideline'.
The Miscarriage	Disagree	This is the opportunity to amend and improve the guidelines in line with feedback from patients as well as from clinicians and researchers. The key points which we believe need amending are:	Thank you for your comment.

Association		Support and information giving (154 – 01): Point 1.1.3 notes the need for 'specific evidence-based information', but two key points are omitted: i) information about what to expect between confirmation of miscarriage and either a management decision or active management (this should come between bullet points 2 and 3). This should include practical advice on managing pain and bleeding. ii) information about the disposal of pregnancy remains: what might be passed, what it may look like and, crucially, what the options are for disposal (see https://www.hta.gov.uk/sites/default/files/Guidance_on_the_disposal_of_pregnancy_remains.pdf). Management of miscarriage (154 – 12): The recommendation of expectant management as the first-line response in confirmed miscarriage is a complete erosion of patient choice, as is the pathway that proposes medical management as the next option along. In our experience, most women have a definite preference for one method over another (or at least for the method they can best tolerate in distressing circumstances). This perspective is backed up by the fact that 42% of patients eligible for the MIST trial refused to be randomised. As long as the woman is clinically stable, we believe she should be offered informed choice of all clinically appropriate and available options for management of confirmed miscarriage or ectopic pregnancy.	The evidence identified during the surveillance review for support and information giving was considered to be consistent with guideline recommendations. Therefore it is not proposed to update this section of the guideline since no evidence has been identified to support a change. The Human Tissue Authority guidance is available for and already used by the NHS therefore it was not considered as part of this surveillance review. The MIST trial you refer to was found and included during the development of NICE guideline CG154. The guideline committee considered the qualitative data (Smith et al. 2006) from the MIST trial to develop recommendations 1.5.2 – 1.5.8. We recognised that expectant management is recommended as first-line management for miscarriage. However, recommendation 1.5.3 suggests offering medical management to women with a confirmed diagnosis of miscarriage if expectant management is not acceptable to the woman.
The Ectopic Pregnancy Trust	Disagree	The EPT are concerned that the guideline has limited credibility amongst medical professionals in the field. Unless this guideline is looked at again, it will continue to be criticised and ignored by medical professionals, potentially leaving patients in a vulnerable or at risk position. While peer pressure alone should not be cause enough for a review, the EPT believes there is enough opportunity for change to the guideline to warrant it being reconsidered. There are key areas that require attention in order to improve care for women experiencing early pregnancy loss and, given we represent the patient's voice alongside medical expertise, we welcome this opportunity to comment on this. Our concerns are as follows: Diagnosing an ectopic pregnancy: A high standard of ultrasonography is imperative in achieving effective diagnosis of an ectopic pregnancy (EP) but ultrasound criteria for diagnosis is not discussed in the NICE guidance and we propose that this be added to a revised guideline. We also would like the guideline to make clear that ultrasound findings should be reviewed by an experienced examiner. Most EPs are visualised on ultrasound as a homogenous mass or 'blob', some EPs may be difficult to visualise and some are not seen on an initial scan simply because they are too small and early in their natural history. Kirk et al showed that 74% of ectopic pregnancies (EP) can be visualised on an initial transvaginal scan (TVS) and 3 of the 91 cases of EP diagnosed on the initial TVS were false-positive test results. To avoid the risk of false-positive it is proposed that such ultrasound findings be defined as 'probable' rather than 'definite' EPs.	Thank you for your comment. This surveillance review searched for systematic reviews and RCTs published between 8 July 2014 to 2 May 2016. The decision to update guideline recommendations is based on published evidence as well as topic expert feedback. Some of the issues highlighted in your comment were not identified during the surveillance review from topic expert feedback or published evidence. Current guidance does not include ultrasound criteria for diagnosing ectopic pregnancy. Therefore, we have proposed an update on the accuracy of ultrasound for diagnosing ectopic pregnancy (for further information see NQ-03 in Appendix A: summary of evidence from surveillance). You suggest that an experienced examiner should review ultrasound findings. We consider that recommendation 1.4.17 already covers your suggestion

		We recommend the development of the guidance to enable medical professionals to clearly distinguish whether they have a 'definite' EP, a 'probable' EP or PUL and what to do in each circumstance. This will require clear definitions. Pregnancy of unknown location (PUL): We consider that it would be beneficial to clearly state types of PUL and appropriate follow up regimens in each instance. For example, clearly defining the parameters that suggest a 'low risk' PUL and add clarity that it is a likely failing PUL or IUP and clearly defining the parameters that suggest a 'high risk' PUL and add clarity this is a 'probable' EP. Identifying low or high risk PUL can be carried out effectively using published prediction models. These models have been shown to outperform hCG and progesterone in large multicentre trials. The guidance discusses the management of PUL but we would like to see more support for medical professionals identifying the location of the pregnancy. This is particularly poignant for the small cohort of women who will have an EP that also have doubling Serum hCG levels, given these are the EPs that will often be asymptomatic until a catastrophic rupture. Waiting 7-14 days in this instance rather than using a hCG of 1000-1500 places women at significant risk. If a woman has an EP that is currently a PUL and has been told 'it is a probable IUP but there is a small chance of an EP' it is natural behaviour for her to 'hang on' to the information she most wants to believe. We have heard stories of patients ignoring the new onset of pain in these instances. Use of Methotrexate: We are pleased that Methotrexate is recommended as first-line treatment for women clearly at risk from an ectopic pregnancy. However, we do not consider it should be offered as first-line treatment to stable women with the diagnosis of an EP on ultrasound scan and hCG <1500 because of the risk of (a) misdiagnosis of EP and therefore viable intrauterine pregnancies being terminated and (b) overtreatment where women would be subjected to a drug treatment that they do not need. We would instead like to propose that the guideline also considers expectant management for ectopic pregnancy. There is a risk that medical professionals may be giving Methotrexate to women whom do not require treatment in one-third of cases. In a recent study of 333 women diagnosed with EP, 146 commenced expectant management and 104 successfully resolved their EP without further intervention (31.2%, 95% confidence interval 26.2– 36.2). While we recognise the absence of any randomised controlled trials considering expectant management means it is not possible to draw an evidence-based conclusion, we do not think current studies should be ignored and strongly believe that a repeat blood test to check hCG levels should first be mandatory to exclude an ongoing pregnancy with a repeat ultrasound before Methotrexate treatment if the hCG is rising to try to ensure an intrauterine pregnancy has not been missed. The American College of Obstetricians and Gynecologists recommend that Methotrexate should only be administered for a 'probable EP', where there is a visible embryonic structure and a less than 53% rise in hCG over a 48-hour period confirm that the increase is incompatible with an ongoing early IUP. We applaud this view but also recognise Condous et al's assertions that a hCG rise of less than 35% is a safer definition of non-viability in women with probable EP when Methotrexate is being considered. As with earlier comments, the quality of ultrasonography is crucial and, when considering medical management, it is essential that the ultrasound findings have been reviewed by an experienced examiner and that there is certainty about the diagnosis. Referrals: We are concerned that the guidance advises referral, in many cases, only when the gestation is over 6 weeks. This increases the risk of EPs being missed when they are often small	because the recommendation suggests that all ultrasound scans should be performed and reviewed by someone with training in, and experience of, diagnosing ectopic pregnancies. Unfortunately we could not review the study by Kirk et al that you have suggested as without a full citation we are unable to identify this study. The study you refer to (n=333 [Mavrelos et al. 2013]) was found and included during the Evidence Update (2014). This evidence has been added to Appendix A: summary of evidence from surveillance under a new review question NQ-04. Due to the increased evidence on expectant management for ectopic pregnancy, the impact statement has been changed to 'New evidence identified that may impact on the guideline'. The American College of Obstetricians and Gynecologists recommendations were not included in the surveillance review as surveillance reviews do not consider other guidelines only published primary studies and systematic reviews. Unfortunately we could not review the study by Condous et al. that you have suggested as without a full citation we are unable to identify this study. The MIST trial you refer to was found and included during the development of NICE guideline CG154. The guideline committee considered the qualitative data (Smith et al. 2006) from the MIST trial to develop recommendations 1.5.2 – 1.5.8. We recognised that expectant management is recommended as first-line management for miscarriage. However, recommendation 1.5.3 suggests offering medical management to women with a confirmed diagnosis of miscarriage if expectant management is not acceptable to the woman. Regarding the evidence on expectant management of miscarriage, the impact statement has been updated to

		and typically most easily treatable. Miscarriage treatment: The guideline recommends that all women miscarrying should be given a period of expectant management as first-line treatment using the MIST trial to suggest that there is equipoise between the different management options and therefore economics should be the main consideration. We have huge concerns that this guidance removes patient choice and can increase the psychological impact of the miscarriage. The assumption that the outcomes of the management options for miscarriage are similar fails to consider that 69% of women who could have entered the MIST trial either exercised their choice to undergo surgery or be applied. The fact that it was so hard to recruit women into this trial and it had to be extended by 33 months should perhaps be seen as an indicator of what patients want – some women want to choose surgery for a variety of reasons. The review of evidence on expectant management of miscarriage shows that there is an increase in the duration of bleeding and unplanned admission. The Impact statement goes on to state that "Expectant management is associated with more risks than surgical management but the evidence base does not indicate superiority for either treatment. The study is in line with current recommendations which offer the choice of both to the woman." This is not correct as the current guidance recommends expectant treatment as first-line management, not that women are offered a choice.. Use of language: The guideline suggests women should be informed that 'the diagnosis of miscarriage using one ultrasound scan cannot be guaranteed to be 100% accurate and there is a small chance that the diagnosis may be incorrect, particularly at very early gestational ages'. This is problematic as (a) it suggests that every scan with a diagnosis of miscarriage needs to be reconfirmed when this is not the case (b) It can have a detrimental psychological impact on women who may cling on to false hope unnecessarily. It is good practice for scans to be crosschecked by a second operator but to make a women wait for a second scan with, for example, an empty gestation sac of 30mm is unnecessary and possibly damaging. Preisler J, Kopeika J, et al. (2015) provide strong evidence regarding the size cut-offs at which the accuracy can be relied upon. They also note that where sizes fall beneath these cut-offs, a diagnosis of miscarriage should not be made and repeat scans carried out. At its simplest level, telling a woman that there is no heart beat and her baby has therefore died and, at the same time, telling her that ultrasound isn't completely accurate seems insensitive. A better use of language would be to suggest that a second scan was being undertaken to ensure that the sonographer was 'doubly sure'. While the two statements have the same meaning, the latter does not supply the false hope that could be attributed when something isn't deemed accurate. Length of time between miscarriage scans: The guideline suggests that 'if the mean gestational sac diameter is less than 25.0 mm with a TVS and there is no visible fetal pole, perform a second scan a minimum of 7 days after the first before making a diagnosis'. We are supportive of the research of Preisler J, Kopeika J, et al. that suggests that gestation sacs with Mean Sac Diameter less than 12mm, should be repeat scanned at a minimum time interval of 14 days to avoid the risk of misdiagnosis and prevent unnecessary demands on EPAU services. Fertility outcomes and success rates: Citations 8 and 12 on pages 15-16 are misplaced, as they relate to ectopic pregnancy, not miscarriage. They should be located in the section on the treatment of ectopic pregnancy. Etonogestrel implants: This study examined whether using contraceptive implants at the time of	reflect the overall conclusion of the systematic review on safety and effectiveness of expectant and surgical management of miscarriage This can be seen in Appendix A: summary of evidence from surveillance under review question 154 – 12. The study you refer to (Preisler et al. 2015) was found and included during this 4-year surveillance review and the impact statement has been updated (see Appendix A: summary of evidence from surveillance under review question 154 – 05). Thank you for highlighting that some studies on ectopic pregnancy had been included under miscarriage. These have now been moved to the correct section of the surveillance review. The impact statement on page 16 has also been amended to reflect the recommendations. Regarding your comment about the use of language in recommendation 1.4.4, we noticed that NICE guideline CG154 refers to a footnote when it is expected that women with early pregnancy complications receive information. This footnote refers to guidance on patient experience in adult NHS services (NICE guideline CG138). Therefore it was considered that health professionals are expected to follow this guidance when providing information to NHS users and that no changes in the wording of recommendation 1.4.4 of NICE guideline CG154 would be needed. Thank you for your comments on etonogestrel implants, this study was reviewed and considered not to be relevant to NICE guideline CG154. Therefore, it has been excluded from Appendix A: summary of evidence from surveillance. For NQ-02, this question has been amended to reflect your suggested change in wording.

		medical terminations reduced the success rate of the procedure as administering a progestogen alongside an antiprogesterone (mifepristone) could counteract its effect. We are of the view that this study is of little relevance to this guideline as it was not evaluating an alternative regimen for medical treatment that could be potentially be extrapolated to miscarriage management. NQ-02: This question should be refined to state 'What is diagnostic accuracy of serum biomarkers for determining a viable intrauterine pregnancy in women with threatened miscarriage or a PUL?' We disagree with the Impact statement which currently states that a follow up scan will always be necessary to determine the location of a pregnancy – this is not necessarily the case if the patient has a clinical history typical of a miscarriage and a very low progesterone level or a rapidly decreasing hCG level.	
NHS England	Disagree	**NQ_03 How effective is expectant management compared to medical management for ectopic pregnancy?** Expectant management for selected patients should be added to the guideline Evidence 1: Data from University College Hospital 2013 evaluation a protocol for expectant management in women with HCG less than 1500 demonstrated a 70% success rate, no major complications and that this strategy was suitable for 30 % women with an ectopic pregnancy. 'Efficacy and safety of a clinical protocol for expectant managent of selected women diagnosed with a tubal ectopic pregnancy. D Mavrelos, H Nicks, A Jamil, E Jauniaux and D Jurkovic. *Ultrasound Obstet Gynaecol 2013; 42: 102-107* Evidence 2: METEX study randomized medical and expectant management in women with ectopic preganacies and pregnancies of unknown location, and low HCG. Expectant management was successful with uneventful disease resolution in 60% women and no less successful that treatment with methotrexate. Benefit demonstrated in reduced side effects and there was cost saving. 'Methotrexate or expectant management in women with an ectopic pregnancy or pregnancy of unknown location and low hCg concentrations.' *N.M.Van Mello et al. Human reproduction, vol28, No1, pp. 60-67, 2103* **154 – 16 Recommendation 'Offer systemic Methotrexate as a first line treatment to women……..a HCG level less than 1500'**. Evidence 1 & 2 (above) demonstrate that Methotrexate has no additional treatment benefit over expectant management, and incurs greater cost and higher risk of side effects. Expectant management should be offered first line in this situation.	Thank you for your comment. The two studies you refer to by Mavrelos et al. (2013) and Van Mello et al. (2013) were found and included during the Evidence Update (2014). This evidence has been added to Appendix A: summary of evidence from surveillance under a new review question NQ-04. Due to the increased evidence on expectant management for ectopic pregnancy, the impact statement has been changed to 'New evidence identified that may impact on the guideline'.
Association of Early Pregnancy Units (AEPU)	Disagree	Currently the NICE early pregnancy guidelines have limited credibility amongst those working in the field and in relation to many areas of practice are ignored. There is a wider issue around how evidence quality is assessed – particularly in relation to diagnostic test studies. However the main concerns of the AEPU – which represents the early pregnancy units in the UK are as follows. **Access:** Which women should be referred to an early pregnancy unit (EPU) because they are at	Thank you for your comment. This surveillance review searched for systematic reviews and RCTs published between 8 July 2014 to 2 May 2016. The decision to update guideline recommendations is based on published evidence as well as topic expert feedback.

		risk of ectopic pregnancy (EP) is unclear. There seems to be the belief that women with vaginal bleeding and no pain are not at risk of EP. NICE advises that such women be told to carry out a urinary pregnancy test in 10 days and "come back if it is positive". This is inappropriate as it is not possible on the basis of symptoms alone to select women in early pregnancy that have an EP, miscarriage or viable intra- uterine pregnancy (IUP). In an unpublished study of 596 women attending our EPU, vaginal bleeding in isolation was a significant risk factor for the presence of an EP particularly if it lasted for more than 3 days. Concerns about EP may also exist whether the gestational age of the pregnancy is greater than or less than 6 weeks. The guidance suggests that there is a specific cut-off in gestational age below which an EP is not dangerous, as they advise referral in many cases only when the gestation is over 6 weeks. Again this will lead to EPs being missed – often when they are small and perhaps most easily treatable. **Miscarriage treatment:** Much of the guidance in relation to miscarriage treatment is taken from the MIST trial of the management of miscarriage. However, although this trial was randomised, drawing conclusions from it is difficult. Of 3905 women attending EPUs, 1621 refused trial entry and 1085 were not eligible. The result is that only 1200/3905 (31%) women were randomised and the trial had to be extended by 33 months to overcome recruitment problems. It is clear that the subjects included represented a highly selected population. Accordingly, making policy on the basis of the outcome of these 1200 women is flawed. This is particularly so for psychological outcomes as the women who consented to take part in the trial may have been more likely to be motivated and so potentially less likely to show psychological morbidity, whichever management option was taken. NICE recommends that all women with miscarriage should be given a trial of expectant management (watch and wait for resolution). This guidance seems to be based purely on an economic argument and uses the MIST trial to suggest that there is 'equipoise' between the different management options, and so argues that economics should be the main driver. Critically, this advice removes patient choice. Furthermore, the assumption that the outcomes of the management options for miscarriage are similar fails to consider the fact that 69% of women who could have entered the MIST trial either exercised their choice to undergo surgery or were not eligible for the trial. That it was so hard to recruit women into this trial should perhaps give pause for thought about what patients want – some want to choose surgery for a variety of reasons. From a practical viewpoint, the NICE guidance does not consider the gestational age of a pregnancy as a factor when counseling women regarding treatment options. However, units often rely on protocols that use ultrasound criteria to decide if medical management is appropriate based on gestation sac and embryo size as well as whether or not the pregnancy is multiple. The experience of a miscarriage may be very different for a pregnancy at 11 weeks' gestation that failed at 6 weeks compared to an 11-week twin pregnancy that has only just failed. Yes, there are no useful data on this, but this does not mean that common sense should not be applied. **Pregnancy of unknown location (PUL)** The guidance defines a PUL as: "A descriptive term used to classify a pregnancy when a woman has a positive pregnancy test but no pregnancy can be seen on an ultrasound scan". This is not	The issues highlighted in your comment were not identified during the surveillance review from topic expert feedback or published evidence. We acknowledge the limitations of the MIST trial. However, the guideline committee also considered the qualitative data from the MIST trial (Smith et al. 2006) to develop recommendations 1.5.2 – 1.5.8. Although the sample was small (n=72 participants), it included participants (n=56) and non-participants (n=16) in the MIST trial. We acknowledge that expectant management is recommended as first-line management for miscarriage. However, recommendation 1.5.3 suggests offering medical management to women with a confirmed diagnosis of miscarriage if expectant management is not acceptable to the woman. Unfortunately we could not review the studies by Cordina et al. and Kirk et al. that you have suggested as without a full citation we are unable to identify these studies. Current guidance does not include ultrasound criteria for diagnosing ectopic pregnancy. Therefore, we have proposed an update on the accuracy of ultrasound for diagnosing ectopic pregnancy (for further information see NQ-03 in Appendix A: summary of evidence from surveillance). The American College of Obstetricians and Gynecologists recommendations were not included in the surveillance review as surveillance reviews do not consider other guidelines only published primary studies and systematic reviews. Unfortunately we could not review the study by Condous et al. that you have suggested as without a full citation we are unable to identify this study. The study you refer to (Preisler et al. 2015) was found and included during this 4-year surveillance review and

		entirely correct. Current publications on the subject of PUL relate to a failure to locate a pregnancy with TVS. Thus in the event of a pregnancy being classified as a PUL using the transabdominal approach, the correct next step is to carry out a TVS. The guidance in relation to the management of PUL does not focus on identifying the location of the pregnancy. This reflects current practice, as the aim now is to evaluate risk, as for many PUL the location of the pregnancy is never known. Whether serial serum measurement of human chorionic gonadotrophin (hCG) can predict an EP and/or an IUP rather misses the point. Serial hCG levels, expressed for example as the hCG ratio (the serum hCG after 48 hours/serum hCG at presentation), are not used to diagnose EP. A PUL is either low risk (failing PUL or IUP) or high risk (probable EP). Accordingly serum hCG levels may be used to predict a failing pregnancy (low risk), and in such cases a urinary pregnancy test in 2 weeks is appropriate follow-up. If a viable IUP (low risk) is predicted, an ultrasound scan 1–2 weeks later may be carried out. Identifying low- or high-risk PUL can be carried out effectively using published, easily used prediction models. Measurements of serum progesterone to triage PUL may also be used in this context, as this is effective at predicting early pregnancy failure. Although measuring serum progesterone is not recommended by NICE, it does offer the advantage of triaging women on the basis of one visit and one blood test, and Cordina et al. have shown that a significant number of women can be triaged using this approach at presentation. The use of prediction models is also not considered in the guidance, which is perverse given they outperform both hCG and progesterone and have been published in large multicentre trials. **Diagnostic criteria for ectopic pregnancy** TVS is a reasonably sensitive test for the detection of an EP, but it is not perfect. Most studies report ultrasound findings immediately prior to surgery. Kirk et al. perhaps give a more realistic picture and showed that 74% of EPs can be visualised on an initial TVS, although 98% were seen prior to surgery. Criticism of this study could be that it was carried out in a specialist referral unit for gynaecological ultrasound, so the results may be over-optimistic. However despite this, 3/91 cases of EP diagnosed on an initial scan were false-positive test results. This may be because most EPs are visualised on ultrasound as a homogenous mass or ‘blob’. To avoid false-positive results in these circumstances it has been proposed that such ultrasound findings are evidence of a probable, rather than a definite, EP. Some EPs may be relatively difficult to visualise and some are not seen on an initial scan simply because they are too small and early in their natural history. The ultrasound criteria to make a diagnosis of EP are not discussed in the NICE guidance, which would seem to be a significant omission given the reliance given to this when considering treatment. **Conservative treatment of Ectopic Pregnancy – risks of methotrexate** This is one of the most concerning parts of the guidance – and many believe is simply dangerous. Some authors consider that a definitive diagnosis of tubal EP can only be made when an extrauterine ges- tation sac containing a yolk sac or embryonic pole is visualised. A recent consensus publication on nomenclature proposed that ‘definite EP’ is used if an extra- uterine gestation sac with a yolk sac and/or embryo (with or without cardiac activity) is seen. As alluded	the impact statement has been updated (see Appendix A: summary of evidence from surveillance under review question 154 – 05).

		to above, a ‘probable EP’ is suggested if only a homo- geneous mass (blob sign) or an extrauterine sac-like structure is visualised. Using this classification, the specificity of ultrasound to detect EP is very high, but at the cost of lowering the sensitivity. Limiting the definitive diagnosis of EP to when embryonic structures are visible is an attempt to reduce false-positive diagnoses which, though rare, do occur due to amongst others the presence of pedunculated or broad ligament fibroids, pelvic inflammation or highly exophytic ovarian cysts. This stringent approach reflects the very high level of diagnostic certainty required in the event that methotrexate treatment is considered. Even in the context of clinical trials, false-positive diagnoses of EP can occur. This may lead to inappropriate use of methotrexate leading to termination of an undetected viable IUP, or to severe abnormalities in surviving pregnancies. The American College of Obstetricians and Gynecologists (ACOG) recommends that methotrexate should only be administered for a ‘probable EP’ (i.e. a homogenous mass with no embryonic features) in cases where serial measurements of serum hCG confirm that the increase is incompatible with an ongoing early IUP. The difficult issue, however, is how to define ‘incompatible’. The ACOG defines this as there being a less than 53% rise in hCG over a 48-hour period. This definition of non-viability is controversial. In a paper addressing the safety of curettage for the management of PUL, Condous et al. showed that a viable IUP may be associated with an hCG rise of significantly less than 50%. Great care must be taken in these circumstances. In the event that the finding of an inhomogeneous mass is a false- positive finding, giving methotrexate with an hCG rise of less than 53% could lead to termination of a wanted pregnancy. An hCG rise of less than 35% is now considered a safer definition of non-viability in women with probable EP when methotrexate is being considered for management. The key issue here is the quality of ultrasonography. When considering methotrexate treatment it is essential that the ultra- sound findings have been reviewed by an experienced examiner and that there is certainty about the diagnosis. Against this background the NICE guideline is concerning. It does not consider expectant management for EP, yet in a recent study of 333 women diagnosed with EP, 146 commenced expectant management and 104 successfully resolved their EP without further intervention (31.2%, 95% confidence interval 26.2– 36.2), although it should be noted that this protocol has not been externally validated. So, whilst one might expect there to be discussion in the guidance about selection criteria, follow-up and economic impact, for expectant management to be omitted entirely is a serious oversight. Unless clinicians choose to disregard the NICE guidance they may be giving methotrexate to women whom they know do not require treatment in perhaps one-third of cases. This raises difficult ethical issues, especially as methotrexate does not have a license for this indication in the UK. So we are left with the guidance recommending the use of methotrexate as the first-line treatment for EP, whilst not considering either how to diagnose EP safely, or to definitively exclude the possibility of a viable IUP. The presumption appears to be that a false-positive misdiagnosis of EP is not possible. If followed, this guidance is likely to lead inevitably in some cases to viable IUPs being terminated due to medical error, whilst in others to women being subjected to potentially hazardous drug treatment that they do not need. This is both dangerous and unethical.	

		More specifically: We would suggest that a significant proportion of section 154-05 should be considered for update based on evidence published in the past 4 years. In particular, the following recommendations warrant consideration based on the study *Preisler J, Kopeika J, Ismail L et al. (2015) Defining safe criteria to diagnose miscarriage: prospective observational multicentre study. BMJ 351:h4579.* *1.4.4 Inform women that the diagnosis of miscarriage using 1 ultrasound scan cannot be guaranteed to be 100% accurate and there is a small chance that the diagnosis may be incorrect, particularly at very early gestational ages.* This statement is not correct – the implication being that EVERY scan with a putative diagnosis of miscarriage requires a follow up scan for it to be confirmed. It is good practice for the findings to be checked by a second operator – but to make a women wait for a second scan with an empty gestation sac of 30 mm is unnecessary and possibly damaging. The above article provides strong evidence regarding the size cut-offs at which the accuracy can be relied upon: at sizes beneath these cut-offs a diagnosis of miscarriage should not be made and repeat scans carried out at an appropriate interval *1.4.9 If the mean gestational sac diameter is less than 25.0 mm with a transvaginal ultrasound scan and there is no visible fetal pole, perform a second scan a minimum of 7 days after the first before making a diagnosis. Further scans may be needed before a diagnosis can be made* For gestation sacs with mean sac diameter (MSD) less than 12mm, a scan should be repeated at a minimum time interval of 14 days to avoid the risk of misdiagnosis. Seven days is not sufficient, and scanning at a non-diagnostic interval puts unnecessary demands on EPAU services. *1.4.12 Do not use gestational age from the last menstrual period alone to determine whether a fetal heartbeat should be visible* We would suggest consideration of the recommendation in the aforementioned paper that, beyond 70 days gestation by certain menstrual dates, an MSD ≥18 mm with no embryo was 100% specific for miscarriage as was an embryo with CRL ≥3 mm with no heart activity. In these circumstances women can be told that the chances of a pregnancy being viable are very low indeed.	
Department of Health	Blank	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your answer.
Royal College of Nursing	Blank	This is to inform you that the Royal College of Nursing have no comments to submit to inform on the above guideline consultation at this time.	Thank you for your answer.

Do you agree with the proposal to remove the research recommendation:

How does the timing and frequency of ultrasound examination affect diagnosis and outcomes of early pregnancy complications, including women's experience and cost effectiveness?			
Stakeholder	**Overall response**	**Comments**	**NICE response**
King's College Hospital NHS Trust	agree	No Comments	Thank you for your answer.
British Society of Gynaecological Endoscopy	Agree	No comments	Thank you for your answer.
The Miscarriage Association	Disagree	With early pregnancy testing comes early recognition of possible problems, yet there is still insufficient knowledge of the best timing, intervals and frequency of scans to aid diagnosis and care. The fact that there has been no research in this area does not mean that there is no need.	Thank you for your comment. The 4-year surveillance review did not identify any new evidence relating to this research recommendation. Based on your comment, we will retain this research recommendation.
The Ectopic Pregnancy Trust	Disagree	Based on the significant changes in ultrasound size cut-offs and the recommendation of repeat scanning before the use of Methotrexate, there is a resulting increase in the proportion of women requiring repeat scans and experiencing a period of uncertainty. We therefore believe that the psychological impact on women and cost effectiveness are important research priorities.	Thank you for your comment. The 4-year surveillance review did not identify any new evidence relating to this research recommendation. Based on your comment, we will retain this research recommendation.
NHS England	Agree	No Comment	Thank you for your answer.
Association of Early Pregnancy Units (AEPU)	Disagree	Based on the dramatic changes in guidance due to new size cut-offs, and thus the significant increase in the proportion of women requiring repeat scans and experiencing a period of uncertainty, we believe this is an important research priority.	Thank you for your comment. The 4-year surveillance review did not identify any new evidence relating to this research recommendation. Based on your comment, we will retain this research recommendation.

Do you agree with the proposal to remove the research recommendation:

Are progesterone or progestogens effective in treating threatened miscarriage?

Stakeholder	**Overall response**	**Comments**	**NICE response**

King's College Hospital NHS Trust	Disagree	There is an ongoing national multicenter study (PRISM) so the research recommendation should be retained and evidence from the ongoing research will be considered when results are published.	Thank you for your comment. The 4-year surveillance review did not identify any new evidence relating to this research recommendation. Based on your comment, we will retain this research recommendation.
British Society of Gynaecological Endoscopy	Agree	No comments	Thank you for your answer.
The Miscarriage Association	Disagree	It is surprising that the review found no evidence of research activity, given the ongoing RCT in this area: the PRISM trial (http://www.medscinet.net/prism/), which began in April 2015.	Thank you for your comment. The 4-year surveillance review did not identify any new evidence relating to this research recommendation. Based on your comment, we will retain this research recommendation.
The Ectopic Pregnancy Trust	Diagree	There is an ongoing national multicenter study (PRISM) that is still actively recruiting so the research recommendation should be retained as evidence from the ongoing research will be considered when results are published.	Thank you for your comment. The 4-year surveillance review did not identify any new evidence relating to this research recommendation. Based on your comment, we will retain this research recommendation.
NHS England	Agree	No Comment	Thank you for your answer.
Association of Early Pregnancy Units (AEPU)	Disagree	There is an NIHR funded research trail being carried out in this area – The PRISM trial, which is still actively recruiting. It would seem odd to remove this as a research priority now – when the support of NICE for this research area probably influenced the decision of the NIHR to fund the trial	Thank you for your comment. The 4-year surveillance review did not identify any new evidence relating to this research recommendation. Based on your comment, we will retain this research recommendation.

Do you agree with the proposal to remove the research recommendation:

In women with confirmed miscarriage, does the type of management strategy (expectant, medical and surgical) impact on women's experience, including psychological and emotional outcomes?

Stakeholder	Overall response	Comments	NICE response
King's College Hospital NHS Trust	disagree	This is still a relevant recommendation and a needed study ven if there is no evidence of a large ongoing study and if NICE retains it as a recommendation it is something that will help when applying for potential funding	Thank you for your comment. The 4-year surveillance review did not identify any new evidence relating to this research recommendation. Based on your comment,

			we will retain this research recommendation.
British Society of Gynaecological Endoscopy	Agree	No comments	Thank you for your answer.
The Miscarriage Association	Disagree	There is a need for high quality research in this area, qualitative as well as quantitative, but not as a RCT. It should include investigation into the impact of informed patient choice on psychological and emotional outcomes and on the factors affecting decision-making (see http://www.miscarriageassociation.org.uk/wp/wp-content/uploads/2011/04/Management-of-miscarriage-2016.pdf).	Thank you for your comment. The 4-year surveillance review did not identify any new evidence relating to this research recommendation. Based on your comment, we will retain this research recommendation.
The Ectopic Pregnancy Trust	Disagree	This is still a much needed study as the current lack of information leads to the flawed MIST trial being cited in recommendations. This leads to the removal of patient choice when we still do not know which treatment methods are best for which women. If NICE retains this as a recommendation it is something that will help when applying for research funding.	Thank you for your comment. The 4-year surveillance review did not identify any new evidence relating to this research recommendation. Based on your comment, we will retain this research recommendation.
NHS England	Agree	No Comment	Thank you for your answer.
Association of Early Pregnancy Units (AEPU)	Blank	Currently we simply do not know which of these strategies is best for which women. The often quoted MIST trail is plagued by bias given the very large proportion of women approached who did not enter the trail as they chose other treatment options – leaving more robust women in the trial. The result is that the current recommendation from NICE to have a period of expectant management for ALL women is likely to be damaging women (and of course removes choice).	Thank you for your comment. The 4-year surveillance review did not identify any new evidence relating to this research recommendation. Based on your comment, we will retain this research recommendation.

Do you agree with the proposal to remove the research recommendation:

In women with ectopic pregnancy, does the type of intervention (laparoscopy or medical management) impact on women's experience, including psychological and emotional outcomes?

Stakeholder	Overall response	Comments	NICE response
King's College Hospital NHS Trust	disagree	As above – this is still needed research	Thank you for your comment. The 4-year surveillance review did not identify any new evidence relating to this research recommendation. Based on your comment, we will retain this research recommendation.
British Society of Gynaecological	Agree	No comments	Thank you for your answer.

Endoscopy			
The Miscarriage Association	Disagree	As with management of miscarriage, this is also a key research topic and should include expectant management. This would add to existing anecdotal evidence about the value (or otherwise) of informed choice and the factors affecting decision-making.	Thank you for your comment. The 4-year surveillance review did not identify any new evidence relating to this research recommendation. Based on your comment, we will retain this research recommendation.
The Ectopic Pregnancy Trust	Disagree	We strongly believe that this remains a relevant recommendation and much-needed study as it is vital we understand the psychological impact of treatment methods on women. Anecdotally, we regularly hear about women's experiences following treatment and there is now data to suggest uncertainty is damaging for women in these circumstances. Having a study would further support the understanding of the impact of EP and its treatment to help inform care. Retaining this as a recommendation would assist research funding applications.	Thank you for your comment. The 4-year surveillance review did not identify any new evidence relating to this research recommendation. Based on your comment, we will retain this research recommendation.
NHS England	Agree	No Comment	Thank you for your answer.
Association of Early Pregnancy Units (AEPU)	Disagree	Similarly to the above as we extend non-surgical management it is vital we understand the psychological impact of these interventions on women. There are now data to suggest uncertainty is damaging for women in these circumstances – this needs to be examined.	Thank you for your comment. The 4-year surveillance review did not identify any new evidence relating to this research recommendation. Based on your comment, we will retain this research recommendation.

Do you have any comments on areas excluded from the scope of the guideline?

Stakeholder	Overall response	Comments	NICE response
King's College Hospital NHS Trust	Yes	As detailed already in the comments above. In addition, re: RR 03 – this is a large RCT that we are currently in the process of applying for national funding for – again, coordinated out of Birmingham, so there should be some more evidence in the future. It would be useful to reference what evidence was found.	Thank you for your comment. The 4-year surveillance review did not identify any new evidence relating to this research recommendation. Based on your comment, we will retain this research recommendation.
British Society of Gynaecological Endoscopy	Agree	No comments	Thank you for your answer.

The Miscarriage Association	Yes	We believe that molar pregnancy should be included in this guideline. This form of pregnancy loss is most often diagnosed after surgical management of miscarriage and we believe the guideline should include a general statement regarding recommended means of contact, information and referral.	Thank you for your comment. Molar pregnancy was excluded from the original scope of the guideline. During the surveillance of this guideline we did not identify any evidence in this area, therefore we have not included it for update.
The Ectopic Pregnancy Trust	Blank	**As detailed above**	Thank you for your comment, please see our response to your above comments.
NHS England	Agree	No Comment	Thank you for your answer.
Association of Early Pregnancy Units (AEPU)	Yes	Non-tubal ectopic pregnancy is important and to have some expert guidance on in particular Interstitial and caesarean scar pregnancy would have been very useful – these ectopic pregnancies are disproportionately responsible for morbidity associated with ectopic pregnancy. Hyperemesis would also have been usefully covered given the large number of women who suffer from this.	Thank you for your comment. During the surveillance of the guideline only limited evidence was identified on the management of non-tubal pregnancy and not felt to impact on the guideline at this time. The remit of this guideline is to cover pain and/or bleeding in early pregnancy therefore hyperemesis is outside the remit of this guideline. No evidence was identified during the surveillance of this guideline and is not considered a priority to request an extension to the remit at this time.

Do you have any comments on equalities issues?

Stakeholder	Overall response	Comments	NICE response
King's College Hospital NHS Trust	Yes	As detailed already in the comments above. In addition, re: RR 03 – this is a large RCT that we are currently in the process of applying for national funding for – again, coordinated out of Birmingham, so there should be some more evidence in the future. It would be useful to reference what evidence was found.	Thank you for your comment. The 4-year surveillance review did not identify any new evidence relating to this research recommendation. Based on your comment, we will retain this research recommendation.
British Society of Gynaecological Endoscopy	Agree	No comments	Thank you for your answer.

The Miscarriage Association	Yes	We believe that molar pregnancy should be included in this guideline. This form of pregnancy loss is most often diagnosed after surgical management of miscarriage and we believe the guideline should include a general statement regarding recommended means of contact, information and referral.	Thank you for your comment. Molar pregnancy was excluded from the original scope of the guideline. During the surveillance of this guideline we did not identify any evidence in this area, therefore we have not included it for update.
The Ectopic Pregnancy Trust	Blank	**As detailed above**	Thank you for your comment, please see our response to your above comments.
NHS England	Agree	No Comment	Thank you for your answer.
Association of Early Pregnancy Units (AEPU)	Yes	Non-tubal ectopic pregnancy is important and to have some expert guidance on in particular Interstitial and caesarean scar pregnancy would have been very useful – these ectopic pregnancies are disproportionately responsible for morbidity associated with ectopic pregnancy. Hyperemesis would also have been usefully covered given the large number of women who suffer from this.	Thank you for your comment. During the surveillance of the guideline only limited evidence was identified on the management of non-tubal pregnancy and not felt to impact on the guideline at this time. The remit of this guideline is to cover pain and/or bleeding in early pregnancy therefore hyperemesis is outside the remit of this guideline. No evidence was identified during the surveillance of this guideline and is not considered a priority to request an extension to the remit at this time.