National Institute for Health and Care Excellence

IP 1720 Fetoscopic prenatal repair for open neural tube defects in the fetus

IPAC date: 14 November 2019

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 3 British Paediatric Neurosurgery Group	**1.3**	The multidisciplinary team should ALWAYS include include a consultant in fetal medicine, an obstetric surgeon, a paediatric neurosurgeon and an anaesthetist.	Thank you for your comment. IPAC considered your comment and amended 1.3
2	Consultee 3 British Paediatric Neurosurgery Group	**1.4**	I would add that research should also record the need for secondary repair of the MMC following delivery , the need for other surgical procedures (specifically CSF shunt) and the presence and severity of any hindbrain herniation (Chiari-2 malformation).	Thank you for your comment. IPAC considered your comment and amended 1.4.
3	Consultee 5 British Maternal & Fetal Medicine Society	**1.1,1.2, 1.3,1.4**	I agree with the draft recommendations of this guideline, in particular that further evidence on the safety and efficacy of fetoscopic prenatal repair of neural tube defects is needed and that for the time-being this procedure should be performed in the context of research. Whether a randomised controlled trials can realistically be performed when women may have a strong individual preference for either open, fetoscopic or postnatal treatment is unclear. We agree that should only be done in specialised centre/s, and by clinicians with specific training and experience in fetal surgery. Patient selection should only be done by a multidisciplinary team. We agree that further research should report risks to the	Thank you for your comments and agreeing with the recommendations in section 1.

			fetus and baby and mother (including her subsequent pregnancies), and long-term outcome after birth.	
4	Consultee 1 NHS professional King's College Hospital	**2.1**	Learning difficulties are more likely associated with severe ventriculomegaly rather than spina bifida itself.	Thank you for your comment. IPAC considered your comment but decided not to amend section 2.1 as it is only a brief description.
5	Consultee 2 NHS Professionals	**2.3**	Comments on fetoscopic consultation document by [redacted].The authors disclose they have a research program into prenatal spina bifida repair, including its fetoscopic modification. **GESTATIONAL AGE AT WHICH THE SURGERY IS DONE: "PRIOR TO 26 WEEKS".** Specifying gestational age at the operation is very important. One needs to realize that some of the data in this report included operations performed at a gestational age that is later than 26 weeks, and that performing the surgery at these later gestational ages has been shown to be less neuroprotective. We concur with the statement that for the time being patients should be informed that the gestational age stipulation of "prior to 26 weeks" should be implemented. Benefit of (open) fetal surgery is demonstrated for procedures done between 19 and 26 weeks, which were the gestational age limits in the MOMS trial (1). These were imposed for two reasons: - Under 19 weeks, often there is not yet a diagnosis is	Thank you for your comments. IPAC considered your comments and amended 2.3. A committee comment was also added to section 3.8 that 'the committee noted that that some of the data considered by the committee included operations performed at a gestational age that is later than 26 weeks'.

			available. Also, it seemed technically difficult to operate that early in pregnancy – though this has not formally been assessed. - above 26 weeks, early clinical studies by Bruner, Tubbs and Tulipan did not suggest that the operation would benefit the fetus (2-4). Following the MOMS trial, a large consecutive single center series on open repair determined that CMS and PPROM were lower if repair was done between 24 and 26 weeks (5). Therefore most procedures done by open access are now carried out between 24 but no later than 26 weeks. It is important to realize that not all fetoscopic procedures included in the literature reviewed for this document were done prior to 26 weeks. In fact, the majority of the patients included in the review were enrolled in programs that allowed inclusion after 26 week, and this is often so for newer fetoscopic programs (6-8). Including later operations has some potential consequences and the magnitude of these consequences is difficult to assess without insight into the raw data: (1) Bias: Inclusion after 26 weeks introduces a bias that makes comparison of series difficult. Including (preferentially) cases operated after 26 weeks, automatically reduces the prematurity rate. In other words, by increasing the gestational age at operation, the gestational age at delivery is systematically biased and is thus not a comparable outcome measure with studies that include patients operated at 24-26 weeks. Future	

			reports and reviews should also include the interval between intervention and delivery. (2) Biologic consequences: By operating at a gestational age after 26 weeks, and hence reducing the degree of prematurity risk, one will also (systematically) reduce the risk of fetal/perinatal mortality. If such effect is not measurable, it is prudent to suspect, or at least consider, that the innovative technique under review may actually have a higher mortality risk than the standard approach (operation <26 weeks). (3) Another biologic consequence is that there may be (a certain) loss of the desired neuroprotective effect. Spina bifida is considered a “progressive” disease, i.e. with the relative impact of the second hit becoming more prominent as the pregnancy progresses. There are data available that confirm this. The Vanderbilt group, who pioneered spina bifida repair, initially operated in a time window between 19 and 30 weeks. They later self-restricted surgery to <26 weeks, based on an analysis of factors that predicted the risk of shunt placement in 176 consecutively operated fetuses. These factors were level of the lesion, preoperative ventricular size, and gestational age at the time of surgery. Their data suggested that a later operation was less neuroprotective (figure below from Bruner, et al) (2, 9). This experience guided the MOMS trial investigators to use an upper gestational age limit of 26 weeks. To our knowledge there are no other studies that systematically assess the effect of gestational age on the	

			neuroprotective effect of fetal surgery with any appropriate statistical power. We are aware of one study (currently in the peer review process, yet presented at the World Congress), that confirms a statistically significant inverse relationship between gestational age and neuroprotective effect, i.e. showing improved neuroprotection when the procedure is done earlier in gestation (Peralta et al, PND 2019). Therefore, one must at least consider the risk that intervention after 26 weeks may reduce the neuroprotective effect as compared to intervention before 26 weeks. Interaction of factors predicting shunt placement: ventricular size and gestational age at surgery. From Bruner et al, 2005(9); original published in 2004 (2). It is therefore of utmost importance that future techniques (open or endoscopic) aim at positively affecting both aspects: earlier intervention and reduction in the risk of prematurity. Clearly, prematurity and delivery at the limits of viability can make this intervention lethal. Earlier intervention may improve neurologic outcome. Close observation and rigorous collection and analysis of data from centers that do offer spina bifida repair at gestational ages after 26 weeks is important (including programs that offer open hysterotomy repair (Brazil, e.g. Moron (<27 weeks; n=237)(10), Poland e.g. Zamlinsky (<27 weeks; n=46)(11)), and fetoscopic programs (Percutaneous - Germany, Kohl (up to 29.1 weeks; n=51;(12)), Brazil, Pedreira (aka Lapa; median GA=27; range: 25-28 weeks; n=10) (7) and hybrid (with	

			exteriorized uterus in Spain, Barcelona(13)) range: 23-5/7 to 27-3/7 weeks. References 1.Adzick NS, Thom EA, Spong CY, Brock JW, 3rd, Burrows PK, Johnson MP, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med. 2011;364(11):993-1004. 2. Bruner JP, Tulipan N, Reed G, Davis GH, Bennett K, Luker KS, et al. Intrauterine repair of spina bifida: preoperative predictors of shunt-dependent hydrocephalus. American journal of obstetrics and gynecology. 2004;190(5):1305-12. 3. Tubbs RS, Chambers MR, Smyth MD, Bartolucci AA, Bruner JP, Tulipan N, et al. Late gestational intrauterine myelomeningocele repair does not improve lower extremity function. Pediatr Neurosurg. 2003;38(3):128-32. 4. Tulipan N, Sutton LN, Bruner JP, Cohen BM, Johnson M, Adzick NS. The effect of intrauterine myelomeningocele repair on the incidence of shunt-dependent hydrocephalus. Pediatr Neurosurg. 2003;38(1):27-33. 5. Soni S, Moldenhauer JS, Spinner SS, Rendon N, Khalek N, Martinez-Poyer J, et al. Chorioamniotic membrane separation and preterm premature rupture of membranes complicating in utero myelomeningocele	

			repair. Am J Obstet Gynecol. 2016;214(5):647 e1-7. 6. Graf K, Kohl T, Neubauer BA, Dey F, Faas D, Wanis FA, et al. Percutaneous minimally-invasive fetoscopic surgery for spina bifida aperta - Part III - Postnatal neurosurgical interventions in the first year of life. Ultrasound Obstet Gynecol. 2015. 7. Pedreira DA, Zanon N, Nishikuni K, De Sa RA, Acacio GL, Chmait RH, et al. Endoscopic surgery for the antenatal treatment of myelomeningocele: the CECAM trial. Am J Obstet Gynecol. 2015. 8. Degenhardt J, Schurg R, Winarno A, Oehmke F, Khaleeva A, Kawecki A, et al. Percutaneous minimally-invasive fetoscopic surgery for spina bifida aperta - Part II Maternal management and outcome. Ultrasound Obstet Gynecol. 2014. 9. Bruner JP, Tulipan N. Intrauterine repair of spina bifida. Clinical obstetrics and gynecology. 2005;48(4):942-55. 10. Moron AF, Barbosa MM, Milani H, Sarmento SG, Santana E, Suriano IC, et al. Perinatal outcomes after open fetal surgery for myelomeningocele repair: a retrospective cohort study. BJOG. 2018;125(10):1280-6. 11. Zamlynski J, Olejek A, Koszutski T, Ziomek G, Horzelska E, Gajewska-Kucharek A, et al. Comparison of prenatal and postnatal treatments of spina bifida in	

			Poland--a non-randomized, single-center study. J Matern Fetal Neonatal Med. 2014;27(14):1409-17	
6	Consultee 1 NHS professional King's College Hospital	**Lay description and 2.3**	Fetoscopic surgery can be done up to 29+6 weeks.	Thank you for your comment. IPAC considered your comment and amended section 2.3. A committee comment was also added to section 3.8 that *'the committee noted that some of the data considered by the committee included operations performed at a gestational age that is later than 26 weeks'.*
7	Consultee 1 NHS professional King's College Hospital	**2.3**	Fetoscopic spina bifida repair is done up to 29+6 weeks. It can be done only under general anaesthesia.	Thank you for your comment. IPAC considered your comments and amended section 2.3. A committee comment was also added to section 3.8 that *'the committee noted that some of the data considered by the committee included operations performed at a gestational age that is later than 26 weeks'.*
8	Consultee 1 NHS professional King's College Hospital	**2.3**	..... the fetal neural placode is dissected from the surrounding skin then a biocellulose patch is placed above the placode. Myofascial flaps are created and sutured on top of the biocellulose patch. The undermined skin is then closed primarily unless the defect is too large in which case a dermal regeneration patch is sutured to the surrounding viable skin with a continuos suture in a watertight fashion.	Thank you for your comment. This section of the guidance is intended to be a short summary description of the procedure. IPAC considered your comment and amended section 2.3.
9	Consultee 2	**2.3**	Factual errors Page 4; 2.3: the procedure has never been done under	Thank you for your comments.

	NHS Professionals		local anesthesia. That is also unlikely to happen. General anesthesia is believed to contribute to uterine relaxation and CO2 insufflation may be painful. Page 4; 2.3: “pediatric laparoscopy set”. The instruments used are not typical pediatric surgical instruments. They include shorter endoscopes from ENT or urology, and in purposely approved custom devices. Page 4; 2.3: “biocellulose patch”. The need and use for patches is controversial; its nature even more. It is not used routinely in all fetoscopic approaches The skin is closed using separate sutures: this is a matter of preference; running barbed sutures have been used as well.	This section of the guidance is intended to be a summary of the procedure. IPAC considered your comment and amended section 2.3.
10	Consultee 2 NHS Professionals	**2.4**	Page 4; 2.4: There are minor variations. We disagree, the differences are significant and definitely clinically relevant.	Thank you for your comments. IPAC considered your comment and amended section 2.4.
11	Consultee 2 NHS Professionals	**2.4**	**Heterogeneous techniques:** We disagree with the statement that there are MINOR differences in the outcomes of different techniques. Moreover the differences observed are clinically extremely relevant. Although both the percutaneous and exteriorized uterus techniques obviate the risk of uterine dehiscence (15, 16), they differ significantly in terms of the neurosurgery technique, and crucially, in the way in which they handle the fetal membranes. There seems to be a direct link between surgical technique and membrane rupture rate, which is in turn related to the risk of PPROM and prematurity. In the report separate numbers are given for	Thank you for your comments. IPAC considered your comment and amended section 2.4. The study by Botelho et al 2017 described fetal MMC repair through a mini-hysterotomy was not included as the mini-hysterotomy approach was not included in this guidance. The guidance does make recommendations about the need for research in 1.1 and ongoing data

			both the percutaneous procedures ,and the “hybrid” procedures (i.e. with exteriorized uterus and fetoscopic cannulation). In the latter technique it is possible to fix the membranes to the uterine wall, consistently giving a later gestational age at delivery (less PPROM, greater gestational age at delivery). Conversely, membrane rupture rates and premature delivery rates reported for the percutaneous approach are consistently higher: e.g. Kohl, mean 33 weeks (12); Pedreira-Lapa; 32.4 weeks (7). Importantly, the systematic review data indicate that membrane rupture rates are higher following percutaneous fetoscopic repair (84-100%) when compared with open hysterotomy repair (46%). Exteriorized uterus PPROM rates have been reported as 23% (presented by Belfort at the World Congress in June and to our knowledge also in press (UOG 2019)), which by the way the systematic review of the literature is currently done, does not show up. To hasten progress in the field, there is an urgent need for selective and appropriate pooling of data from innovating centers with experience. It is only in this way that we will be able to determine the most important (technical) factors triggering prematurity. The current situation of uncoordinated experimentation and modification of techniques every 5 to 10 procedures is not ideal. The most up to date experience was presented at the world congress of the Fetal Medicine Foundation in Alicante in June 2019, demonstrating that the hybrid (exteriorized uterus) technique currently shows the highest gestational age at birth. This technique is however a two port technique, as opposed to a 3 port	collection in 1.4 and identifies key efficacy and safety outcomes.

			technique which is technically less demanding, and thus the 2 port technique may render the surgery slower and more difficult. Currently, there are a number of sites world-wide investigating a 3 port hybrid approach (Leuven, Monterrey, Barcelona, Buenos Aires, Bogota) and data on gestational age at delivery will be forthcoming. All have to contribute to proper data generation; whereas meanwhile patients should be informed about the investigational character of these novel procedures. Review is incomplete in terms of techniques: The “mini-hysterotomy” technique, as described by Peralta et al, is not mentioned in this review. (17) Purportedly, the mini-hyterotomy technique affords the same maternal beneficial effects as the endoscopic techniques (no uterine dehiscence), as well as fetal beneficial effects (less prematurity), and in addition, actually permits the surgeon to mimic the neurosurgical repair technique that is generally applied through larger incisions. <u>References:</u> 7. Pedreira DA, Zanon N, Nishikuni K, De Sa RA, Acacio GL, Chmait RH, et al. Endoscopic surgery for the antenatal treatment of myelomeningocele: the CECAM trial. Am J Obstet Gynecol. 2015. 12. Kohl T. Percutaneous minimally-invasive fetoscopic surgery for spina bifida aperta - Part I Surgical technique and perioperative outcome. Ultrasound Obstet Gynecol. 2014. 15. Joyeux L, Engels AC, Russo FM, Jimenez J, Van Mieghem T, De Coppi P, et al. Fetoscopic versus Open	

			Repair for Spina Bifida Aperta: A Systematic Review of Outcomes. Fetal Diagn Ther. 2016;39(3):161-71. 16. Kabagambe SK, Jensen GW, Chen YJ, Vanover MA, Farmer DL. Fetal Surgery for Myelomeningocele: A Systematic Review and Meta-Analysis of Outcomes in Fetoscopic versus Open Repair. Fetal Diagn Ther. 2018;43(3):161-74. 17. Botelho RD, Imada V, Rodrigues da Costa KJ, Watanabe LC, Rossi Junior R, De Salles AAF, et al. Fetal Myelomeningocele Repair through a Mini-Hysterotomy. Fetal Diagn Ther. 2017;42(1):28-34.	
12	Consultee 3 British Paediatric Neurosurgery Group	**3.2**	I would add to the fetal efficacy outcomes: the need for early post-natal secondary repair of the MMC (fetoscopic patches may require revision surgery following delivery).	Thank you for your comment. Section 3.2 is the opinion of the specialist advisers and IPAC and not intended to be definitive. IPAC considered your comment and amended section 3.2.
13	Consultee 1 NHS professional King's College Hospital	**3.3**	... key safety outcomes for the mother are: operative morbidity, incisional hernia uterine dehiscence in the current pregnancy and subsequent pregnancies and morbidly adherent placenta in subsequent pregnancies.	Thank you for your comment. Section 3.3 is the opinion of the specialist advisers and IPAC and not intended to be definitive. IPAC considered your comment and amended section 3.2.
14	Consultee 3 British Paediatric Neurosurgery Group	**3.3**	Safety outcomes for fetus/newborn - I would add: infection, requirement for further surgery including secondary repair of MMC, CSF diversion and surgery for Chiari 2 malformation and would also want to know the long term risks of problems related to spinal cord tethering. SAfety outcomes for mother should include: maternal mortality, amniotic fluid leakage	Thank you for your comments. Section 3.3 is the opinion of the specialist advisers and IPAC and not intended to be definitive. IPAC considered your comment and amended section 3.3.

15	Consultee 2 NHS Professionals	**3.3**	Page 4, 3.3: incisional hernia for mother: this does not seem so relevant.	Thank you for your comments. Section 3.3 is the opinion of the specialist advisers and IPAC and not intended to be definitive. Inclusion of 'incisional hernia' as key safety outcome has been supported by other consultees and the committee felt it was a potential complication. (see comment 6 7). So, the committee decided not to remove this.
16	Consultee 2 NHS Professionals	**3.4**	Page 5, 4.1: There are more than two variations. It may be fair to say that (1) exteriorized uterus versus the totally percutaneous approach, has a significant impact on membrane rupture rates and perhaps may have other contra-indications; (2) use of two or three ports and using different neuro-surgery techniques may have an impact on the neuroprotective effect. It is probably also fair to say that it is uncertain if fetoscopic neurosurgical repair is truly identical to open neurosurgical repair. Also, the "mini-hysterotomy" technique has been ignored in the document (17), although it fulfills the same maternal beneficial effects as the endoscopic ones (diminished (if not abolished) risk of uterine dehiscence), as well as fetal beneficial effects (less prematurity), and permits an open neurosurgical repair. For the exteriorized uterus hybrid technique, single, double and three layer neurosurgical repairs have been described. References: 17. Botelho RD, Imada V, Rodrigues da Costa KJ, Watanabe LC, Rossi Junior R, De Salles AAF, et al. Fetal	Thank you for your comments. IPAC considered your comment and deleted 3.4. The study on fetal MMC repair through a mini-hysterotomy (Botelho et al 2017) was not included as it is out of the remit of this guidance.

			Myelomeningocele Repair through a Mini-Hysterotomy. Fetal Diagn Ther. 2017;42(1):28-34.	
17	Consultee 2 NHS Professionals	**3.5**	Page 5: 3: The committee was advised that fetoscopic techniques are more frequently used than open ones. This is to our knowledge wrong both for the UK, Europe or worldwide.	Thank you for your comments. IPAC considered your comment and amended section 3.5.
18	Consultee 3 British Paediatric Neurosurgery Group	**3.5**	Fetoscopic repair is not undertaken more commonly than open repair (either for fetus or newborn) either in the UK por internationally. I do not think that the risks for the mother have been established -while uterine rupture may be lower other risks may be higher - the phrasing could be regarded as misleading.	Thank you for your comments. IPAC considered your comment and amended section 3.5.
19	Consultee 1 NHS professional King's College Hospital	**3.5**	The committe was advised that fetoscopic approach are increasingly more common but not comparison was made directly with the open repair. It is almos certain that the open procedure are still more commonplace.	Thank you for your comment. IPAC considered your comment and amended section 3.5.
20	Consultee 3 British Paediatric Neurosurgery Group	**3.6**	I am aware of a registry being run in the USA https://ichgcp.net/clinical-trials-registry/NCT03090633 I am not certain this is open to UK recruitment. I do not know of a National UK registry specifically for fetal repair of myelomeningocele.	Thank you for your comments. IPAC considered your comment and amended section 3.6.
21	Consultee 2 NHS Professionals	**3.6**	4. Registry There is a registry for open and fetoscopic surgeries. The scientific community as well as patients would benefit from a merged registry.	Thank you for your comments. IPAC considered your comment and amended section 3.6.
22	Consultee 3	**3.7**	There may be long term risks of this procedure and the need for longer term surveillance/trials should be	Thank you for your comments.

	British Paediatric Neurosurgery Group		discussed particularly with regard to the incidence of long term requirement for surgery for spinal cord tethering and late complications such as syringomyelia. Long term functional outcomes (cognitive outcome, wheelchair dependence etc) for child following delivery should be monitored.	IPAC considered your comment and amended section 3.7.
23	Consultee 2 NHS Professionals	**3.7**	5. Risk benefits. Though we agree that these must be shared with parents, it is impossible today, based on available data, to be able to make conclusive statements during the counseling of patients.	Thank you for your comments.
24	Consultee 2 NHS Professionals	**3.1**	**Technical challenges and technical variation with clinical consequences.** Learning curve: The document acknowledges that the fetoscopic procedure is challenging. This was recently confirmed in an analysis of the learning curve based on raw data of high volume centers, including fetoscopic centers(**14**). That work demonstrated that for open repairs, the learning curve was shorter than for fetoscopic repairs, where at least 58 procedures would be required. We think this information should be included in the report. Reference: 14. Joyeux L, De Bie F, Danzer E, Russo FM, Javaux A, Peralta CFA, et al. Learning curves of open and endoscopic fetal spina bifida closure: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2019.	Thank you for your comments. The team found this study on steep learning curve (Joyeux et al 2019) in the update search and it has now been added to table 2 in the overview and considered by the committee.
25	Consultee 2 NHS Professionals	**General**	**Patches** Patches have indeed been popular in fetoscopic repairs both as a skin substitute (12, 18) as well as a dural substitute for covering the spinal cord after untethering although several fetoscopic approaches do not use a	Thank you for your comments. Section 2.3 (a summary of the procedure description) refers to the use of patches in occasional cases to repair defects. This has been amended.

			patch at all. Patches may make the surgery less complex as their use has the potential to reduce manipulation and dissection, translating into reduced anesthesia and operating time. The use of a patch(es) may improve the chances of a water tight repair (which is generally accepted to improve neuroprotection (19)). They may also potentially prevent later cord tethering (and hence reduce pain and avoid recurrent surgery), but this suggested benefit has not yet been clinically proven and will require diligent long term follow-up. It is our opinion that the current experimental approaches investigating whether patches reduce local inflammation and adhesions are not conclusive. The experimental model of primary repair may have limitations, and the current anatomic assessments may not reflect functional impact. It is thus not currently possible to specify if and what type of patch that should be used.(19, 20). The use of a patch to repair defects deemed too large for primary skin closure has been reported in up to 20% of open cases. The hypothesis is that such patches reduce tension at the skin edges and obviates the need for relaxing incisions, and that this may avoid aesthetic and other incisional morbidity (21) (22)). References 12. Kohl T. Percutaneous minimally-invasive fetoscopic surgery for spina bifida aperta - Part I Surgical technique and perioperative outcome. Ultrasound Obstet Gynecol. 2014. 18. Kohl T, Tchatcheva K, Merz W, Wartenberg HC, Heep A, Muller A, et al. Percutaneous fetoscopic patch closure of human spina bifida aperta: advances in fetal surgical techniques may obviate the need for early	

			postnatal neurosurgical intervention. Surgical endoscopy. 2009;23(4):890-5. 8/7 (continued) 19. Joyeux L, De Bie F, Danzer E, Van Mieghem T, Flake AW, Deprest J. Safety and efficacy of fetal surgery techniques to close a spina bifida defect in the fetal lamb model: A systematic review. Prenat Diagn. 2018;38(4):231-42. 20. Sanchez e Oliveira Rde C, Valente PR, Abou-Jamra RC, Araujo A, Saldiva PH, Pedreira DA. Biosynthetic cellulose induces the formation of a neoduramater following pre-natal correction of meningomyelocele in fetal sheep. Acta Cir Bras. 2007;22(3):174-81. 21. Meuli M, Meuli-Simmen C, Flake AW, Zimmermann R, Ochsenbein N, Scheer I, et al. Premiere use of Integra artificial skin to close an extensive fetal skin defect during open in utero repair of myelomeningocele. Pediatr Surg Int. 2013;29(12):1321-6. 22. Ewing DC, Dempsey R, Belfort MA, Olutoye OO, Whitehead WE, Hollier LH, Jr., et al. An Unreported Complication After Fetoscopic Myelomeningocele Closure. J Craniofac Surg. 2019;30(2):578-80.	
26	Consultee 2 NHS Professionals	**3.1**	**Data interpretation** We think the current literature is inconclusive. Fetoscopic repair is an evolving technique, with changes within the same series and significant differences in access technique, selection criteria, gestational age at surgery, use of humidification and heating of the CO2, membrane	Thank you for your comments and agreeing with our recommendations. The guidance does make recommendations about the need for research in 1.1 and ongoing data

			protection, surgery duration, and postoperative management protocols between centers. General trends were filtered via three systematic reviews, though none of them included a RCT. The data therefore have to be interpreted carefully. We agree that the clinical conclusions that can be drawn from the literature reviewed in this document are: (1) from a neurosurgical viewpoint (using pooled data from both percutaneous and early single layer exteriorized uterus repairs) there is a trend to a higher immediate CSF leakage rate with fetoscopic surgery (up to 8-10%), with persisting leakage at birth (over one in four). This may not be true for a multi-layered closure (13)but further data are needed to confirm this. Surprisingly, a higher CSF leakage at birth does not appear to translate into measurably significant differences in hindbrain reversal rates or shunt rates. It should be remembered however, that standardized measurement methods for the latter do not currently exist. Regardless of this, CSF leakage at birth is obviously not a desirable outcome. Also, operations that are done later in gestation, do not offer the same neuroprotective effect. (2) from a fetal viewpoint there is a (a) higher fetal and perinatal mortality rate with currently reported fetoscopic repairs; (b) higher risk preterm delivery which coincides with a higher membrane rupture rate;	collection in 1.4 and identifies key efficacy and safety outcomes.

			Because these are highly relevant side effects for a condition that is in itself neither lethal nor naturally associated with prematurity, and because both adverse outcomes occur more frequently with the percutaneous fetoscopic approach, the impact of one or another fetoscopic technique needs to be studied. In order to do that, the literature on fetoscopy needs to expanded and reanalyzed, discriminating data generated through different techniques. Before this is done, the above remains valid, i.e. that the fetoscopic approach until further notice cannot be considered equivalent. (3) from a maternal viewpoint there is apparently (based on small numbers) no risk for uterine dehiscence and normal labour management (induction and augmentation) and spontaneous (or operative) vaginal delivery appear to be safe. The outcomes are to some extent better for the hybrid technique (less prematurity), yet data all derive from few centers, and are recent (Houston, Baltimore and Barcelona). We advocate that the outcomes of the different fetoscopic techniques should be meticulously monitored going forward. Given these uncertainties, and the steep learning curve (14), we concur with the conclusion that fetoscopic repair is to be considered experimental, and that it should only be done by well-trained multidisciplinary teams within the frame of a clinical study. We would like to encourage	

			sharing of raw data, to speed up our understanding of prenatal spina bifida repair.	
27	Consultee 2 NHS Professionals	**Overview**	Overview document Unfortunately the impression is given that repairs are for cystic lesions, while rachisisis is included as well (and actually has a better prognosis)(23). 23. Farmer DL, Thom EA, Brock JW, 3rd, Burrows PK, Johnson MP, Howell LJ, et al. The Management of Myelomeningocele Study: full cohort 30-month pediatric outcomes. Am J Obstet Gynecol. 2018;218(2):256 e1-e13.	Thank you for your comments. This study reports 30 month cognitive and motor function outcomes for patients treated with either prenatal open repair versus postnatal repair in the original Management of Myelomeningocele Study and does not include Fetoscopic repair.
28	Consultee 3 British Paediatric Neurosurgery Group	**General**	Fetoscopic repair remains a experimental procedure, the efficacy of which has not been established. Techniques vary and the technique used may have a significant impact on both the surgical outcome and procedural risk. Does the nature of the patch need to be discussed (biomaterial/ CE approval etc)?	Thank you for your comments. IPAC considered your comments and amended section 2.3 and 2.4. This section of the guidance is intended to be a summary description of the procedure and does not recommend the use of any patch.
29	Consultee 4 Royal College Of Physicians (RCP)	**General**	The RCP is grateful for the opportunity to respond to the above consultation. We have liaised with our Obstetrics experts and agreed that adequate detail of the key risks to the mother are included in this short document.	Thank you for your comments.