NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional Procedures Programme

Specialist Adviser questionnaire

Before completing this questionnaire, please read Conflicts of Interest for Specialist Advisers. Certain conflicts exclude you from offering advice, however, please return the questionnaire to us incomplete for our records.

Please respond in the boxes provided.

Please complete and return to: azad.hussain@nice.org.uk and IPSA@nice.org.uk

Procedure Name:	**Fetal surgery for Open/fetoscopic neural tube defects**
Name of Specialist Advisor:	Anna David
Specialist Society:	Royal College of Obstetricians and Gynaecologists (RCOG)

1 Do you have adequate knowledge of this procedure to provide advice?

☒ Yes.

☐ No – please return the form/answer no more questions.

1.1 Does the title used above describe the procedure adequately?

☐ Yes.

☒ No. If no, please enter any other titles below.

Comments:

Open or fetoscopic fetal surgery to treat fetuses with open spina bifida would be a better title. This is because the term “open spina bifida” covers both myelomeningocoele and myeloschisis which the fetal surgery treats.

2 Your involvement in the procedure

2.1 Is this procedure relevant to your specialty?

☒ Yes.

☒ Is there any kind of inter-specialty controversy over the procedure?

☐ No. If no, then answer no more questions, but please give any information you can about who is likely to be doing the procedure.

Comments:

There is no controversy that open surgery improves neonatal outcome as there is level 1 evidence of benefit (N Scott Adzick et al., 2011). Most centres use the same technique and inclusion/exclusion criteria as in the MOMS trial (Sacco, Simpson, Deprest, & David, 2018).

There is controversy around whether fetoscopic surgery is as effective as open surgery to improve neonatal outcome and currently no RCT evidence. There may be fewer complications for the mother –meta-analyses of cohort studies suggest this (Joyeux et al., 2016; Kabagambe, Jensen, Chen, Vanover, & Farmer, 2018).

The next 2 questions are about whether you carry out the procedure, or refer patients for it. If you are in a specialty that normally carries out the procedure please answer question 2.2.1. If you are in a specialty that normally selects or refers patients for the procedure, please answer question 2.2.2.

2.2.1 If you are in a specialty that does this procedure, please indicate your experience with it:

☐ I have never done this procedure.

☐ I have done this procedure at least once.

☒ I do this procedure regularly.

Comments:

2.2.2 If your specialty is involved in patient selection or referral to another specialty for this procedure, please indicate your experience with it.

☐ I have never taken part in the selection or referral of a patient for this procedure.

☐ I have taken part in patient selection or referred a patient for this procedure at least once.

☒ I take part in patient selection or refer patients for this procedure regularly.

Comments:

2.3 Please indicate your research experience relating to this procedure (please choose one or more if relevant):

☒ I have done bibliographic research on this procedure.

☒ I have done research on this procedure in laboratory settings (e.g. device-related research).

☒ I have done clinical research on this procedure involving patients or healthy volunteers.

☐ I have had no involvement in research on this procedure.

☐ Other (please comment)

Comments:

3 Status of the procedure

3.1 Which of the following best describes the procedure (choose one):

☒ Established practice and no longer new (open fetal surgery)

☐ A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.

☒ Definitely novel and of uncertain safety and efficacy. (fetoscopic surgery)

☐ The first in a new class of procedure.

Comments:

Open fetal surgery is an established practice around the world. Fetoscopic fetal surgery for open fetal spina bifida is not established practice although there are a number of centres around the world now testing it out. It has an emerging evidence base for safety and efficacy (Joyeux et al., 2016; Kabagambe et al., 2018).
See this for a map of the world illustrating the centres that do open and those that are doing fetoscopic surgery for open fetal spina bifida.
https://ispdhome.org/ISPD/SIGs/Fetal_Therapy_Map.aspx

3.2 What would be the comparator (standard practice) to this procedure?

Postnatal closure of open fetal spina bifida

3.3 Please estimate the proportion of doctors in your specialty who are doing this procedure (choose one):

☐ More than 50% of specialists engaged in this area of work.

☐ 10% to 50% of specialists engaged in this area of work.

☒ Fewer than 10% of specialists engaged in this area of work.

☐ Cannot give an estimate.

Comments:

This is a highly specialist procedure which requires a large team of healthcare professionals: anaesthetists, fetal medicine, obstetrics, neurosurgery, radiology, scrub nurses and neurosurgical scrub nurses.

4 Safety and efficacy

4.1 What is the potential harm of the procedure?

Please list adverse events and major risks (even if uncommon) and, if possible, estimate their incidence, as follows:

1. Adverse events reported in the literature (if possible please cite literature)

Maternal risks include pulmonary oedema (not so common in those centres that do not use Magnesium sulphate for tocolysis, our centre uses Atosiban, an oxytocin receptor antagonist), placental abruption, chorioamnionitis, blood transfusion (at procedure or delivery), uterine scar dehiscence/ rupture

Pregnancy: chorionic membrane separation, cervical shortening, oligohydramnios, preterm premature rupture of the membranes, preterm birth

Fetal/neonatal: bradycardia during procedure requiring resuscitation, preterm birth, perinatal death, respiratory distress syndrome, incomplete scar healing requiring further surgical closure,

Future pregnancies: subfertility, preterm birth, uterine scar dehiscence or rupture, blood transfusion at delivery.

Open fetal surgery risks: (N.S. Adzick et al., 2011; Wilson et al., 2004)(Moldenhauer & Adzick, 2017; Moldenhauer et al., 2015; Soni et al., 2016)(Johnson et al., 2016)

Fetoscopic surgery risks (Graf et al., 2016)(Pedreira et al., 2016) (Belfort et al., 2017)

2. Anecdotal adverse events (known from experience)

Pressure sore, wound seroma.

3. Theoretical adverse events

Maternal death, hysterectomy, massive postpartum haemorhage

4.2 What are the key efficacy outcomes for this procedure?

Neurological and functional assessments at birth, 12 and 30 months including ventriculoperitoneal shunt requirements and mobility. Later bladder and bowel outcomes become more important.

4.3 Are there uncertainties or concerns about the *efficacy* of this procedure? If so, what are they?

Long-term outcomes (eg 5-8 years and adolescents) from the MOMS RCT are awaited although case series suggest improvement in bladder and bowel function occur and that improvement in mobility is maintained.

There are no long term data on fetoscopic closure which is made more difficult by the lack of consistency in repair techniques.

4.4 What training and facilities are needed to do this procedure safely?

A multidisciplinary team is required that works together to train, perform and follow up patients with regular MDT review of outcomes:
Fetal medicine, obstetric surgeons, fetal medicine midwives, theatre nurses, paediatric neurosurgeons and neurosurgical theatre nurses, anaesthetists, operating department practitioners, neonatologists, radiologists including ability to perform and interpret MRI, anaesthetists.
Guidelines from the US and Asia describe the appropriate team and training (Cohen et al., 2014)(Moon-Grady et al., 2017)(Wataganara et al., 2017).

4.5 Are there any major trials or registries of this procedure currently in progress? If so, please list.

No ongoing multicentre RCTs although MOMS trial follow up is occurring. NAFTNet runs an optional registry of fetal surgery cases to which a number of centres outside North America contribute. There is a fetoscopic surgery group being set up in Europe but not sure if they plan to collect their data.

4.6 Are you aware of any abstracts that have been *recently* presented/ published on this procedure that may not be listed in a standard literature search, for example PUBMED? (This can include your own work). If yes, please list.
Please note that NICE will do a literature search: we are only asking you for any very recent or potentially obscure abstracts and papers. Please do not feel the need to supply a comprehensive reference list (but you may list any that you think are particularly important if you wish).

Presentations of data planned at Fetal Medicine Foundation meeting in Alicante in June and at IFMSS/European Club of Fetal Surgery meeting in September 2019.

4.7 Is there controversy, or important uncertainty, about any aspect of the way in which this procedure is currently being done or disseminated?

There have been concerns about the way that fetoscopic surgery is being introduced to patients as currently the efficacy is unproven. Some have even considered it to be experimental when there is ongoing lack of efficacy (Flake, 2014) and centres in the US performing fetoscopic surgery have registered their work as a clinical trial (Belfort personal communication).

5 Audit Criteria

Please suggest a minimum dataset of criteria by which this procedure could be audited.

5.1 Outcome measures of benefit (including commonly used clinical outcomes, both short and long - term; and quality-of-life measures). Please suggest the most appropriate method of measurement for each:

Best to use the NHS Commissioning Service Specification - Open Fetal Surgery To Treat Fetuses with Open Spina Bifida (Table 2) which was developed by consensus of UK experts.

5.2 Adverse outcomes (including potential early and late complications). Please state timescales for measurement e.g. bleeding complications up to 1 month post-procedure:

Best to use the outcomes from MOMS trial Adzick at el 2011

6 Trajectory of the procedure

6.1 In your opinion, how quickly do you think use of this procedure will spread?

We started a charity funded service for open fetal surgery in Feb 2018 and since then have received more referrals that we initially anticipated. We use the MOMS criteria and around one-third of our patients are therefore ineligible. Of those eligible, most have opted for fetal surgery. Since Feb 2018 referrals have been received from England, Wales, Scotland, Northern Ireland and the Republic of Ireland; 16 surgeries have been performed (Deprest, oral presentation June 2019).
I believe that eventually it will become either partly or wholly a fetoscopic procedure. But this can only happen when the technique is fully worked up and surgeons are fully trained on it.

6.2 This procedure, if safe and efficacious, is likely to be carried out in (choose one):

☐ Most or all district general hospitals.

☐ A minority of hospitals, but at least 10 in the UK.

☒ Fewer than 10 specialist centres in the UK.

☐ Cannot predict at present.

Comments:

6.3 The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is:

☐ Major.

☐ Moderate.

☒ Minor.

Comments:

7 Other information

7.1 Is there any other information about this procedure that might assist NICE in assessing the possible need to investigate its use?

Further meta-analyses are anticipated. It is worth checking out the detail in them as they describe the various types of procedure that are being used for fetoscopic surgery. Some units open the abdomen and go through the uterine wall only, others perform it percutaneously. Some use 2 or 3 ports. Some use patches to repair it. None of the fetoscopic techniques recapitulate the open fetal surgery or postnatal surgery neurological repair which is done in 3 layers. This is a useful up to date review of the literature in this area (Joyeux, Danzer, Flake, & Deprest, 2018)

Adzick, N.S., Thom, E. A., Spong, C. Y., Brock, J. W., Burrows, P. K., Johnson, M. P., … Farmer, D. L. (2011). A randomized trial of prenatal versus postnatal repair of myelomeningocoele. *New England Journal of Medicine*, *364*, 993–1004. https://doi.org/10.1056/NEJMoa1404304

Adzick, N Scott, Thom, E. a, Spong, C. Y., Brock, J. W., Burrows, P. K., Johnson, M. P., … Farmer, D. L. (2011). MOMS Trial Protocol. *The New England Journal of Medicine*, *364*, 993–1004. https://doi.org/10.1056/NEJMoa1014379.Management

Belfort, M. A., Whitehead, W. E., Shamshirsaz, A. A., Bateni, Z. H., Olutoye, O. O., Olutoye, O. A., … Cass, D. L. (2017). Fetoscopic open neural tube defect repair: Development and refinement of a two-port, carbon dioxide insufflation technique. *Obstetrics and Gynecology*, *129*(4), 734–743. https://doi.org/10.1097/AOG.0000000000001941

Cohen, A. R., Couto, J., Cummings, J. J., Johnson, A., Joseph, G., Kaufman, B. a., … Wax, J. R. (2014). Position statement on fetal myelomeningocele repair. *American Journal of Obstetrics and Gynecology*, *210*(2), 107–111. https://doi.org/10.1016/j.ajog.2013.09.016

Flake, A. W. (2014). Percutaneous minimal-access fetoscopic surgery for myelomeningocele – not so minimal! *Ultrasound in Obstetrics & Gynecology*, 499–500. https://doi.org/10.1002/uog.14673

Graf, K., Kohl, T., Neubauer, B. A., Dey, F., Faas, D., Wanis, F. A., … Kolodziej, M. A. (2016). Percutaneous minimally invasive fetoscopic surgery for spina bifida

aperta. Part III: Neurosurgical intervention in the first postnatal year. *Ultrasound in Obstetrics and Gynecology*. https://doi.org/10.1002/uog.14937

Johnson, M. P., Bennett, K. A., Rand, L., Burrows, P. K., Thom, E. A., Thom, L. J., … Adzick, N. S. (2016). The Management of Myelomeningocele Study: obstetrical outcomes and risk factors for obstetrical complications following prenatal surgery. *American Journal of Obstetrics and Gynecology*, *215*(October), 1–9. https://doi.org/10.1016/j.ajog.2016.07.052

Joyeux, L., Danzer, E., Flake, A. W., & Deprest, J. (2018). Fetal surgery for spina bifida aperta. *Archives of Disease in Childhood: Fetal and Neonatal Edition*, 1–7. https://doi.org/10.1136/archdischild-2018-315143

Joyeux, L., Engels, A. C., Russo, F. M., Jimenez, J., Van Mieghem, T., De Coppi, P., … Deprest, J. (2016). Fetoscopic versus Open Repair for Spina Bifida Aperta: A Systematic Review of Outcomes. *Fetal Diagnosis and Therapy*, *39*(3), 161–171. https://doi.org/10.1159/000443498

Kabagambe, S. K., Jensen, G. W., Chen, Y. J., Vanover, M. A., & Farmer, D. L. (2018). Fetal Surgery for Myelomeningocele: A Systematic Review and Meta-Analysis of Outcomes in Fetoscopic versus Open Repair. *Fetal Diagnosis and Therapy*, *43*(3), 161–174. https://doi.org/10.1159/000479505

Moldenhauer, J. S., & Adzick, N. S. (2017). Fetal surgery for myelomeningocele : After the Management of Myelomeningocele Study (MOMS). *Seminars in Fetal and Neonatal Medicine*, 1–7. https://doi.org/10.1016/j.siny.2017.08.004

Moldenhauer, J. S., Soni, S., Rintoul, N. E., Spinner, S. S., Khalek, N., Martinez-Poyer, J., … Adzick, N. S. (2015). Fetal myelomeningocele repair: The post-MOMS experience at the children's hospital of Philadelphia. *Fetal Diagnosis and Therapy*, *37*(3), 235–240. https://doi.org/10.1159/000365353

Moon-Grady, A. J., Baschat, A., Cass, D., Choolani, M., Copel, J. A., Crombleholme, T. M., … Harrison, M. (2017). Fetal Treatment 2017: The Evolution of Fetal Therapy Centers - A Joint Opinion from the International Fetal Medicine and Surgical Society (IFMSS) and the North American Fetal Therapy Network (NAFTNet). *Fetal Diagnosis and Therapy*, *42*(4), 241–248. https://doi.org/10.1159/000475929

Pedreira, D. A. L., Zanon, N., Nishikuni, K., Moreira De Sá, R. A., Acacio, G. L., Chmait, R. H., … Quintero, R. A. (2016). Endoscopic surgery for the antenatal treatment of myelomeningocele: The CECAM trial. *American Journal of Obstetrics and Gynecology*, *214*(1), 111.e1-111.e11. https://doi.org/10.1016/j.ajog.2015.09.065

Sacco, A., Simpson, L., Deprest, J., & David, A. (2018). A Study to Assess Global Availability of Fetal Surgery for Myelomeningocele. *Prenatal Diagnosis*. https://doi.org/10.1002/pd.5383.

Soni, S., Moldenhauer, J. S., Spinner, S. S., Rendon, N., Khalek, N., Martinez-Poyer, J., … Adzick, N. S. (2016). Chorioamniotic membrane separation and preterm premature rupture of membranes complicating in utero myelomeningocele repair. *American Journal of Obstetrics and Gynecology*, *214*(5), 647e1-647e7. https://doi.org/10.1016/j.ajog.2015.12.003

Wataganara, T., Seshadri, S., Leung, T. Y., Matter, C., Ngerncham, M., Triyasunant, N., … Choolani, M. (2017). Establishing Prenatal Surgery for Myelomeningocele in Asia: The Singapore Consensus. *Fetal Diagnosis and Therapy*, *41*(3), 161–178. https://doi.org/10.1159/000452218

Wilson, R. D., Johnson, M. P., Flake, A. W., Crombleholme, T. M., Hedrick, H. L., Wilson, J., & Adzick, N. S. (2004). Reproductive outcomes after pregnancy complicated by maternal-fetal surgery. *American Journal of Obstetrics and Gynecology*, *191*(4), 1430–1436. https://doi.org/10.1016/j.ajog.2004.05.054

8 Data protection and conflicts of interest

8. Data protection, freedom of information and conflicts of interest

8.1 Data Protection

The information you submit on this form will be retained and used by the NICE and its advisers for the purpose of developing its guidance and may be passed to other approved third parties. Your name and specialist society will be published in NICE publications and on the NICE website. The specialist advice questionnaire will be published in accordance with our guidance development processes and a copy will be sent to the nominating Specialist Society. Please avoid identifying any individual in your comments.

√ I have read and understood this statement and accept that personal information sent to us will be retained and used for the purposes and in the manner specified above and in accordance with the Data Protection Act 1998.

8.2 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

Nothing in your submission shall restrict any disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

Please submit a conflicts of interest declaration form listing any potential conflicts of interest including any involvement you may have in disputes or complaints relating to this procedure.

Please use the "Conflicts of Interest for Specialist Advisers" policy as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if needed from the Associate Director – Interventional Procedures.

Do you or a member of your family[1] have a **personal pecuniary** interest? The main examples are as follows:

Consultancies or directorships attracting regular or occasional payments in cash or kind	☐ **YES** ☒ **NO**
Fee-paid work – any work commissioned by the healthcare industry **– this includes income earned in the course of private practice**	☐ **YES** ☒ **NO**

[1] 'Family members' refers to a spouse or partner living in the same residence as the member or employee, children for whom the member or employee is legally responsible, and adults for whom the member or employee is legally responsible (for example, an adult whose full power of attorney is held by the individual).

Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry	☐	**YES**
	☒	**NO**
Expenses and hospitality – any expenses provided by a healthcare industry company beyond those reasonably required for accommodation, meals and travel to attend meetings and conferences	☐	**YES**
	☒	**NO**
Investments – any funds that include investments in the healthcare industry	☐	**YES**
	☒	**NO**
Do you have a **personal non-pecuniary** interest – for example have you made a public statement about the topic or do you hold an office in a professional organisation or advocacy group with a direct interest in the topic?	☒	**YES**
	☐	**NO**

Do you have a **non-personal** interest? The main examples are as follows:

Fellowships endowed by the healthcare industry	☐	**YES**
	☒	**NO**
Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts	☐	**YES**
	☒	**NO**

If you have answered YES to any of the above statements, please describe the nature of the conflict(s) below.

Comments:
I was a member of:
1. UK NHS Commissioning Board Clinical Reference Group for Fetal Medicine 2012-2015. I contributed to the definition of the Fetal Medicine scope, the first quality patient dashboard, and the first Commissioning for Quality and Innovation (CQUINs) in the specialty.
2. Innovation Lead for UK NHS Commissioning Board Clinical Reference Group for Fetal Medicine 2013-2015. I worked in the CRG to consider bringing in open fetal surgery for spina bifida to the UK.
3. Lead for Urgent Policy Clinical Application NHS England Specialised Services for "Open Fetal Surgery to treat fetuses with congenital open spina bifida" September 2017.
4. Member of NHS England Specialised Services Fetal Surgery for MMC Working Group that developed the Preliminary Policy Proposal for "Open Fetal Surgery to treat fetuses with congenital open spina bifida" October 2017 to December 2018.
5. My hospital UCLH has applied to be one of the two commissioned centres to perform the above procedures.
6. I am co-Director (Research Lead) of the Centre for Prenatal Therapy at UCL, with Professors Jan Deprest (Fetal Surgery Lead), Donald Peebles (Clinical Lead) and Paolo de Coppi (Paediatric Surgery Lead). The centre is multidisciplinary, cross organisational involving Great Ormond St Hospital, University College Hospital and the UCL Institutes of Women's Health, Child Health and Bioengineering. To date the Centre has been funded £458,700 (GOSHCC, UCLH Charity and CDH-UK) to implement new prenatal clinical services to treat fetal malformations such as Open fetal surgery for myelomeningocoele. The Centre performed the first open fetal surgery for spina bifida in the UK in May 2018 with a successful outcome.

7. I have worked with SHINE, the UK spina bifida charity, to disseminate information about fetal surgery for spina bifida around the UK.
8. I have taken part in radio, television and newspaper articles about fetal surgery for spina bifida.
9. I am a co-applicant on the following grant that is funding innovations in fetal surgery for spina bifida such as flexible fetoscopes and novel patches to close the defect.
GIFT-Surg: Image-guided intrauterine minimally invasive fetal diagnosis and therapy. £9,982,215. Wellcome Trust/EPSRC Innovative Engineering for Health Award. July 2014-June 2020. PI: Professor Sebastien Ourselin, KCL

Thank you very much for your help.

Dr Tom Clutton-Brock, Interventional Procedures Advisory Committee Chair

Mark Campbell
Acting Programme Director
Devices and Diagnostics

June 2018

Conflicts of Interest for Specialist Advisers

1 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

1.1 Any conflicts of interest set out below should be declared on the questionnaire the Specialist Adviser completes for the procedure.

1.2 Specialist Advisers should seek advice if required from the Associate Director – Interventional Procedures.

2 Personal pecuniary interests

2.1 A personal pecuniary interest involves a current personal payment to a Specialist Adviser, which may either relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as **'specific'** or to the industry or sector from which the product or service comes, in which case it is regarded as **'non-specific'**. The main examples are as follows.

2.1.1 **Consultancies** – any consultancy, directorship, position in or work for the healthcare industry that attracts regular or occasional payments in cash or kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.2 **Fee-paid work** – any work commissioned by the healthcare industry for which the member is paid in cash or in kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.3 **Shareholdings** – any shareholding, or other beneficial interest, in shares of the healthcare industry that are either held by the individual or for which the individual has legal responsibility (for example, children, or relatives whose full Power of Attorney is held by the individual). This does not include shareholdings through unit trusts, pensions funds, or other similar arrangements where the member has no influence on financial management.

2.1.4 **Expenses and hospitality** – any expenses provided by a healthcare industry company beyond that reasonably required for accommodation, meals and travel to attend meetings and conferences (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place.

2.1.5 **Investments** – any funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

2.2 No personal interest exists in the case of:

2.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

2.2.2 accrued pension rights from earlier employment in the healthcare industry.

3 **Personal family interest**

3.1 This relates to the personal interests of a family member and involves a **current payment** to the family member of the Specialist Adviser. The interest may relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as '**specific**', or to the industry or sector from which the product or service comes, in which case it is regarded as '**non-specific**'. The main examples include the following.

3.1.1 Any consultancy, directorship, position in or work for a healthcare industry that attracts regular or occasional payments in cash or in kind.

3.1.2 Any fee-paid work commissioned by a healthcare industry for which the member is paid in cash or in kind.

3.1.3 Any shareholdings, or other beneficial interests, in a healthcare industry which are either held by the family member or for which an individual covered by this Code has legal responsibility (for example, children, or adults whose full Power of Attorney is held by the individual).

3.1.4 Expenses and hospitality provided by a healthcare industry company (except where they are provided to a general class of people such as attendees at an open conference)

3.1.5 Funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

3.2 No personal family interest exists in the case of:

3.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

3.2.2 accrued pension rights from earlier employment in the healthcare industry.

4 **Personal non-pecuniary interests**

These might include, but are not limited to:

4.1 a clear opinion, reached as the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review

4.2 a public statement in which an individual covered by this Code has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence

4.3 holding office in a professional organisation or advocacy group with a direct interest in the matter under consideration

4.4 other reputational risks in relation to an intervention under review.

5 Non-personal interests

5.1 A non-personal interest involves payment that benefits a department or organisation for which a Specialist Advisor is responsible, but that is not received by the Specialist Advisor personally. This may either relate to the product or service being evaluated, in which case it is regarded as **'specific,'** or to the manufacturer or owner of the product or service, but is unrelated to the matter under consideration, in which case it is regarded as **'non-specific'**. The main examples are as follows.

5.1.1 **Fellowships** – the holding of a fellowship endowed by the healthcare industry.

5.1.2 **Support by the healthcare industry or NICE** – any payment, or other support by the healthcare industry or by NICE that does not convey any pecuniary or material benefit to a member personally but that does benefit his/her position or department. For example:

- a grant from a company for the running of a unit or department for which a Specialist Advisor is responsible
- a grant, fellowship or other payment to sponsor a post or member of staff in the unit for which a Specialist Adviser is responsible. This does not include financial assistance for students
- the commissioning of research or other work by, or advice from, staff who work in a unit for which the specialist advisor is responsible
- one or more contracts with, or grants from, NICE.

5.2 Specialist Advisers are under no obligation to seek out knowledge of work done for, or on behalf of, the healthcare industry within departments for which they are responsible if they would not normally expect to be informed.

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Interventional Procedures Programme

Specialist Adviser questionnaire

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Please respond in the boxes provided.

Please complete and return to: azad.hussain@nice.org.uk and IPSA@nice.org.uk

Procedure Name:	**Fetal surgery for open/fetoscopic neural tube defects**
Name of Specialist Advisor:	Bassel Zebian
Specialist Society:	Society of British Neurological Surgeons

1 Do you have adequate knowledge of this procedure to provide advice?

☒ Yes.

☐ No – please return the form/answer no more questions.

1.1 Does the title used above describe the procedure adequately?

☐ Yes.

☒ No. If no, please enter any other titles below.

Comments:

Fetal surgery (open/fetoscopic) for open neural tube defects

2 Your involvement in the procedure

2.1 Is this procedure relevant to your specialty?

☒ Yes.

☐ Is there any kind of inter-specialty controversy over the procedure?

☐ No. If no, then answer no more questions, but please give any information you can about who is likely to be doing the procedure.

Comments:

The next 2 questions are about whether you carry out the procedure, or refer patients for it. If you are in a specialty that normally carries out the procedure please answer question 2.2.1. If you are in a specialty that normally selects or refers patients for the procedure, please answer question 2.2.2.

2.2.1 If you are in a specialty that does this procedure, please indicate your experience with it:

☐ I have never done this procedure.

☐ I have done this procedure at least once.

☒ I do this procedure regularly.

Comments:

I have performed fetoscopic repairs of open neural tube defects alongside my fetal medicine colleagues

2.2.2 If your specialty is involved in patient selection or referral to another specialty for this procedure, please indicate your experience with it.

☐ I have never taken part in the selection or referral of a patient for this procedure.

☐ I have taken part in patient selection or referred a patient for this procedure at least once.

☒ I take part in patient selection or refer patients for this procedure regularly.

Comments:

2.3 Please indicate your research experience relating to this procedure (please choose one or more if relevant):

☒ I have done bibliographic research on this procedure.

☐ I have done research on this procedure in laboratory settings (e.g. device-related research).

☐ I have done clinical research on this procedure involving patients or healthy volunteers.

☐ I have had no involvement in research on this procedure.

☒ Other (please comment)

Comments:

I observed the procedure (percutaneous fetoscopic repair) being performed by the fetal medicine specialist who first performed it and I took part in simulation of the procedure under her supervision.

3 Status of the procedure

3.1 Which of the following best describes the procedure (choose one):

☒ Established practice and no longer new.

☐ A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.

☐ Definitely novel and of uncertain safety and efficacy.

☐ The first in a new class of procedure.

Comments:

The gold standard for open neural tube defects until a few years ago has been post-natal repair 24-48 hours after birth. More recently centres around the world have taken up open fetal repair whilst others have opted for fetoscopic repair. The latter is performed in 2 main different ways (with uterus exteriorised vs. completely percutaneously). There was a tender for the open fetal repair sent out to units around the UK that had expressed an interest. There is currently on-going discussion regarding the fetoscopic technique being offered in the UK at NHSE level.

3.2 What would be the comparator (standard practice) to this procedure?

Post-natal repair of open neural tube defects

3.3 Please estimate the proportion of doctors in your specialty who are doing this procedure (choose one):

☐ More than 50% of specialists engaged in this area of work.

☐ 10% to 50% of specialists engaged in this area of work.

☐ Fewer than 10% of specialists engaged in this area of work.

☒ Cannot give an estimate.

Comments:

To the best of my knowledge, I am the only neurosurgeon in the UK performing the fetoscopic approach alongside fetal medicine colleagues. I am aware that one other colleague is performing the open fetal repair in the UK.

4 Safety and efficacy

4.1 What is the potential harm of the procedure?

Please list adverse events and major risks (even if uncommon) and, if possible, estimate their incidence, as follows:

1. Adverse events reported in the literature (if possible please cite literature)

The main adverse event is that of premature rupture of membranes leading to premature birth and the ensuing potential complications.

Operative risks to the mother and future pregnancies have also been reported with the open fetal repair.

2. Anecdotal adverse events (known from experience)

As above.

3. Theoretical adverse events

4.2 What are the key efficacy outcomes for this procedure?

Reduction in the rate of hydrocephalus and need for shunting.
Improvement in the severity of Chiari 2.
Improvement in cognitive function.
Improvement of the motor function in the lower limbs.

4.3 Are there uncertainties or concerns about the *efficacy* of this procedure? If so, what are they?

Current discussions/debates regarding open vs. fetoscopic approaches.

4.4 What training and facilities are needed to do this procedure safely?

An appropriately trained team of obstetric/fetal medicine specialists, paediatric neurosurgeons, anaesthetists, scrub team and ODPs with appropriate support from radiologists (paediatric neuroradiologists with interest in fetal imaging), midwives and neonatologists as well as paediatric neurologists and bladder specialists. Access to orthopaedic services and involvement of therapies (physiotherapy and OT) also essential after birth.
Training should start with observing the procedure at centres experienced at performing it followed by simulation training and finally performing it with support from established centres.

The centre performing the procedure should have an MDT meeting to discuss referrals and consider inclusion/exclusion criteria.
The centre will need appropriately equipped theatres, obstetric and neonatal units as well as paediatric neurosurgical unit.
There needs to be an MDT clinic follow up of the patients to be assessed regularly after birth and preferably transitioned into an equivalent adult clinic in their late teens.

4.5 Are there any major trials or registries of this procedure currently in progress? If so, please list.

Management of Myelomeningocele Study compared open fetal repair with post-natal repair and demonstrated benefit in the outcome measures listed in section 4.2
Various publications since then assessing fetoscopic repairs and most recent discussion in Fetoscopic Consortium demonstrating advantages and drawbacks of the fetoscopic approach.
International registries already exist for both types of repair (open and fetoscopic).

4.6 Are you aware of any abstracts that have been *recently* presented/ published on this procedure that may not be listed in a standard literature search, for example PUBMED? (This can include your own work). If yes, please list.
Please note that NICE will do a literature search: we are only asking you for any very recent or potentially obscure abstracts and papers. Please do not feel the need to supply a comprehensive reference list (but you may list any that you think are particularly important if you wish).

This is being provided by a fetal medicine colleague who is also a Specialist Advisor to NICE for this procedure.

4.7 Is there controversy, or important uncertainty, about any aspect of the way in which this procedure is currently being done or disseminated?

The discussion/debate regarding open vs. fetoscopic as well as the gestational age at the time of performing the procedure.

5 Audit Criteria

Please suggest a minimum dataset of criteria by which this procedure could be audited.

Demographics of the patients as well as inclusion criteria.
Antenatal ultrasound scans assessing the open neural tube defect as well as the rest of the neural axis (ventricular size and presence of Chiari 2 and the degree of tonsillar descent as well as any kyphosis or scoliosis) followed by MRI. Functional motor level on ultrasound as well as anatomical level.
Results of amniocentesis.
Duration of procedure and any intraoperative adverse events.
PROM and gestational age at delivery as well as post-natal adverse events.
Obstetric complications including infection and uterine dehiscence.
Post-natal neurological assessment to include lower limb function as well as assessment for hydrocephalus and need for CSF diversions.

Assessment of repair including any CSF leak or need for further repair.
Bladder ultrasound to assess voiding and bladder function.
Development of dermoids (inclusion cysts).
Cognitive function.

5.1 Outcome measures of benefit (including commonly used clinical outcomes, both short and long - term; and quality-of-life measures). Please suggest the most appropriate method of measurement for each:

See above.

5.2 Adverse outcomes (including potential early and late complications). Please state timescales for measurement e.g. bleeding complications up to 1 month post-procedure:

See above.

6 Trajectory of the procedure

6.1 In your opinion, how quickly do you think use of this procedure will spread?

It is likely that a single centre in the UK will be able to deal with the workload which is likely to be around 1-2 patients a month.

6.2 This procedure, if safe and efficacious, is likely to be carried out in (choose one):

☐ Most or all district general hospitals.

☐ A minority of hospitals, but at least 10 in the UK.

☒ Fewer than 10 specialist centres in the UK.

☐ Cannot predict at present.

Comments:

6.3 The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is:

☐ Major.

☐ Moderate.

☒ Minor.

Comments:

Although the cost is minor as long as no major complications of prematurity occur, it is likely that the procedure will prevent post-natal procedures and complications associated with open neural tube defects repaird post-natally and thus reduce cost.

7 Other information

7.1 Is there any other information about this procedure that might assist NICE in assessing the possible need to investigate its use?

We have patient information sheets for the fetoscopic repair.

8 Data protection and conflicts of interest

8. Data protection, freedom of information and conflicts of interest

8.1 Data Protection

The information you submit on this form will be retained and used by the NICE and its advisers for the purpose of developing its guidance and may be passed to other approved third parties. Your name and specialist society will be published in NICE publications and on the NICE website. The specialist advice questionnaire will be published in accordance with our guidance development processes and a copy will be sent to the nominating Specialist Society. Please avoid identifying any individual in your comments.

X I have read and understood this statement and accept that personal information sent to us will be retained and used for the purposes and in the manner specified above and in accordance with the Data Protection Act 1998.

8.2 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

Nothing in your submission shall restrict any disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

Please submit a conflicts of interest declaration form listing any potential conflicts of interest including any involvement you may have in disputes or complaints relating to this procedure.

Please use the “Conflicts of Interest for Specialist Advisers” policy as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if needed from the Associate Director – Interventional Procedures.

Do you or a member of your family[1] have a **personal pecuniary** interest? The main examples are as follows:

Consultancies or directorships attracting regular or occasional payments in cash or kind	☐	**YES**
	☒	**NO**
Fee-paid work – any work commissioned by the healthcare industry **– this includes income earned in the course of private practice**	☐	**YES**
	☒	**NO**
Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry	☐	**YES**
	☒	**NO**
Expenses and hospitality – any expenses provided by a healthcare industry company beyond those reasonably required for accommodation, meals and travel to attend meetings and conferences	☐	**YES**
	☒	**NO**
Investments – any funds that include investments in the healthcare industry	☐	**YES**
	☒	**NO**
Do you have a **personal non-pecuniary** interest – for example have you made a public statement about the topic or do you hold an office in a professional organisation or advocacy group with a direct interest in the topic?	☒	**YES**
	☐	**NO**

Do you have a **non-personal** interest? The main examples are as follows:

Fellowships endowed by the healthcare industry	☐	**YES**
	☒	**NO**
Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts	☐	**YES**
	☒	**NO**

If you have answered YES to any of the above statements, please describe the nature of the conflict(s) below.

Comments:
I am the clinical lead for the policy proposal for fetoscopic repair of open neural tube defects for NHSE.
I also am part of the team currently performing the procedure at King's College Hospital.

Thank you very much for your help.

Dr Tom Clutton-Brock, Interventional Procedures Advisory Committee Chair

Mark Campbell
Acting Programme Director
Devices and Diagnostics

June 2018

[1] 'Family members' refers to a spouse or partner living in the same residence as the member or employee, children for whom the member or employee is legally responsible, and adults for whom the member or employee is legally responsible (for example, an adult whose full power of attorney is held by the individual).

Conflicts of Interest for Specialist Advisers

1 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

1.1 Any conflicts of interest set out below should be declared on the questionnaire the Specialist Adviser completes for the procedure.

1.2 Specialist Advisers should seek advice if required from the Associate Director – Interventional Procedures.

2 Personal pecuniary interests

2.1 A personal pecuniary interest involves a current personal payment to a Specialist Adviser, which may either relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as **'specific'** or to the industry or sector from which the product or service comes, in which case it is regarded as **'non-specific'**. The main examples are as follows.

2.1.1 **Consultancies** – any consultancy, directorship, position in or work for the healthcare industry that attracts regular or occasional payments in cash or kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.2 **Fee-paid work** – any work commissioned by the healthcare industry for which the member is paid in cash or in kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

2.1.3 **Shareholdings** – any shareholding, or other beneficial interest, in shares of the healthcare industry that are either held by the individual or for which the individual has legal responsibility (for example, children, or relatives whose full Power of Attorney is held by the individual). This does not include shareholdings through unit trusts, pensions funds, or other similar arrangements where the member has no influence on financial management.

2.1.4 **Expenses and hospitality** – any expenses provided by a healthcare industry company beyond that reasonably required for accommodation, meals and travel to attend meetings and conferences (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place.

2.1.5 **Investments** – any funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

2.2 No personal interest exists in the case of:

2.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

2.2.2 accrued pension rights from earlier employment in the healthcare industry.

3 Personal family interest

3.1 This relates to the personal interests of a family member and involves a **current payment** to the family member of the Specialist Adviser. The interest may relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as '**specific**', or to the industry or sector from which the product or service comes, in which case it is regarded as '**non-specific**'. The main examples include the following.

3.1.1 Any consultancy, directorship, position in or work for a healthcare industry that attracts regular or occasional payments in cash or in kind.

3.1.2 Any fee-paid work commissioned by a healthcare industry for which the member is paid in cash or in kind.

3.1.3 Any shareholdings, or other beneficial interests, in a healthcare industry which are either held by the family member or for which an individual covered by this Code has legal responsibility (for example, children, or adults whose full Power of Attorney is held by the individual).

3.1.4 Expenses and hospitality provided by a healthcare industry company (except where they are provided to a general class of people such as attendees at an open conference)

3.1.5 Funds which include investments in the healthcare industry that are held in a portfolio over which individuals have the ability to instruct the fund manager as to the composition of the fund.

3.2 No personal family interest exists in the case of:

3.2.1 assets over which individuals have no financial control (for example, wide portfolio unit trusts and occupational pension funds) and where the fund manager has full discretion as to its composition (for example, the Universities Superannuation Scheme)

3.2.2 accrued pension rights from earlier employment in the healthcare industry.

4 Personal non-pecuniary interests

These might include, but are not limited to:

4.1 a clear opinion, reached as the conclusion of a research project, about the clinical and/or cost effectiveness of an intervention under review

4.2 a public statement in which an individual covered by this Code has expressed a clear opinion about the matter under consideration, which could reasonably be interpreted as prejudicial to an objective interpretation of the evidence

4.3 holding office in a professional organisation or advocacy group with a direct interest in the matter under consideration

4.4 other reputational risks in relation to an intervention under review.

5 Non-personal interests

5.1 A non-personal interest involves payment that benefits a department or organisation for which a Specialist Advisor is responsible, but that is not received by the Specialist Advisor personally. This may either relate to the product or service being evaluated, in which case it is regarded as **'specific,'** or to the manufacturer or owner of the product or service, but is unrelated to the matter under consideration, in which case it is regarded as **'non-specific'**. The main examples are as follows.

5.1.1 **Fellowships** – the holding of a fellowship endowed by the healthcare industry.

5.1.2 **Support by the healthcare industry or NICE** – any payment, or other support by the healthcare industry or by NICE that does not convey any pecuniary or material benefit to a member personally but that does benefit his/her position or department. For example:

- a grant from a company for the running of a unit or department for which a Specialist Advisor is responsible
- a grant, fellowship or other payment to sponsor a post or member of staff in the unit for which a Specialist Adviser is responsible. This does not include financial assistance for students
- the commissioning of research or other work by, or advice from, staff who work in a unit for which the specialist advisor is responsible
- one or more contracts with, or grants from, NICE.

5.2 Specialist Advisers are under no obligation to seek out knowledge of work done for, or on behalf of, the healthcare industry within departments for which they are responsible if they would not normally expect to be informed.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional Procedures Programme

Specialist Adviser questionnaire

Before completing this questionnaire, please read Conflicts of Interest for Specialist Advisers. Certain conflicts exclude you from offering advice, however, please return the questionnaire to us incomplete for our records.

Please respond in the boxes provided.

Please complete and return to: azad.hussain@nice.org.uk and IPSA@nice.org.uk

Procedure Name:	**Fetal surgery for fetoscopic neural tube defects**
Name of Specialist Advisor:	Marta Santorum-Perez
Specialist Society:	Royal College of Obstetricians and Gynaecologists (RCOG)

1 Do you have adequate knowledge of this procedure to provide advice?

X Yes.

☐ No – please return the form/answer no more questions.

1.1 Does the title used above describe the procedure adequately?

☐ Yes.

X No. If no, please enter any other titles below.

Comments:

Fetoscopic surgery for fetal neural tube defects

2 Your involvement in the procedure

2.1 Is this procedure relevant to your specialty?

x Yes.

☐ Is there any kind of inter-specialty controversy over the procedure?

☐ No. If no, then answer no more questions, but please give any information you can about who is likely to be doing the procedure.

Comments:

The next 2 questions are about whether you carry out the procedure, or refer patients for it. If you are in a specialty that normally carries out the procedure please answer question 2.2.1. If you are in a specialty that normally selects or refers patients for the procedure, please answer question 2.2.2.

2.2.1 If you are in a specialty that does this procedure, please indicate your experience with it:

☐ I have never done this procedure.

x I have done this procedure at least once.

☐ I do this procedure regularly.

Comments:

2.2.2 If your specialty is involved in patient selection or referral to another specialty for this procedure, please indicate your experience with it.

☐ I have never taken part in the selection or referral of a patient for this procedure.

☐ I have taken part in patient selection or referred a patient for this procedure at least once.

☐ I take part in patient selection or refer patients for this procedure regularly.

Comments:

2.3 Please indicate your research experience relating to this procedure (please choose one or more if relevant):

x I have done bibliographic research on this procedure.

☐ I have done research on this procedure in laboratory settings (e.g. device-related research).

☐ I have done clinical research on this procedure involving patients or healthy volunteers.

☐ I have had no involvement in research on this procedure.

☐ Other (please comment)

Comments:

3 Status of the procedure

3.1 Which of the following best describes the procedure (choose one):

☐ Established practice and no longer new.

x A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.

Definitely novel and of uncertain safety and efficacy.

x The first in a new class of procedure.

Comments:

Our group is the first to perform this procedure in the UK but the procedure itself has been carried out several times abroad. We have modified the procedure (carried out abroad) by reducing the numbers of trocars from 4 to 3 and it is therefore likely to be safer.

3.2 What would be the comparator (standard practice) to this procedure?

Postnatal repair

Open fetal repair

3.3 Please estimate the proportion of doctors in your specialty who are doing this procedure (choose one):

☐ More than 50% of specialists engaged in this area of work.

☐ 10% to 50% of specialists engaged in this area of work.

x Fewer than 10% of specialists engaged in this area of work.

☐ Cannot give an estimate.

Comments:

We are the only ones in the UK

4 Safety and efficacy

4.1 What is the potential harm of the procedure?

Please list adverse events and major risks (even if uncommon) and, if possible, estimate their incidence, as follows:

1. Adverse events reported in the literature (if possible please cite literature)

    - Premature rupture or membranes
    - Preterm birth
    - Chorioamnionitis

2. Anecdotal adverse events (known from experience)

    - Bleeding
    - Local wound infection
    - Amniotic fluid leakage through the port insertion into the maternal abdomen.

3. Theoretical adverse events
    - Complication related to general aesthesia

4.2 What are the key efficacy outcomes for this procedure?

- Reduces the need for ventriculoperitoneal shunt during the first 12 months of age.
- Improves the motor function and ability to walk at 30 months of age.
- Improves the bladder function.

The additional benefits of the the fetoscopic approach compared to the open fetal repair are:

- Gives the option of vaginal delivery.

- No risk of uterine dehiscence and /or rupture during the pregnancy or during future pregnancies (10% of women have uterine complications in the following pregnancy).

- Reduces the risk of having a placenta accreta in subsequent pregnancies.

- Reduction of maternal morbidity due to shorter hospitalization.

- Reduction of the need for tocolytics and maternal medication with the associated maternal side effects.

4.3 Are there uncertainties or concerns about the *efficacy* of this procedure? If so, what are they?

No, in 2011, evidence from the Management of Myelomeningocele Study (MOMS trial) showed how prenatal repair of the defect by maternal laparotomy and hysterectomy decreased the need for shunt placement and improved motor function. Several publications have shown the additional benefits of the fetoscopic approach reducing significantly maternal morbidity with similar or better outcomes for the babies.

4.4 What training and facilities are needed to do this procedure safely?

- Laparoscopic simulators/ training lab.
- Fully equipped laparoscopic theatre.
- Fetal medicine expertise and laparoscopic surgery expertise.

4.5 Are there any major trials or registries of this procedure currently in progress? If so, please list.

There is a registry based at Houston Children's Hospital, the purpose of the registry is to collect data on obstetric, perinatal and neonatal outcomes from all centers that are currently performing fetoscopic neural tube defect repair (regardless of the specific surgical approach) in order to get an unbiased and true representation of the potential and prospects for this new modality. The registry is funded by the UK charity The Fetal Medicine Foundation.

4.6 Are you aware of any abstracts that have been *recently* presented/ published on this procedure that may not be listed in a standard literature search, for example PUBMED? (This can include your own work). If yes, please list.
Please note that NICE will do a literature search: we are only asking you for any very recent or potentially obscure abstracts and papers. Please

do not feel the need to supply a comprehensive reference list (but you may list any that you think are particularly important if you wish).

The results of the international fetoscopic registry will be published in Ultrasound of Obstetrics and Gynaecology within the next month.

Proceedings of the First Annual Meeting of the International Fetoscopic Myelomeningocele Repair Consortium

M.SanzCortes, D.A.Lapa, G.L.Acacio, M.Belfort, E.Carreras, N.Maiz, JLPeiro, F.Y.Lim, J.Miller, A.Baschat, G.Sepulveda, I.Davila, Y.Gielchinsky, M.Benifla, J.Stirnemann, Y.Ville, M.Yamamoto, H.Figueroa, L.Simpson and K.H.Nicolaides

4.7 Is there controversy, or important uncertainty, about any aspect of the way in which this procedure is currently being done or disseminated?

There are several variations of the fetoscopic approach to fetal surgery and the members of the consortium have agreed that if one of these variations shows to be superior than the others then it will be adopted by all the members.

5 Audit Criteria

Please suggest a minimum dataset of criteria by which this procedure could be audited.

5.1 Outcome measures of benefit (including commonly used clinical outcomes, both short and long - term; and quality-of-life measures). Please suggest the most appropriate method of measurement for each:

Reversal of hindbrain herniation (MRI scan)

Shunt placement/ETV during the first 12 months of age

Motor level at birth vs at diagnosis:

- 2 or more levels better
- 1 level better
- No change
- One level worse
- 2 or more levels worse

Bladder function:

- Residual urine volume
- Need of catheterisation

Ability to walk at 30 months of age

5.2 Adverse outcomes (including potential early and late complications). Please state timescales for measurement e.g. bleeding complications up to 1 month post-procedure:

Fetal neonatal /adverse outcomes:

Fetal or neonatal demise
CSF leak
Need for postnatal repair
Intraoperative fetal bradycardia
RDS
NEC
PVL
PDA
Sepsis
Retinopathy
Hydrocephalus
Wound infection
Repair dehiscence
Preterm birth
Shunt placement/ETV
Surgery for tethered cord

Maternal adverse outcomes:

Maternal death
Admission to ITU
Placental abruption
Pulmonary oedema
Amniotic fluid embolism
Chorioamniotic membrane separation
Chorioamnionitis
Haemorrhage requiring transfusion
Prolonged maternal hospital stay after the procedure
Oligohydramnios
Uterine thinning or dehiscence
Caesarean section

6 Trajectory of the procedure

6.1 In your opinion, how quickly do you think use of this procedure will spread?

Very soon. We have an increasing number of requests from patients for consultation that are considering to have the surgery.

6.2 This procedure, if safe and efficacious, is likely to be carried out in (choose one):

☐ Most or all district general hospitals.

☐ A minority of hospitals, but at least 10 in the UK.

x Fewer than 10 specialist centres in the UK.

☐ Cannot predict at present.

Comments:

Two to three hospitals in the UK.

6.3 The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is:

☐ Major.

☐ Moderate.

X Minor.

Comments:

Potentially 10 to 15 operations per year within the next 3 to 4 years.

7 Other information

7.1 Is there any other information about this procedure that might assist NICE in assessing the possible need to investigate its use?

There is an increasing demand for the procedure and it is currently being carried out in several super specialist centres in the US and Europe.

8 Data protection and conflicts of interest

8. Data protection, freedom of information and conflicts of interest

8.1 Data Protection

The information you submit on this form will be retained and used by the NICE and its advisers for the purpose of developing its guidance and may be passed to other approved third parties. Your name and specialist society will be published in NICE publications and on the NICE website. The specialist advice questionnaire will be published in accordance with our guidance development processes and a copy will be sent to the nominating Specialist Society. Please avoid identifying any individual in your comments.

X I have read and understood this statement and accept that personal information sent to us will be retained and used for the purposes and in the manner specified above and in accordance with the Data Protection Act 1998.

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Do you or a member of your family[1] have a **personal pecuniary** interest? The main examples are as follows:

Consultancies or directorships attracting regular or occasional payments in cash or kind	☐	**YES**
	x	**NO**
Fee-paid work – any work commissioned by the healthcare industry **– this includes income earned in the course of private practice**	☐	**YES**
	x	**NO**
Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry	☐	**YES**
	x	**NO**
Expenses and hospitality – any expenses provided by a healthcare industry company beyond those reasonably required for accommodation, meals and travel to attend meetings and conferences	☐	**YES**
	x	**NO**
Investments – any funds that include investments in the healthcare	☐	**YES**

[1] 'Family members' refers to a spouse or partner living in the same residence as the member or employee, children for whom the member or employee is legally responsible, and adults for whom the member or employee is legally responsible (for example, an adult whose full power of attorney is held by the individual).

industry	x	**NO**
Do you have a **personal non-pecuniary** interest – for example have you made a public statement about the topic or do you hold an office in a professional organisation or advocacy group with a direct interest in the topic?	☐	**YES**
	x	**NO**
Do you have a **non-personal** interest? The main examples are as follows:		
Fellowships endowed by the healthcare industry	☐	**YES**
	x	**NO**
Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts	☐	**YES**
	x	**NO**

If you have answered YES to any of the above statements, please describe the nature of the conflict(s) below.

Comments:

Thank you very much for your help.

Dr Tom Clutton-Brock, Interventional Procedures Advisory Committee Chair

Mark Campbell
Acting Programme Director
Devices and Diagnostics

June 2018

Conflicts of Interest for Specialist Advisers

1 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

1.1 Any conflicts of interest set out below should be declared on the questionnaire the Specialist Adviser completes for the procedure.

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2.1 A personal pecuniary interest involves a current personal payment to a Specialist Adviser, which may either relate to the manufacturer or owner of a product or service being evaluated, in which case it is regarded as **'specific'** or to the industry or sector from which the product or service comes, in which case it is regarded as **'non-specific'**. The main examples are as follows.

2.1.1 **Consultancies** – any consultancy, directorship, position in or work for the healthcare industry that attracts regular or occasional payments in cash or kind (this includes both those which have been undertaken in the 12 months preceding the point at which the declaration is made and which are planned but have not taken place).

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These might include, but are not limited to:

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- a grant from a company for the running of a unit or department for which a Specialist Advisor is responsible
- a grant, fellowship or other payment to sponsor a post or member of staff in the unit for which a Specialist Adviser is responsible. This does not include financial assistance for students
- the commissioning of research or other work by, or advice from, staff who work in a unit for which the specialist advisor is responsible
- one or more contracts with, or grants from, NICE.

5.2 Specialist Advisers are under no obligation to seek out knowledge of work done for, or on behalf of, the healthcare industry within departments for which they are responsible if they would not normally expect to be informed.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Interventional Procedures Programme

Specialist Adviser questionnaire

Before completing this questionnaire, please read Conflicts of Interest for Specialist Advisers. Certain conflicts exclude you from offering advice, however, please return the questionnaire to us incomplete for our records.

Please respond in the boxes provided.

Please complete and return to: azad.hussain@nice.org.uk and IPSA@nice.org.uk

Procedure Name:	**Fetal surgery for open/fetoscopic neural tube defects**
Name of Specialist Advisor:	Pranav Pandya
Specialist Society:	Royal College of Obstetricians and Gynaecologists (RCOG)

1 Do you have adequate knowledge of this procedure to provide advice?

☐ Yes

1.1 Does the title used above describe the procedure adequately?

☐ No. If no, please enter any other titles below.

The title suggests that the NTDs themselves are open/fetoscopic rather than the surgery; also it suggests that all NTDs are covered. A more correct title would be: Open and Fetoscopic Fetal Surgery for Open Spina Bifida (or Myelomeningocele)

Comments:

2 Your involvement in the procedure

2.1 Is this procedure relevant to your specialty?

☐ Yes. X

☐ Is there any kind of inter-specialty controversy over the procedure?

For open surgery there is level 1 evidence of benefit (Adzick 2011); this RCT specified a standard surgical technique and inclusion/exclusion criteria. Although this procedure is now performed outside of a trial situation, it appears that the vast majority of centres use the same technique and inclusion/exclusion criteria with relatively little controversy (Sacco 2018).

For fetoscopic surgery there is controversy regarding the optimum technique of surgery, with several groups performing different surgeries globally (Sacco 2018 as before). There is also some concern regarding the use of carbon dioxide for intrauterine insufflation (Skinner 2018).

There is extensive debate regarding whether fetoscopic surgery has equivalent, better or worse outcomes than open surgery for both the mother and the fetus. No RCT has been performed yet; two meta-analyses of cohort studies have not shown clear benefit (Joyeux 2016, Kabagambe 2017).

Comments:

The next 2 questions are about whether you carry out the procedure, or refer patients for it. If you are in a specialty that normally carries out the procedure please answer question 2.2.1. If you are in a specialty that normally selects or refers patients for the procedure, please answer question 2.2.2.

2.2.1 If you are in a specialty that does this procedure, please indicate your experience with it:

☐ I do this procedure regularly. Yes

Comments:

We have performed 5 procedures at UCLH

2.2.2 If your specialty is involved in patient selection or referral to another specialty for this procedure, please indicate your experience with it.

☐ I take part in patient selection or refer patients for this procedure regularly. Yes

Comments:

2.3 Please indicate your research experience relating to this procedure (please choose one or more if relevant):

☐ I have done clinical research on this procedure involving patients or healthy volunteers. Yes

Comments:

3 Status of the procedure

3.1 Which of the following best describes the procedure (choose one):

☐ Established practice and no longer new. – True for Open surgery

☐ Definitely novel and of uncertain safety and efficacy. - Fetoscopic surgery - not novel outside the UK (has been performed for a number of years in some centres) but, assuming open surgery is now established practice, fetoscopic is more than a minor variation of this and still of uncertain safety/ efficacy.

Comments:

3.2 What would be the comparator (standard practice) to this procedure?

Postnatal repair of open spina bifida.

3.3 Please estimate the proportion of doctors in your specialty who are doing this procedure (choose one):

☐ Fewer than 10% of specialists engaged in this area of work. Yes

Comments:

4 Safety and efficacy

4.1 What is the potential harm of the procedure?

Please list adverse events and major risks (even if uncommon) and, if possible, estimate their incidence, as follows:

1. Adverse events reported in the literature (if possible please cite literature)

Maternal: pulmonary oedema, placental abruption, chorioamnionitis, blood transfusion (at procedure or delivery), uterine scar dehiscence/ rupture

Pregnancy: chorionic membrane separation, oligohydramnios, spontaneous rupture of membranes, preterm labour/ delivery

Fetal/neonatal: bradycardia/ distress during procedure, prematurity, perinatal death, respiratory distress syndrome

Future pregnancies: preterm delivery, uterine scar dehiscence, blood transfusion at delivery

Risks of open surgery quoted in: Wilson 2010, Adzick 2011, Zamylinska 2014, Moldenhauer 2015, Johnson 2016, Moron 2018

Risks of fetoscopic surgery quoted in: Khol 2014, Pedreira (Lapa) 2016, Belfort 2017

2. Anecdotal adverse events (known from experience)

It has been suggested that some fetoscopic techniques are associated with higher levels of prematurity than the open surgery but we do not have the data to confirm this.

3. Theoretical adverse events

Maternal hysterectomy due to uterine rupture or placental abruption and haemorrhage. Maternal death has never been reported for any fetal surgery (systematic review - Sacco 2019) but is still a theoretical possibility.

4.2 What are the key efficacy outcomes for this procedure?

Efficacy outcomes used in the MOMS trial were assessments of the infant/ child at birth, 12 and 30 months, mostly focusing on survival, prematurity, ventriculoperitoneal shunt requirements and mobility. The trial protocol sets out the assessments/ scoring used. Follow up at 5-8 years will look at mobility, further surgery required and bladder outcomes.

4.3 Are there uncertainties or concerns about the *efficacy* of this procedure? If so, what are they?

Long-term outcomes from open surgery have not yet been published (5-8yrs awaited) and even longer term outcomes are not available. It is not known if the benefits of open surgery from the MOMS trial persist into late childhood, adolescence and adulthood.

Fetoscopic techniques have generally been reported in case series or cohort studies and not in any RCT comparing it to postnatal surgery or open fetal surgery. As mentioned previously, there is no single agreed method. The majority of studies of fetoscopic surgery have reported outcomes until birth or discharge from hospital but not much later.

4.4 What training and facilities are needed to do this procedure safely?

For both open and fetoscopic fetal surgery, a multidisciplinary team comprising of fetal medicine specialists, obstetricians, midwives, theatre nurses, paediatric neurosurgeons, anaesthetists, operating department practitioners and anaesthetists

are needed. Training requires exposure to the surgery in a centre already performing it and/or with an established surgeon or team present. There are international guidelines setting out appropriate team and training (Cohen 2013, Moon-Grady 2017).

4.5 Are there any major trials or registries of this procedure currently in progress? If so, please list.

There are currently no multi-centre trials of either open or fetoscopic surgery to my knowledge. Individual centres are monitoring their outcomes and investigating these in ways which may include comparison to historical cohorts or other published groups. NAFTNet host a registry of open fetal surgery patients which is open to non-US groups.

4.6 Are you aware of any abstracts that have been *recently* presented/ published on this procedure that may not be listed in a standard literature search, for example PUBMED? (This can include your own work). If yes, please list.
Please note that NICE will do a literature search: we are only asking you for any very recent or potentially obscure abstracts and papers. Please do not feel the need to supply a comprehensive reference list (but you may list any that you think are particularly important if you wish).

The groups of Professor Belfort (Texas, fetoscopic), Professor Lapa (Brazil, fetoscopic), Professor Carreras (Spain, fetoscopic) and Professor Flake (Philadelphia, open) presented their outcomes to date in a standardised format at the FMF/Eurofetus meeting in Athens 2018; all groups and Professor Khol (Germany, fetoscopic) will again be invited to the next meeting, which will be in Alicante June 2019.

4.7 Is there controversy, or important uncertainty, about any aspect of the way in which this procedure is currently being done or disseminated?

Media and social media coverage of the recent fetoscopic surgery performed at Kings College Hospital has reported that the procedure has equal benefits/ efficacy as the open technique without the maternal risks but this has not been shown in evidence yet.

5 Audit Criteria

Please suggest a minimum dataset of criteria by which this procedure could be audited.

Potential audit standards have been specified in the NHS Commissioning Service Specification - Open Fetal Surgery To Treat Fetuses with Open Spina Bifida (Table 2). These standards were reached by a multi-disciplinary working party and seem appropriate for the fetoscopic technique also.

5.1 Outcome measures of benefit (including commonly used clinical outcomes, both short and long - term; and quality-of-life measures). Please suggest the most appropriate method of measurement for each:

As per MOMS trial:

Ventriculoperitoneal shunt placement; neurological imaging (resolution of hindbrain herniation, ventriculomegaly), neurological/motor examination (Bayley/ Peabody Scales), urodynamics/ bladder ultrasound, IQ and executive functioning (several listed in MOMS2 protocol), quality of life (Parkin Spina Bifida Health Related QoL Questionnaire), family stress (Parenting Stress Index)

5.2 Adverse outcomes (including potential early and late complications). Please state timescales for measurement e.g. bleeding complications up to 1 month post-procedure:

Intraoperative: pulmonary oedema, fetal bradycardia/ distress during procedure (and if resuscitation is required)

Postoperative: chorioamnionitis, oligohydramnios, spontaneous rupture of membranes, preterm labour/ delivery

Either intra- or post-operative: placental abruption, chorioamnionitis, blood transfusion, perinatal death

At delivery: blood transfusion, uterine scar dehiscence/ rupture, prematurity (gestational age), perinatal death

After delivery: neonatal death, respiratory distress syndrome, preterm delivery in future pregnancy, uterine scar dehiscence at future delivery, blood transfusion at future delivery

6 Trajectory of the procedure

6.1 In your opinion, how quickly do you think use of this procedure will spread?

In brief – quickly in appropriately selected cases. This procedure has been available on a private funding basis in the UK for 16 months and appears to be widely known now. Over this time period 45 referrals have been received from England, Wales, Scotland, Northern Ireland and the Republic of Ireland; 16 surgeries have been performed (Deprest, oral presentation 2019).

6.2 This procedure, if safe and efficacious, is likely to be carried out in (choose one):

☐ Fewer than 10 specialist centres in the UK. Yes

Comments:

6.3 The potential impact of this procedure on the NHS, in terms of numbers of patients eligible for treatment and use of resources, is:

☐ Minor. Yes

Comments:

7 Other information

7.1 Is there any other information about this procedure that might assist NICE in assessing the possible need to investigate its use?

The draft procedure description of the fetoscopic approach as below describes one particular technique of repair, but there are several others being used clinically which should also be included (Sacco 2018).

"In the fetoscopic approach the procedure is performed under general anaesthesia and with partial CO2 insufflation of the uterine cavity. After preparation and draping and under ultrasound guidance the paediatric laparoscopy set (a fetoscope) is introduced through a port followed by the introduction of further 3 ports to allow the passage of instruments. Once the fetus is positioned adequately, the skin around the fetal neural placode/elements is dissected. A biocellulose patch (e.g. Bionext) is placed between the neural elements (defect) and skin. The skin is then sutured using interrupted stitches over the patch, without dissecting or suturing the dura mater. When the defect is large a dermal regeneration patch (e.g. Nevelia patch) is used."

8 Data protection and conflicts of interest

8. Data protection, freedom of information and conflicts of interest

8.1 Data Protection

The information you submit on this form will be retained and used by the NICE and its advisers for the purpose of developing its guidance and may be passed to other approved third parties. Your name and specialist society will be published in NICE publications and on the NICE website. The specialist advice questionnaire will be published in accordance with our guidance development processes and a copy will be sent to the nominating Specialist Society. Please avoid identifying any individual in your comments.

☑ I have read and understood this statement and accept that personal information sent to us will be retained and used for the purposes and in the manner specified above and in accordance with the Data Protection Act 1998.

8.2 Declarations of interest by Specialist Advisers advising the NICE Interventional Procedures Advisory Committee

Nothing in your submission shall restrict any disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

Please submit a conflicts of interest declaration form listing any potential conflicts of interest including any involvement you may have in disputes or complaints relating to this procedure.

Please use the "Conflicts of Interest for Specialist Advisers" policy as a guide when declaring any conflicts of interest. Specialist Advisers should seek advice if needed from the Associate Director – Interventional Procedures.

Do you or a member of your family[1] have a **personal pecuniary** interest? The main examples are as follows:

Consultancies or directorships attracting regular or occasional payments in cash or kind ☐ **NO**

Fee-paid work – any work commissioned by the healthcare industry **– this includes income earned in the course of private practice** ☐ **NO**

Shareholdings – any shareholding, or other beneficial interest, in shares of the healthcare industry ☐ **NO**

Expenses and hospitality – any expenses provided by a healthcare industry company beyond those reasonably required for accommodation, meals and travel to attend meetings and conferences ☐ **NO**

Investments – any funds that include investments in the healthcare industry ☐ **NO**

Do you have a **personal non-pecuniary** interest – for example have you made a public statement about the topic or do you hold an office in a professional organisation or advocacy group with a direct interest in the topic? ☐ **NO**

Do you have a **non-personal** interest? The main examples are as follows:

Fellowships endowed by the healthcare industry ☐ **NO**

Support by the healthcare industry or NICE that benefits his/her position or department, eg grants, sponsorship of posts ☐ **NO**

If you have answered YES to any of the above statements, please describe the nature of the conflict(s) below.

Comments:

Thank you very much for your help.

[1] 'Family members' refers to a spouse or partner living in the same residence as the member or employee, children for whom the member or employee is legally responsible, and adults for whom the member or employee is legally responsible (for example, an adult whose full power of attorney is held by the individual).

Dr Tom Clutton-Brock, Interventional Procedures Advisory Committee Chair

Mark Campbell
Acting Programme Director
Devices and Diagnostics

June 2018

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