NICE National Institute for Health and Care Excellence

Professional Expert Questionnaire

Technology/Procedure name & indication: IP1936 Removal, preservation and re-implantation of ovarian tissue to restore fertility

Your information

Name:	Cheryl Dunlop
Job title:	Subspecialist Trainee in Reproductive Medicine
Organisation:	NHS Lothian
Email address:	[redacted]
Professional organisation or society membership/affiliation:	British Society for Gynaecological Endoscopy
Nominated/ratified by (if applicable):	British Society for Gynaecological Endoscopy
Registration number (e.g. GMC, NMC, HCPC)	GMC 6165973

How NICE will use this information: the advice and views given in this questionnaire will form part of the information used by NICE and its advisory committees to develop guidance or a medtech innovation briefing on this procedure/technology. Information may be disclosed to third parties in accordance with the Freedom of Information Act 2000 and the Data Protection Act 2018, complying with data sharing guidance issued by the Information Commissioner's Office. Your advice and views represent your individual opinion and not that of your employer, professional society or a consensus view. Your name, job title, organisation and your responses, along with your declared interests will also be published online on the NICE website as part of the process of public consultation on the draft guidance, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate.

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☒ I give my consent for the information in this questionnaire to be used and may be published on the NICE website as outlined above. If consent is NOT given, please state reasons below:

Click here to enter text.

Please answer the following questions as fully as possible to provide further information about the procedure/technology and/or your experience.

Please note that questions 10 and 11 are applicable to the Medical Technologies Evaluation Programme (MTEP). We are requesting you to complete these sections as future guidance may also be produced under their work programme.

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it? – Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? – Is this procedure/technology performed/used by clinicians in specialities other than your own? – If your specialty is involved in patient selection or referral to another specialty for this	I am a Subspecialist Trainee in Reproductive Medicine in South-East Scotland and completed a PhD in the area of female fertility preservation in 2017. During my PhD I was one of the research team members in Edinburgh who performed the first re-implantations of cryopreserved ovarian cortex in the UK. I played a key role in this small team caring for the first two patients undergoing this experimental treatment, with my contribution including preparation of the tissue for reimplantation and monitoring of post-operative ovarian function by hormone profiles and ultrasonography. One of these procedures resulted in the first pregnancy and livebirth secondary to reimplantation in the UK and I performed the patient's early pregnancy scan, followed her through her pregnancy, and assisted with her Caesarean Section. I was the lead author on the subsequent published case report. I also attended and assisted in the laparoscopic removal of ovarian tissue for cryopreservation, including in Paediatric patients. In my current role, I am involved in the counselling of women seeking fertility preservation, including discussion regarding ovarian tissue cryopreservation, and have been involved in the management of a patient undergoing IVF following reimplantation of her cryopreserved ovarian tissue. I work closely with Prof Richard Anderson who helped pioneer the use of ovarian tissue cryopreservation in Edinburgh, the first centre in the UK to do so. I will be attending and assisting in both laparoscopic removal of ovarian tissue for cryopreservation and reimplantation of tissue when these cases occur during my Subspecialist training. Currently, only two centres in the UK are performing these operations – Edinburgh and Oxford. They take referrals from across the UK. The procedure is performed by Gynaecologists, or, in the Paediatric population, by Paediatric Surgeons with Gynaecology input. The vast majority of patients are cancer patients and are therefore referred by the Haematology/Oncology/Breast etc. team. There are patient selection criteria in Edinburgh, and only eligible patients will be seen by a Fertility specialist for discussion surrounding fertility preservation options.

	procedure/technology, please indicate your experience with it.	
2	– 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 clinical research on this procedure involving patients or healthy volunteers. I have published this research.
3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	The ovarian tissue cryopreservation procedure is established practice in Edinburgh (first performed over 20 years ago) but the reimplantation procedure remains novel as has been performed on only a few occasions to date. Both procedures would be novel elsewhere in the UK with the exception of Oxford who also now perform them. None of the options below best describe the procedure, unfortunately – it is a mixture of: Established practice and no longer new. And Definitely novel and of uncertain safety and efficacy (although safety and efficacy has been documented well globally).
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	It would be used as an addition to the current standard fertility preservation care (i.e. oocyte or embryo cryopreservation), primarily for those patients who do not have time to undergo ovarian stimulation (e.g. oncology patients) or are pre-pubertal.

Current management

5	Please describe the current standard of care that is used in the NHS.	**Postpubertal Females:** Oocyte or embryo cryopreservation

		Bilateral oophoropexy if pelvic radiotherapy indicated Ovarian tissue cryopreservation in UK research centres **Prepubertal Females:** Bilateral oophoropexy if pelvic radiotherapy indicated Ovarian tissue cryopreservation in UK research centres
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	No

Potential patient benefits and impact on the health system

7	What do you consider to be the potential benefits to patients from using this procedure/technology?	It provides the opportunity for patients who are not able to undergo ovarian stimulation for oocyte/embryo cryopreservation (e.g. need to commence gonadotoxic treatment immediately, or are prepubertal) to preserve their fertility. This is becoming increasingly important as cancer survival rates are increasing, and there is a need to improve quality of life as well as quantity. It also can, temporarily, restore reproductive endocrinological function (i.e. reverse the menopause), whilst the graft is functioning.
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Prepubertal patients Oncology patients/other patients with benign conditions requiring gonadotoxic treatment (e.g. bone marrow transplant)
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	It has the potential to improve clinical outcomes with regards fertility in a cohort of patients in whom fertility preservation would otherwise not have been possible.
10 - MTEP	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	It is likely to cost more as it will require the following, in addition to the current standard of care: - Laparoscopy/operation for removal of ovarian tissue (requiring staff, equipment, operating theatre) and again for reimplantation of tissue - Storage facilities (e.g. in Scotland, the Scottish National Blood Transfusion Service store all cryopreserved ovarian tissue) - Pathology expertise (a sample of all stored tissue is examined histologically) - Subsequent hormone and ultrasonography monitoring following reimplantation - Subsequent ovulation induction +/- IVF treatment following reimplantation if required However, ~50% of patients won't require IVF following reimplantation of the tissue – in the case of patients who conceive naturally, the costs of ovulation induction/IVF would be negated.
11 - MTEP	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost	It will likely cost more, for the reasons detailed above.

	more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Operating theatre with laparoscopic equipment (which will already be available in Gynaecology units) Tissue storage facilities (could use existing Blood Transfusion Service as in Scotland) Access to ultrasound machine
13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Laparoscopic training to remove/reimplant tissue (should be able to be performed by Gynaecologists with laparoscopic skills) Training in tissue cryopreservation/thawing

Safety and efficacy of the procedure/technology

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	• Operative risks: COMMON - bleeding, infection, pain UNCOMMON - blood transfusion, return to theatre, visceral damage (1:1000), VTE, port site hernia, oophorectomy (due to ongoing bleeding/prepubertal ovary too small to remove cortex alone) These operative risks can be increased by the patient's underlying health condition, e.g. immunosuppression • Risk of graft failure (i.e. never functions) ~7% • No conception ~ 70% • Theoretical risk of reimplantation of malignant cells within the ovarian tissue in oncology patients (no events reported in the literature)
15	Please list the key efficacy outcomes for this procedure/technology?	1) Restoration of ovarian function 2) Conception/livebirths

16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	There remain concerns regarding the possibility of reintroduction of malignant cells within the ovarian cortex which could cause a patient to relapse with their original cancer. If malignant cells are seen in the sample of tissue sent to Pathology following the removal of ovarian cortex, then the tissue will not be reimplanted. A recent case report describes use of RNA analysis of frozen tissue for the BCR-ABL transcript found in the patient's Philadelphia chromosome positive acute lymphoblastic leukaemia prior to reimplantation – results showed a low likelihood of malignant cell seeding and the patient has not relapsed following reimplantation of her tissue.
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	It has been suggested that the ovarian tissue could be reimplanted for pubertal induction or reversal of the menopause instead of being used for fertility purposes primarily. This would be considered controversial in the UK and reimplantation is not performed for these reasons here.
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Fewer than 10 specialist centres in the UK.

Abstracts and ongoing studies

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	N/A
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	All patients undergoing the procedure in Edinburgh are on a local register, but there are no major trials/registries globally that I am aware of.

Other considerations

21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Currently, approximately 50 cryopreservation procedures are performed annually across Edinburgh and Oxford. Only a couple of reimplantation procedures are performed a year. These numbers would likely increase if the procedure became available in more centres across the UK, as more patients would have easy access to cryopreservation. With time, the numbers of reimplantation procedures will also likely increase as the patients who had tissue stored years ago get to at a stage in their life where they would like to start a family. (There will usually be a reasonable time lag between the two operative procedures, especially in the Paediatric population, obviously).
22	Are there any issues with the usability or practical aspects of the procedure/technology?	No
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Funding (operating theatre time, staff, storage facilities) Availability of operating theatre space at short notice
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	No
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: – Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured.	Beneficial outcome measures: • Restoration of ovarian function – measured by gonadotrophin/AMH levels/recording of menstrual cycles/menopausal symptoms; graft function should be regularly assessed for the length of the graft • Pregnancy and livebirths – any conception, method of conception (natural vs assisted) and pregnancy outcome should be recorded • Quality of life - measured by appropriate questionnaire, both in the short term and long-term following graft reimplantation Adverse outcome measures:

	– Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured:	• Operative complications (both following removal and reimplantation) – both short term (less than ~4 weeks post-op) and long term (>4 weeks post-op) adverse events • Reintroduction of malignancy – all oncology patients should have any relapse of their original disease reported (lifelong reporting)
26	Is there any other data (published or otherwise) that you would like to share with the committee?	Nil

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	N/A

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Declarations of interests

Please state any potential conflicts of interest relevant to the procedure/technology (or competitor technologies) on which you are providing advice, or any involvements in disputes or complaints, in the previous **12 months** or likely to exist in the future. Please use the NICE policy on declaring and managing interests as a guide when declaring any interests. Further advice can be obtained from the NICE team.

Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Choose an item.	N/A		
Choose an item.			
Choose an item.			

☒ I confirm that the information provided above is complete and correct. I acknowledge that any changes in these declarations during the course of my work with NICE, must be notified to NICE as soon as practicable and no later than 28 days after the interest arises. I am aware that if I do not make full, accurate and timely declarations then my advice may be excluded from being considered by the NICE committee.

Please note, all declarations of interest will be made publicly available on the NICE website.

Print name:	**CHERYL DUNLOP**
Dated:	**9th November 2022**

NICE National Institute for Health and Care Excellence

Professional Expert Questionnaire

Technology/Procedure name & indication: IP1936 Removal, preservation and re-implantation of ovarian tissue to restore fertility

Your information

Name:	Christian Becker
Job title:	Associate Professor, Consultant Gynaecologist and Subspecialist in Reproductive Medicine
Organisation:	University of Oxford, Oxford University Hospitals NHS Foundation Trust
Email address:	[redacted]
Professional organisation or society membership/affiliation:	British Society of Gynaecological Endoscopy
Nominated/ratified by (if applicable):	Mr Kirana Arambage and Mr Martin Hirsch (members of the BSGE council)
Registration number (e.g. GMC, NMC, HCPC)	GMC 6138375

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1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it? – Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? – Is this procedure/technology performed/used by clinicians in specialities other than your own? – If your specialty is involved in patient selection or referral to another specialty for this	I have been involved in building up the Oxford Tissue Cryopreservation Service over 9 years. As such, as a team in a hub and spoke system we have collected tissue from more than 1000 children and young adults. Together with my paediatric colleague Prof Lakhoo, we removed the first ovarian tissue in 2013 from a young cancer patient and since then have led the surgical tissue cryopreservation service for adolescents and young adults of 16 and above. I have removed tissue from approximately 80-100 patients over those years. In addition, I have laparoscopically re-transplanted tissue of five patients which has resulted in the return of endocrine function in four out of five women and has led to one life birth and currently two ongoing pregnancies in three patients. This is a fantastic team effort. My colleague Dr Sheila Lane, who is the lead of the Oxford Tissue Cryopreservation Service, and I run a bi-weekly clinic for children and young adults who require fertility preservation advice both for egg/embryo freezing and ovarian tissue cryopreservation. We are actively collaborating in the field with colleagues at the University of Edinburgh and University College London Hospitals and have close ties with OTC centres in Europe and the USA. As a RCOG subspecialist in reproductive medicine and surgery I have the knowledge and skills to decide together with the patients about the best method of preserving fertility. I have been a consultant gynaecologist since May 2009 and as such have extensive laparoscopic surgical experience. As an Associate Professor at the University of Oxford I possess the skills to assess and undertake clinical, translational and research studies.

	procedure/technology, please indicate your experience with it.	
2	– 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 published this research. Islam R, Lane S, Williams SA, Becker CM, Conway GS, Creighton SM Establishing reproductive potential and advances in fertility preservation techniques for XY individuals with differences in sex development Clin Endocrinol (Oxf). 2019 Aug;91(2):237-244. doi: 10.1111/cen.13994. Epub 2019 May 2. There are active research collaborations between the University of Oxford and the University of Edinburgh.
3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	Ovarian tissue cryopreservation is not regarded as experimental anymore. However, in the UK it is new and there are only less than a handful centres which offer the procedure under an HTA license. Oocyte or embryo freezing are the current gold standard of fertility preservation, but ovarian tissue cryopreservation should be offered if there are contraindications for ovarian stimulation and egg collection such as the age of the patient, financial constraints or time before gonadotoxic therapy.
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	It would complement the existing standard which is oocyte/embryo cryopreservation.

Current management

5	Please describe the current standard of care that is used in the NHS.	Currently, ovarian tissue cryopreservation is only offered on the back of local funding schemes.

		Oocyte or embryo cryopreservation is only offered before/during gonadotoxic therapy, not afterwards. Oxford offers a hub and spoke ovarian tissue cryopreservation service to children and young adults, but is not (yet) funded by NHSE.
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	Oocyte/embryo cryopreservation is available before/during gonadotoxic treatment. Often, however, there is not enough time to go through ovarian stimulation and egg collection which means that OTC is the only option to preserve fertility.

Potential patient benefits and impact on the health system

7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Fertility preservation Options for the future Children, happiness Restoration of endocrine function A psychological boost during very difficult times
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Cancer patients undergoing gonadotoxic therapy which is more likely than not to impair or destroy her ability to have children of her own and who are not eligible for oocyte/embryo cryopreservation. Children with chromosomal aberrations such as mosaic Turner's syndrome patients. Patient with haematological disorders undergoing gonadotoxic therapy who are not eligible for oocyte/embryo cryopreservation.
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	It will give patients and their families hope for the future as the focus is on fertility preservation which may reduce the risk of mental health issues. It will result in further births which health economic experts have calculated to massively outweigh the initial investment in fertility preservation. As endocrine function is restored in >90% of cases, the need for HRT and consultions will be redcued/unneccessary.
10 - MTEP	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	TBD
11 - MTEP	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about	TBD

	same-in terms of staff, equipment, and care setting)?	
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Two to Three hubs in England/Wales where collections are coordinated from, teaching is provided, tissue is stored. Collections of tissue can be done in peripheral centers after quality management systems are in place, the team has been taught and there is excellent communication with the relevant hub. The peripheral centres can be any hospital (NHS or in the private sector) with a named lead for the local service. The service will be required for children from youngest age to female patients up to the age of 35. Re-transplantation should be in the hubs with associated research in further improving the outcome for patients.
13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	For the removal of ovarian tissue/an ovary solid laparoscopic skills are required which should be available in most if not all hospitals in the UK nowadays. For the paediatric patients (up to the age of 15) similar skills should be available. If not, these patients need to be urgently referred to a centre which can provide this service, possibly the relevant hub. In times of crisis (winter pressures, COVID etc), if the procedure cannot not be done locally, the Hub will need to coordinate an alternative. These patients have to have priority over elective procedures due to the time sensitivities.

Safety and efficacy of the procedure/technology

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	General risks of laparoscopic surgery. Earlier menopause, but this is mostly reduced due to the gonadotoxic therapy and only little as a result of the surgery. Contamination of the tissue. Loss of oocytes prior to the freezing procedure and after the implantation. Need for repat re-implantation. If no spontaneous pregnancy occurs, IVF.

15	Please list the key efficacy outcomes for this procedure/technology?	Life birth rate Resumption of endocrine function and no requirement of HRT. Avoidance of poor mental health.
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	The surgical techniques are still evolving. Size, number of tissue slices to be stored. Number of tissue slices to be re-transplanted.
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	These are now established procedures in many European centers and abroad. See above.
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Most hospitals with oncology for the removal of ovarian tissue. One to two hubs for coordination and re-transplantation.

Abstracts and ongoing studies

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Too many. Meirow D, Levron J, Eldar-Geva T, Hardan I, Fridman E, Zalel Y, Schiff E, Dor J.Pregnancy after transplantation of cryopreserved ovarian tissue in a patient with ovarian failure after chemotherapy. N Engl J Med. 2005 Jul 21;353(3):318-21. doi: 10.1056/NEJMc055237. Epub 2005 Jun 27.
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Not in the UK (no funding). There are efforts on the European level (ESHRE).

Other considerations

21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Approx 500 patients a year will want to store ovarian tissue. The number of patients wanting to use tissue will increase as the number of patients reaching child bearing age increases.
22	Are there any issues with the usability or practical aspects of the procedure/technology?	The processing, storage and re-transplantation should be done in the hubs as this requires high skills.
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Money, money, money. In Oxford, we have been able to build this on the back of normal NHS funding and a lot of charity money. With this, we have very successfully built a nationwide hub and spoke system.
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	Plenty. Processing, storage conditions; best transplantation options.
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications. Please state the post	Beneficial outcome measures: Resumption of endocrine function after re-transplantation. Life birth rate, clinical pregnancy rate. Quality of life. Mental well-being for both patients and family Adverse outcome measures: Intra-/post-operative complications Obstetric complications

	procedure timescales over which these should be measured:	Requirement for HRT Bone, cardiac, brain health Peri- and post-natal outcomes Recurrence of cancer/risk of other cancers/diseases
26	Is there any other data (published or otherwise) that you would like to share with the committee?	n/a

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	This is an absolute game changer especially for children and their families but also for adolescents and young adults as we can offer during dark times real hope for the future. The procedures are successful as we have demonstrated in Oxford and colleagues in Edinburgh. As a result, it is now expected standard practice for oncologists to discuss the options of fertility preservation with their patiens and their families prior to the initiation of treatment.

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Declarations of interests

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Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Choose an item.			
Choose an item.			
Choose an item.			

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Print name:	**Christian Becker**
Dated:	**09 November 2022**

NICE National Institute for Health and Care Excellence

Professional Expert Questionnaire

Technology/Procedure name & indication: IP1936 Removal, preservation and re-implantation of ovarian tissue to restore fertility

Your information

Name:	Miss Ephia Yasmin
Job title:	Consultant Gynaecologist, sub-specialist in reproductive medicine and surgery
Organisation:	University College London Hospital NHS Foundation Trust
Email address:	[redacted]
Professional organisation or society membership/affiliation:	Member of the Royal Society of Obstetricians and Gynaecologists; Executive member of British Fertility Society and chair of special interest group of fertility preservation; Executive member of British Society of Paediatric and Adolescent Gynaecology
Nominated/ratified by (if applicable):	British Fertility Society
Registration number (e.g. GMC, NMC, HCPC)	6082598

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1	Please describe your level of experience with the procedure/technology, for example:	I am familiar with removal, preservation, re-implantation, endocrine follow up after re-implantation and assisted conception after re-implantation.
	Are you familiar with the procedure/technology?	I set up the ovarian tissue cryo-preservation service at University College London Hospital in 2017. We collaborate with Oxford bio-bank to store tissue. I counsel, consent and perform laparoscopy to obtain ovarian tissue. I have not performed any auto-transplantation yet but in the UK, there have been about 3-4 auto-transplants so far. I have the requisite laparoscopic skills. Additionally, I am a paediatric and adolescent gynaecologist and perform surgical procedures in this age group.
	Have you used it or are you currently using it?	I am using this technology.
	– Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake?	The procedure/technology is variably used in the UK. There are several reasons for this. The funding for these procedures is variable. There are 3 bio-banks and centres have to establish third party agreements.
	– Is this procedure/technology performed/used by clinicians in specialities other than your own?	This procedure is used by paediatric surgeons, oncologists and definitely reproductive medicine specialists.
	– If your specialty is involved in patient selection or referral to another	Our specialty is involved in patient selection. We perform risk assessment, evaluate gonadotoxicity, assess ovarian reserve where applicable, assess suitability for the procedure.

	specialty for this procedure/technology, please indicate your experience with it.	
2	– Please indicate your research experience relating to this procedure (please choose one or more if relevant):	I have done bibliographic research on this procedure : Yes **Yasmin E**, Mitchell R, Lane S. Preservation of fertility in teenagers and young adults treated for haematological malignancies. Lancet Haematol. 2021 Feb;8(2):e149-e160. doi: 10.1016/S2352-3026(20)30324-0. PMID: 33513374. Copy 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 published this research. Yes Latif S, Martins Da Silva S, Davies M, Mavrelos D, Foo X, Sangster P, Lane S, **Yasmin E**. Fertility preservation provision in the NHS: a national assessment of care policies. Hum Fertil (Camb). 2022 Apr 10:1-6. doi: 10.1080/14647273.2022.2045519. Ingley KM, Maleddu A, Grange FL, Gerrand C, Bleyer A, **Yasmin E**, Whelan J, Strauss SJ. Current approaches to management of bone sarcoma in adolescent and young adult patients. Pediatr Blood Cancer. 2022 Feb;69(2):e29442. doi: 10.1002/pbc.29442. Epub 2021 Nov 12. PMID: 34767314. I have had no involvement in research on this procedure. Other (please comment): I have a few more abstracts presented at British Fertility Society and European Society of Human Reproduction and Embryology 1. Fertility preservation in minors 2. Permissive vs restrictive fertility preservation
3	How innovative is this procedure/technology, compared to the current standard of care? Is	The procedure has become current standard of care globally and in the UK. However, in the UK, the delivery of the service has gained momentum since 2016. It cannot be considered novel anymore.

	it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please 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. The first in a new class of procedure.
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	As an addition to existing care.

Current management

5	Please describe the current standard of care that is used in the NHS.	Except for Scotland and a few CCGs in England, there is no clear funding for ovarian tissue cryo-preservation. The existing funding mainly comes from charitable donations.
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	No competing alternative. There are various techniques of fertility preservation. They do not compete but are often complementary.

Potential patient benefits and impact on the health system

7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Having an option for fertility preservation when other techniques (like egg or embryo freezing) are not feasible.
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Pre-pubertal patients and patient who cannot wait 2-3 weeks for egg freezing.
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Yes. The procedure will allow more opportunity for parenthood with own eggs. The replacement of tissue will also provide endocrine support and therefore the need for HRT will be lower. The need for egg donation will be lower. Egg donation has a strong demand with not enough donors in the UK. Recipients for egg donation have long waits. Funding for egg donation is also patchy. The procedure involves invasive treatments (laparoscopy) and therefore does not reduce need for invasive treatments.
10 - MTEP	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	
11 - MTEP	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	

12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Existing operating theatres and the need for HTA lab. HTS labs exist to provide stem cell transplants. Ovarian tissue cryo-preservation can be caried out in these facilities by increasing capacity.
13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Yes, training is required to perform ovarian tissue retrieval and replacement. Training is required for processing ovarian tissue, freezing and thawing.

Safety and efficacy of the procedure/technology

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Risks of laparoscopy. Injury to organs or vascular injury during laparoscopy (Risk 1-5 in 1000) https://www.bsge.org.uk/wp-content/uploads/2016/03/GtG-no-49-Laparoscopic-Injury-2008.pdf
15	Please list the key efficacy outcomes for this procedure/technology?	Pregnancy and live birth Return of endocrine function Quality of life
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	There are just over 200 live births from auto-transplantation of ovarian tissue but numbers are increasing. Overall, these numbers are low. However when compared with the denominator (i.e ovarian tissue transplanted), the success rates quoted by different groups are 25-45%.
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	There is uncertainty and concern about auto-transplantation of tissue in the context of leukaemia and metastatic disease. This is due to risk of re-implantation of malignancy and

		relapse. In other conditions like above the diaphragm Hodgkin's lymphoma, breast cancer, the safety is established.
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Most or all district general hospitals. No A minority of hospitals, but at least 10 in the UK. Yes. Safe in tertiary hospitals. But the key is in the training and the right conditions for procurement of tissue. Fewer than 10 specialist centres in the UK. Cannot predict at present.

Abstracts and ongoing studies

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Dolmans MM, von Wolff M, Poirot C, Diaz-Garcia C, Cacciottola L, Boissel N, Liebenthron J, Pellicer A, Donnez J, Andersen CY. Transplantation of cryopreserved ovarian tissue in a series of 285 women: a review of five leading European centers. Fertil Steril. 2021 May;115(5):1102-1115. doi: 10.1016/j.fertnstert.2021.03.008. PMID: 33933173. Consortium and the Danish Fertility-Preservation Networks - What Can We Learn From Their Experiences? Clin Med Insights Reprod Health. 2019 Apr 30;13:1179558119845865. doi: 10.1177/1179558119845865. PMID: 31068758; PMCID: PMC6495450. ESHRE Guideline Group on Female Fertility Preservation, Anderson RA, Amant F, Braat D, D'Angelo A, Chuva de Sousa Lopes SM, Demeestere I, Dwek S, Frith L, Lambertini M, Maslin C, Moura-Ramos M, Nogueira D, Rodriguez-Wallberg K, Vermeulen N. ESHRE guideline: female fertility preservation. Hum Reprod Open. 2020 Nov 14;2020(4):hoaa052. doi: 10.1093/hropen/hoaa052. PMID: 33225079; PMCID: PMC7666361.
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	The Danish, Swedish and German maintain strong registries and publish regularly. https://clinicaltrials.gov/ct2/show/NCT04948658

Other considerations

21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	About 200-300. The use in the UK is very restrictive at the moment because of funding and lack of access.
22	Are there any issues with the usability or practical aspects of the procedure/technology?	No issues with usability.
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	None now. This process was labelled experimental until 2018. This label has now been removed.
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	Every ovarian tissue cryo-preservation programme must be linked to maintenance of a registry and regular outcome data published. Research to improve survival of tissue is ongoing in keeping with the ethos of continuous improvement.
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: – Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured.	Beneficial outcome measures: Pregnancy, live birth, nature of conception, endocrine function, ovulation, longevity of endocrine and reproductive function of transplanted tissue, quality of life. Adverse outcome measures: Risks of laparoscopy, relapse of malignancy

	– Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured:	
26	Is there any other data (published or otherwise) that you would like to share with the committee?	

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	

NICE National Institute for Health and Care Excellence

Declarations of interests

Please state any potential conflicts of interest relevant to the procedure/technology (or competitor technologies) on which you are providing advice, or any involvements in disputes or complaints, in the previous **12 months** or likely to exist in the future. Please use the NICE policy on declaring and managing interests as a guide when declaring any interests. Further advice can be obtained from the NICE team.

Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Indirect	I am an NHS doctor and honorary academic. I have a private practice but do not carry out ovarian tissue cryo-preservation in the private sector.	**2016**	
Non-financial professional	I am a member of the working group 'Ovarian and testicular tissue cryopreservation and re-implantation' for NHS England	**2019**	
Choose an item.			

☒ I confirm that the information provided above is complete and correct. I acknowledge that any changes in these declarations during the course of my work with NICE, must be notified to NICE as soon as practicable and no later than 28 days after the interest arises. I am aware that if I do not make full, accurate and timely declarations then my advice may be excluded from being considered by the NICE committee.

Please note, all declarations of interest will be made publicly available on the NICE website.

Print name:	**Ephia Yasmin**
Dated:	**15.11.2022**

NICE National Institute for Health and Care Excellence

Professional Expert Questionnaire

Technology/Procedure name & indication: IP1936 Removal, preservation and re-implantation of ovarian tissue to restore fertility

Your information

Name:	Fevzi Shakir
Job title:	Consultant Gynaecologist
Organisation:	Royal Free Hospital, London, NW3 2QG
Email address:	[redacted]
Professional organisation or society membership/affiliation:	BSGE – Honorary Treasurer
Nominated/ratified by (if applicable):	Click here to enter text.
Registration number (e.g. GMC, NMC, HCPC)	GMC: 6120945

How NICE will use this information: the advice and views given in this questionnaire will form part of the information used by NICE and its advisory committees to develop guidance or a medtech innovation briefing on this procedure/technology. Information may be disclosed to third parties in accordance with the Freedom of Information Act 2000 and the Data Protection Act 2018, complying with data sharing guidance issued by the Information Commissioner's Office. Your advice and views represent your individual opinion and not that of your employer, professional society or a consensus view. Your name, job title, organisation and your responses, along with your declared interests will also be published online on the NICE website as part of the process of public consultation on the draft guidance, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate.

For more information about how we process your data please see our privacy notice.

Yes ☐ I give my consent for the information in this questionnaire to be used and may be published on the NICE website as outlined above. If consent is NOT given, please state reasons below:

Click here to enter text.

Please answer the following questions as fully as possible to provide further information about the procedure/technology and/or your experience.

Please note that questions 10 and 11 are applicable to the Medical Technologies Evaluation Programme (MTEP). We are requesting you to complete these sections as future guidance may also be produced under their work programme.

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it? − Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? − Is this procedure/technology performed/used by clinicians in specialities other than your own? − If your specialty is involved in patient selection or referral to another specialty for this	I am familiar with the technology. It is only used in a few trusts which have the appropriate infrastructure and HTA licence that is required to store ovarian tissue. This technology is used only in Gynaecology for preservation of ovarian tissue. We accept referrals in our trust for consideration of this technology. If appropriate we then arrange for the patient to have the procedure performed either in isolation or in combination with another procedure.

	procedure/technology, please indicate your experience with it.	
2	– 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 published this research. – I have a joint publication** https://doi.org/10.1093/humrep/deac144 I have had no involvement in research on this procedure. Other (please comment) – We aim to research the outcomes/ways to improve outcomes as our patient base grows.
3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	The procedure is well established worldwide with over >100 live births following transplantation. Endocrine function is also restored in most individuals. The issue has always been around funding and tissue storage costs, but the benefits far outweigh this. **Established practice and no longer new – There is significant worldwide data to suggest it is safe and effective. It is no longer new but has taken time to be adopted in the UK. IVF for instance provides fertility preservation however cryopreservation with subsequent transplantation provides fertility and endocrine function spontaneously.** 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.
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	This procedure is complimentary to the other technologies with assisted fertility. But as stated has the advantage to providing endocrine function.

Current management

5	Please describe the current standard of care that is used in the NHS.	Cryopreservation is only available in a few UK hospitals. At the Royal Free, where I work we established the first NHS funded service initially for local patients but then also expanding it Nationwide. We have the necessary HTA licence which permits storage of tissue for up to 55 years.
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	The alterative would be assisted fertility techniques but that requires a rigorous medication protocol and does not restore endocrine function. Meta analysis are starting to demonstrate that there are not significant differences between fertility outcomes of IVF vs transplanted ovarian tissue.

Potential patient benefits and impact on the health system

7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Patient who are undergoing cancer treatment which would render them infertile/have premature ovarian failure afterwards without this technology.
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Cancer patients and in those patient who would have reduced fertility (such as endometriosis patients or in patient who have had multiple ovarian cystectomies).
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	If a patient would otherwise have premature ovarian failure and no oocytes then they would require potentially fertility treatments and multiple visits to address hormonal treatments to treat their low oestrogen and progesterone levels.
10 - MTEP	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	There would be initial/ongoing costs for the technology but long terms this is likely to prove to be cost effective.
11 - MTEP	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Same as 10 - MTEP
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Endoscopic service required, access to theatre required especially in the context of cancer patients where procedure need to be performed in a timely fashion. Also a laboratory with HTA licence is required.

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Yes training is required for the ovarian tissue cryopreservation and also when transplantation is required.

Safety and efficacy of the procedure/technology

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	No harms other than a low risk laparoscopy in most cases.
15	Please list the key efficacy outcomes for this procedure/technology?	
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	No concerns as it is established.
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	No controversy. Has benefit in terms of providing fertility and endocrine restoration.
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please 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.

Abstracts and ongoing studies

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	A comparison of fertility preservation outcomes in patients who froze oocytes, embryos, or ovarian tissue for medically indicated circumstances: a systematic review and meta-analysis Oocyte, embryo, and ovarian tissue cryopreservation yield comparable rates of live birth and clinical pregnancy in women who preserved fertility before gonadotoxic therapy, but further studies are required to confirm this. Published Apr 30, 2022  Fertility and Sterility Editorial Office, American Society for Reproductive Medicine
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	

Other considerations

21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	>500 per year
22	Are there any issues with the usability or practical aspects of the procedure/technology?	No

23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	No – already established in our hospital
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	-
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured:	Beneficial outcome measures: Successful cryopreservation. Successful transplantation. Restoration of endocrine function post transplantation. Fertility outcome data. Adverse outcome measures: Any surgical complications.
26	Is there any other data (published or otherwise) that you would like to share with the committee?	-

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	-

NICE National Institute for Health and Care Excellence

Declarations of interests

Please state any potential conflicts of interest relevant to the procedure/technology (or competitor technologies) on which you are providing advice, or any involvements in disputes or complaints, in the previous **12 months** or likely to exist in the future. Please use the NICE policy on declaring and managing interests as a guide when declaring any interests. Further advice can be obtained from the NICE team.

Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Choose an item.			
Choose an item.			
Choose an item.			

☐ I confirm that the information provided above is complete and correct. I acknowledge that any changes in these declarations during the course of my work with NICE, must be notified to NICE as soon as practicable and no later than 28 days after the interest arises. I am aware that if I do not make full, accurate and timely declarations then my advice may be excluded from being considered by the NICE committee.

Please note, all declarations of interest will be made publicly available on the NICE website.

Print name:	**Fevzi Shakir**
Dated:	**15 November 2022**

NICE National Institute for Health and Care Excellence

Professional Expert Questionnaire

Technology/Procedure name & indication: IP1936 Removal, preservation and re-implantation of ovarian tissue to restore fertility

Your information

Name:	Hajra Khattak
Job title:	Specialty Registrar in Obstetrics and Gynaecology, Post-Doctoral Research Fellow
Organisation:	Birmingham Women's and Children's NHS Foundation (present), UCL EGA Institute for Womens Health, University College Hospital London (UCLH) (incoming)
Email address:	[redacted]
Professional organisation or society membership/affiliation:	British Fertility Society (BFS), British Society of Gynaecological Endoscopy (BSGE), European Society of Human Reproduction and Embryology (ESHRE). European Society of Gynaecological Endoscopy (ESGE)
Nominated/ratified by (if applicable):	British Society of Gynaecological Endoscopy (BSGE)
Registration number (e.g. GMC, NMC, HCPC)	7456151

How NICE will use this information: the advice and views given in this questionnaire will form part of the information used by NICE and its advisory committees to develop guidance or a medtech innovation briefing on this procedure/technology. Information may be disclosed to third parties in accordance with the Freedom of Information Act 2000 and the Data Protection Act 2018, complying with data sharing guidance issued by the Information Commissioner's Office. Your advice and views represent your individual opinion and not that of your employer, professional society or a consensus view. Your name, job title, organisation and your responses, along with your declared interests will also be published online on the NICE website as part of the process of public consultation on the draft guidance, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate.

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Click here to enter text.

Please answer the following questions as fully as possible to provide further information about the procedure/technology and/or your experience.

Please note that questions 10 and 11 are applicable to the Medical Technologies Evaluation Programme (MTEP). We are requesting you to complete these sections as future guidance may also be produced under their work programme.

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it? – Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? – Is this procedure/technology performed/used by clinicians in specialities other than your own? – If your specialty is involved in patient selection or referral to another specialty for this	I am training in obstetrics and gynaecology. I am familiar with technology having done my research in looking at reproductive and endocrine outcomes from ovarian transplantation (after cryopreservation and thawing). Furthermore, through my research I have also learnt to cryopreserve ovarian tissue (both bovine and human) using the slow freezing technique. I have visited centres that offer this procedure routinely to patients undergoing gonadotoxic anti-cancer therapies (Univeristie Catholique de Louvain, Brussels, Belgium and Laboratory of Reproductive Biology, Rigshospitalet, Copenhagen, Denmark). Given an increase in the number of young cancer patients who survive, this procedure will greatly benefit young girls and women in preserving their fertility and being able to have biological children. There is evidence to suggest that there is already a discrepancy in provision of fertility preservation techniques in females with cancer nationally (Latif et al. 2022). This is especially true in pre-pubertal girls in whom oocyte cryopreservation is not applicable. One would therefore anticipate for this procedure to be extremely beneficial in this group of female patients. This technology involves harvesting ovarian tissue via laparoscopy or laparotomy where a part of an ovary or whole ovary is retrieved, prepared by removal of the inner layer of the ovary (medulla), and cryopreserving the cortex (outer layer). In prepubertal girls, it is usually performed by paediatric surgeons. For teenage and young adolescent cancer patients, some gynaecologists with an interest in paediatric adolescent gynaecology and surgery, may also be able to retrieve the tissue. The tissue is cryopreserved by individuals trained in the procedure formally and can range from being laboratory technicians, embryologists, biologists, veterinarians or O&G trainees with an interest in this technology like myself. The transplantation procedure is usually performed

	procedure/technology, please indicate your experience with it.	by a gynaecologist with an interested in reproductive medicine and surgery and/or advanced laparoscopy/minimal invasive gynaecology. References used: Sania Latif, Sarah Martins Da Silva, Melanie Davies, Dimitrios Mavrelos, Xulin Foo, Philippa Sangster, Sheila Lane & Ephia Yasmin (2022): Fertility preservation provision in the NHS: a national assessment of care policies, Human Fertility, DOI: 10.1080/14647273.2022.2045519
2	– 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. I have done clinical research on this procedure involving patients or healthy volunteers. I have published this research. I have received formal training in cryopreserving ovarian tissue (bovine and human). My postgraduate degree was based on this topic. Other (please comment)
3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	The only established method of female fertility preservation in the UK are embryo cryopreservation and oocyte cryopreservation. Embryo cryopreservation is not applicable to women who do not have a male partner and oocyte cryopreservation is not feasible in prepubertal girls. Ovarian tissue cryopreservation therefore provides an alternative method. Although novel, it is already applied in many European countries. Established practice and no longer new. Rational for above: Ovarian tissue cryopreservation and transplantation has been developed over 2 decades ago and is no longer considered experimental by the American Society of Reproductive Medicine (ASRM).
4	Does this procedure/technology have the potential to replace current standard care or	I anticipate and hope that OTC is used as an addition to existing standard care. Female reproductive life span is already finite. With diseases that pose a risk to fertility potential in

	would it be used as an addition to existing standard care?	women, the reproductive life span in these patients is shortened further. Providing an additional fertility preservation technique therefore will only help many young girls and women achieve biological motherhood.

Current management

5	Please describe the current standard of care that is used in the NHS.	For female patients with cancer, where the CCG funding allows, oocyte cryopreservation is offered as a method of fertility preservation. OTC is only offered in a select group of centres.
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	Alternative to OTC is oocyte cryopreservation. Oocyte cryopreservation however is not possible in cancer patients who are unwell to undergo ovulation induction or do not have time to do so, as need to start anti-cancer therapy imminently. OTC can be conducted imminently as long as the patient is well enough to undergo general anaesthetic.

Potential patient benefits and impact on the health system

7	What do you consider to be the potential benefits to patients from using this procedure/technology?	-The chance of spontaneous conception after transplantation -An additional method of fertility preservation for women -The potential of return of hormonal function
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Pre pubertal female cancer patients Cancer patients who do not have the time or are too unwell to undergo ovulation induction Potential elective fertility preservation method in women wishing to delay child bearing
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Yes. Patients can benefit from the potential of spontaneous conception which will prevent the need to undergo assisted reproductive techniques. With the potential of return of hormonal function, this will improve the quality of life in cancer patients significantly.
10 - MTEP	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Although it will cost more to start with, overall the benefits of this procedure outweigh the risks.
11 - MTEP	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Unable to comment.

12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Additional theatre time and use of biobank for tissue storage.
13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Surgical technique for tissue retrieval and transplant, tissue preparation, cryopreservation technique and storage.

Safety and efficacy of the procedure/technology

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Risks associated are those related to laparoscopic surgery/laparotomy. There is the chance of malignant tissue being transplanted back however there is an international consensus on the type of cancers in which this procedure is contraindicated (such as haematological malignancies). For adverse reported events, please see list of publications I have provided.
15	Please list the key efficacy outcomes for this procedure/technology?	The chance of spontaneous conception and potential return of hormonal function.
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	The number of pregnancy/live births that can be achieved and how long the tissue will function for. There is also uncertainty regarding the amount of tissue that should be cryopreserved and transplanted to achieve the desired outcome for the patient.
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Although there is evidence that transplantation of the cryopreserved-thawed tissue also returns ovarian endocrine function, and cancer patients who have received this procedure have informed of reversal of menopausal symptoms, there is uncertainty as to how long the tissue will function for in each individual patient.

18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	The procedure does not come without its risks in that the patient is required to undergo either laparoscopy or laparotomy and that itself has its risks. There is also the risk of cancer in the transplanted tissue (either from the previous cancer or a new cancer). The procedure however has been developed meticulously over the last two decades in many centres globally and it is recommended for a small piece of tissue to be transplanted to SCID mice (xenotransplantation) followed by assessment through immunohistochemistry for malignant cells. Furthermore, an advantage of this technique is the chance of natural conception. After having gone through cancer, cancer treatment and the difficult decision of having to undergo fertility preservation, for these patients undergoing further fertility treatment has an additional negative psychological impact. OTC and transplantation are therefore a better option in some women.

Abstracts and ongoing studies

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Attached to email
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Attached to email.

Other considerations

21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Difficult to quantify but it will be applicable in prepubertal girls and young adolescents as well as women with cancer that require gonadotoxic treatment.
22	Are there any issues with the usability or practical aspects of the procedure/technology?	The tissue retrieval is not onerous for advanced laparoscopic surgeons. Tissue preparation and cryopreservation requires skilled personnel, which is costly and requires training time. Also lack of available biobanks.
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Lack of funding, lack of expertise and lack of dedicated laboratory space. There is also the issue of general lack of funding into both research and innovation in women's health.
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	Although being developed over the last 20 years, there are still many unanswered questions. Some areas of research are described below: Long term outcomes (reproductive and endocrine) from OTC and transplantation Long term complications from transplantation of the ovarian tissue Assessment of longevity of the ovarian graft Prediction of longevity of the ovarian graft
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: – Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured.	Beneficial outcome measures: Short term measures: Ovarian reserve test + hormonal status prior to tissue harvest Type of cancer Chemotherapy/treatment Whether tissue harvested prior to anti-cancer treatment Age at tissue retrieval Tissue harvest technique Amount of tissue cryopreserved

	– Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured:	Size of tissue (three-dimensional measurement) Cryopreservation technique in detail (use of media etc.) Long term measures: Time to transplant Amount of tissue transplanted (three-dimensional measurement) Ovarian reserve test + hormonal status prior to tissue transplant Periodic hormonal tests (ideally weekly if hoping for spontaneous conception) Pregnancy Live birth Miscarriage Adverse pregnancy outcomes Pregnancy complications Adverse outcome measures: Early: Complications from the operation Late: If oophorectomy performed, there is evidence to suggest that these women will undergo menopause approximately 2 years earlier. Risk of malignancy in transplanted tissue (either metastasis from underlying cancer or as a new cancer). The tissue however is transplanted to SCID mice to assess for underlying malignancy and thus far only a handful of cases have been reported.
26	Is there any other data (published or otherwise) that you would like to share with the committee?	As above

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	Nil

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Declarations of interests

Please state any potential conflicts of interest relevant to the procedure/technology (or competitor technologies) on which you are providing advice, or any involvements in disputes or complaints, in the previous **12 months** or likely to exist in the future. Please use the NICE policy on declaring and managing interests as a guide when declaring any interests. Further advice can be obtained from the NICE team.

Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Choose an item.			
Choose an item.			
Choose an item.			

☒ I confirm that the information provided above is complete and correct. I acknowledge that any changes in these declarations during the course of my work with NICE, must be notified to NICE as soon as practicable and no later than 28 days after the interest arises. I am aware that if I do not make full, accurate and timely declarations then my advice may be excluded from being considered by the NICE committee.

Please note, all declarations of interest will be made publicly available on the NICE website.

Print name:	**Click here to enter text.Hajra Khattak**
Dated:	**Click here to enter text.13/12/22**

NICE National Institute for Health and Care Excellence

Professional Expert Questionnaire

Technology/Procedure name & indication: IP1936 Removal, preservation and re-implantation of ovarian tissue to restore fertility

Your information

Name:	Dr Yuliya (Julia) Kopeika
Job title:	Consultant Gynaecologist, Subspecialist in Reproductive Medicine
Organisation:	Assisted Conception Unit, Guys and St Thomas NHS Trust
Email address:	[redacted]
Professional organisation or society membership/affiliation:	British Fertility Society
Nominated/ratified by (if applicable):	British Fertility Society
Registration number (e.g. GMC, NMC, HCPC)	GMC 6097179

How NICE will use this information: the advice and views given in this questionnaire will form part of the information used by NICE and its advisory committees to develop guidance or a medtech innovation briefing on this procedure/technology. Information may be disclosed to third parties in accordance with the Freedom of Information Act 2000 and the Data Protection Act 2018, complying with data sharing guidance issued by the Information Commissioner's Office. Your advice and views represent your individual opinion and not that of your employer, professional society or a consensus view. Your name, job title, organisation and your responses, along with your declared interests will also be published online on the NICE website as part of the process of public consultation on the draft guidance, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate.

For more information about how we process your data please see our privacy notice.

☒ I give my consent for the information in this questionnaire to be used and may be published on the NICE website as outlined above. If consent is NOT given, please state reasons below:

Click here to enter text.

Please answer the following questions as fully as possible to provide further information about the procedure/technology and/or your experience.

Please note that questions 10 and 11 are applicable to the Medical Technologies Evaluation Programme (MTEP). We are requesting you to complete these sections as future guidance may also be produced under their work programme.

1	Please describe your level of experience with the procedure/technology, for example:	I am the lead clinician for one of the biggest fertility preservation clinics in the UK and I am not only UpToDate with all existing fertility preservation options available for patients of reproductive age, but I also utilise them in everyday practice and provide the training to doctors in the UK and overseas. I am the lead of the Fertility Preservation Module of the British Fertility Society
	Are you familiar with the procedure/technology?	I am familiar with Ovarian Tissue Preservation/Implantation.
	Have you used it or are you currently using it?	Yes, I have introduced an ovarian tissue preservation service at GSTT and have received a full licence for its use from Human Tissue Authority.
	− Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake?	Until now this technology has not been used as widely as it has potential for, due to a lack of established NHS funding. Our current service provision is supported by Cancer Charity. However, this is a very important method of fertility preservation widely used across the world for children and young patients of reproductive age.
	− Is this procedure/technology performed/used by clinicians in specialities other than your own?	This a highly specialised technology that is usually performed within the remit of Reproductive Medicine. High-quality control assurance including specific laboratory training distinct from that in 'standard' medically assisted reproduction and an appropriate medical environment are essential. However, procurement/collection of tissues can be performed by any gynecologist who can perform laparoscopy and ovarian sampling/oophorectomy. Re-implantation of tissues can also be done by a gynecologist with advanced laparoscopic skills (some training may be required). Tissue

	− If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.	processing, assessment freezing, storing and thawing can be done only by a highly specialised team. Access to dedicated tissue processing facilities and licence from HTA is essential. Patient selection and counseling for this procedure need to be done by Reproductive Medicine Specialists who are familiar with all current methods and technologies available for Fertility preservation. The patient selection and fitness assessment for the process need to involve a multidisciplinary team of oncologists, hematologists, radiologists, and anesthetists. The original referral to the reproductive team is usually done by oncologists. I provide care to a large population of patients in a tertiary hospital. We receive annually at least 300 referrals from London and South-East England. This number continues to rise. Approximately 6 to10 % of patients who need fertility preservation would benefit from Ovarian tissue preservation.
2	− 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. To secure HTA licence, on the first instance, we had to provide evidence that we can perform ovarian tissue collection, freezing, and thawing, according to the internationally reported standards. To achieve the above, I have done an extensive literature search and secured Ethic Approval to allow us to perform the first stage of process validation. As part of the process validation, I had to perform bibliographic laboratory and clinical research. I have not published specifically on Ovarian Tissue Preservation. We have not published the data on our process validation and implementation as it did not carry any novel scientific findings as we used methods that have already been described in the literature. However, a detailed process validation report is available on request. I have completed my Ph.D. in Cryobiology and I have in-depth knowledge of the processes of slow freezing and vitrification for cells and tissues.
3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design?	This procedure is not considered any more as experimental by different reproductive societies, such as ESHRE or ASRM. ESHRE Fertility Guideline 2020 strongly recommends OTC in patients undergoing moderate/high-risk gonadotoxic treatment where oocyte/embryo cryopreservation is not feasible. This is a widely used practice across Europe, the US, Australia, and Israel. In

	Which of the following best describes the procedure (please choose one):	Denmark, this program has been launched since 1999. It is estimated, based on Denmark's experience, that 18 people per year per 1 million population would benefit from OTC.
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	This is not a replacement for currently existing processes, but the addition that is essential for some groups of patients who currently have no options at all. This is the only available option for pre-pubertal girls. Therefore, if this option is not available in the UK, young children who require high-risk gonadotoxic treatment, will be left without any option for fertility preservation. It's also the only option available in post-pubertal patients who cannot delay the start of chemotherapy by 3 weeks or who needed to have an escalation of chemotherapy from low risk to moderate/high risk of menopause. The currently available option of egg/embryo freeze would usually require 2.5-3 weeks which is not always possible.

Current management

5	Please describe the current standard of care that is used in the NHS.	The current model of care offers patients to undergo controlled ovarian stimulation and egg/embryo freeze. However, this process requires the patient to be post-pubertal and it takes 2.5-3 weeks. This can delay the cancer treatment, be physically and emotionally challenging and involve internal scans and examinations that may not be acceptable to young patients. The alternative option could be the preservation of ovarian tissues. The introduction of ovarian tissue preservation service will allow patients who are pre-pubertal or cannot afford to delay their cancer treatment to have an option of fertility preservation within 24-72 hours.

6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	No other options are available for the patient groups described above. Not applicable

Potential patient benefits and impact on the health system

7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Efforts to improve the quality of life among cancer survivors are increasingly a priority. Loss of fertility following cancer treatment is considered by cancer survivors as one of the most distressing outcomes of the therapy. The potential benefit of this service: - Being able to offer a comprehensive complete range of fertility preservation services to young cancer patients in line with top international standards of care - Auto-transplantation of ovarian tissues back to a patient will give them the opportunity of restoring not only reproductive function but also menstrual and hormonal - Give potential for natural conception - Having a bank of ovarian tissues that patients may opt to donate for research in the future could also be a platform for basic research on mechanisms of chemotherapy damage on ovarian function with the potential to develop protective “antidotes” in the future
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	-Children and pre-pubertal girls (no other options of fertility preservation are available for this group of patients) Post-pubertal patients where controlled ovarian stimulation and egg freeze are not feasible due to time/safety concerns Patients who have had already recent exposure to chemotherapy (egg freezing is not recommended within 6 months after recent chemotherapy. Therefore, in patients where the escalation of chemotherapy is required, there are no other options for fertility preservation Potential for using this service for some carefully selected patients with genetic conditions that predispose to premature ovarian insufficiency or in benign conditions where stem cell transplant may be needed
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits, or less invasive treatment?	Yes. The advantages of ovarian tissue preservation include the possibility to restore natural ovarian function (including non-reproductive endocrine effects) after ovarian tissue transplantation (OTT) and achieving (several) natural pregnancies without further medical intervention. Therefore, these patients would have potentially a better quality of life and fewer visits to the hospital as they would not require hormone replacement therapy or treatment with donor eggs.

10 - MTEP	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting, etc)	In the beginning, additional costs might be required to set up the process nationally. The procedure of OTC requires high-quality control assurance including specific laboratory training distinct from 'standard' assisted reproduction. Even though there are already several centers in the UK that have established such services with the support of cancer charities. To increase the cost-effectiveness of the process, it's feasible to have only several highly specialised centers in the UK, that can provide this service nationwide via the established network.
11 - MTEP	What do you consider to be the resource impact of adopting this procedure/technology (is it likely to cost more or less than standard care, or about the same-in terms of staff, equipment, and care setting)?	Specially trained staff and facilities for tissues processing, storage, and distribution would have an additional cost
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	There is no change in clinical facilities required for this service. However, the specialised facilities for tissue procurement, processing, testing, storage, distribution, and disposal of ovarian tissue are required in line with the HTA licence regulations
13	Is any specific training needed to use the procedure/technology concerning efficacy or safety?	Specialised training would be required for: - procurement, processing, testing, storage, distribution, and disposal of ovarian tissue - clinical assessment, patient selection, counseling, and consenting - surgical training for tissue transplantation

Safety and efficacy of the procedure/technology

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence:	Risks associated with laparoscopy as per RCOG: The overall risk of serious complications from laparoscopy is approximately 2 in 1000 women (uncommon). This includes damage to the bowel, bladder, ureters, uterus, or major blood vessels which would require immediate repair by laparoscopy or laparotomy (open surgery is uncommon). Hernia at the site of entry (less than 1 in 100; uncommon).

	Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Thromboembolic complications (rare or very rare). Death; 3–8 in 100 000 women (very rare) undergoing laparoscopy may die as a result of complications. As for risks related specifically to ovarian tissues - Risk of finding malignant cells in the removed ovaries and not being able to transplant them back - Removal of ovaries on its own is estimated to bring the age of menopause by 1-2 years - Risk of process failure (failure of tissue survival, failure of tissue to start functioning after re-implantation; failure to conceive) - Risk of re-introducing cancer cells - Need for further surgery to reintroduce the tissues
15	Please list the key efficacy outcomes for this procedure/technology.	- Restoration of fertility potential including natural (The current success rate is reported to be between 20 to 40% over a relatively short period of time. With half of the reported pregnancies achieved naturally.) - Restoration of endocrine function (The chance of menses return is reported to be 94%)
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	- The data on long-term outcomes is still relatively limited (approximately 250 babies born now across the world). - Risk of introduction minimal residual disease (especially for certain types of cancers, like leukemia); further methods need to be developed to be more certain - Also if patients require further assisted conception with transplanted ovaries, they would most likely require more than 1 IVF cycle (more likely to have a very small number of eggs, the higher chance of not reaching embryo transfer; lower chance of successful outcome per one stimulation)
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	- Potentially more tests can be developed to ensure the safety of tissue re-transplantation in cases of leukemia.

		- In cases of cancer where there is a risk of it being in ovaries, potential new methods may be developed in the future to allow culturing of mature follicles from primordial ones from ovarian tissues
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Fewer than 10 specialist centers in the UK.

Abstracts and ongoing studies

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented/published on this procedure/technology (this can include your work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings that might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	I have just returned today from the 7th World Congress of the International Society for Fertility Preservation, where the abstract on Ovarian tissue Preservation in Leukaemia survivors was presented by Hila Raanani from Professor Meirow's group. 21 Leukaemia patients had an assessment for Minimal Residual Disease in the ovaries before transplantation. They have done extensive MRD assessments and approved 15 out of 21 examined cases (70%). The rest showed evidence of disease. 9 of these patients had tissues transplanted. No evidence of leukemia recurrence yet
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list them.	Not known

Other considerations

21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an	The estimated number of patients who potentially can benefit from this process in 1 year in the UK is somewhere between 500 to 900

	estimated number, or a proportion of the target population)?	
22	Are there any issues with the usability or practical aspects of the procedure/technology?	No
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	We have already introduced this procedure in our trust. However, the sustainability of this service would rely on NHS funding availability as currently it is supported by charity grant
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	It would be important to have a prospective database of all the cases with monitoring: - Indication - Patient characteristics - Complications - Rate of premature ovarian insufficiency - Utilisation rate - Restoration of the menstrual cycle - Pregnancy rate (including natural) - Recurrence of cancer - Mortality rate
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: – Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures, and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured.	Beneficial outcome measures: - Utilisation rate - Restoration of the menstrual cycle - Length of transplant functionality - Pregnancy rate (including natural with and without ovarian tissue transplant) - Patient satisfaction (quality of life questionnaires) Adverse outcome measures: - Surgical complications - Rate of POI in patients who have undergone OTC and further chemotherapy

	− Adverse outcome measures. These should include early and late complications. Please state the post-procedure timescales over which these should be measured:	- Cancer recurrence - Mortality rate - Failure of the procedure (absence of menstrual function) - Failure to conceive - Anxiety and depressions
26	Is there any other data (published or otherwise) that you would like to share with the committee?	no

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	

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Declarations of interests

Please state any potential conflicts of interest relevant to the procedure/technology (or competitor technologies) on which you are providing advice, or any involvements in disputes or complaints, in the previous **12 months** or likely to exist in the future. Please use the NICE policy on declaring and managing interests as a guide when declaring any interests. Further advice can be obtained from the NICE team.

Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Choose an item.			
Choose an item.			
Choose an item.			

☒ I confirm that the information provided above is complete and correct. I acknowledge that any changes in these declarations during my work with NICE must be notified to NICE as soon as practicable and no later than 28 days after the interest arises. I am aware that if I do not make full, accurate, and timely declarations then my advice may be excluded from being considered by the NICE committee.

Please note, all declarations of interest will be made publicly available on the NICE website.

Print name:	**Click here to enter text.Yuliya (Julia) Kopeika**
Dated:	**Click here to enter text.13 November 2022**

NICE National Institute for Health and Care Excellence

Professional Expert Questionnaire

Technology/Procedure name & indication: IP1936 Removal, preservation and re-implantation of ovarian tissue to restore fertility

Your information

Name:	Neelam Potdar
Job title:	Consultant Reproductive Medicine & Gynaecologist, Honorary Associate Professor
Organisation:	University Hospitals of Leicester NHS Trust & University of Leicester
Email address:	[redacted]
Professional organisation or society membership/affiliation:	RCOG:127832; BSGE: 1394; BFS: 121746
Nominated/ratified by (if applicable):	BSGE
Registration number (e.g. GMC, NMC, HCPC)	GMC:5207836

How NICE will use this information: the advice and views given in this questionnaire will form part of the information used by NICE and its advisory committees to develop guidance or a medtech innovation briefing on this procedure/technology. Information may be disclosed to third parties in accordance with the Freedom of Information Act 2000 and the Data Protection Act 2018, complying with data sharing guidance issued by the Information Commissioner's Office. Your advice and views represent your individual opinion and not that of your employer, professional society or a consensus view. Your name, job title, organisation and your responses, along with your declared interests will also be published online on the NICE website as part of the process of public consultation on the draft guidance, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate.

For more information about how we process your data please see our privacy notice.

☒ I give my consent for the information in this questionnaire to be used and may be published on the NICE website as outlined above. If consent is NOT given, please state reasons below:

Click here to enter text.

Please answer the following questions as fully as possible to provide further information about the procedure/technology and/or your experience.

Please note that questions 10 and 11 are applicable to the Medical Technologies Evaluation Programme (MTEP). We are requesting you to complete these sections as future guidance may also be produced under their work programme.

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology?	This procedure started initially as research and is now being offered to appropriate patients more frequently. Working as a reproductive medicine consultant and offering fertility preservation, I am familiar with the procedure, however do not perform it myself. We are planning to start performing the procedure locally.
	Have you used it or are you currently using it? – Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? – Is this procedure/technology performed/used by clinicians in specialities other than your own? – If your specialty is involved in patient selection or referral to another specialty for this	This procedure is offered as a fertility preservation option to young pre-pubertal/adolescent girls diagnosed with cancer, and are at a risk of gonadotoxic effect of chemo/radio therapy. Currently, we refer our patients to another centre for the procedure. This procedure is being used more often in the NHS, however, considered under research umbrella. Young girls diagnosed with cancer are offered this fertility preservation option frequently. If made widely available, this is likely to benefit a great number of patients, especially for those that cannot be referred to the specific centres. In addition to Reproductive Medicine specialists, this procedure is performed/used by Oncologists/Paediatric surgeons.

	procedure/technology, please indicate your experience with it.	Teenage and Young Adults Oncologists and Reproductive Medicine specialists are involved in patient selection and referral o another centre for the procedure. I have been involved in discussions about patient selection and appropriate option for fertility preservation.
2	− 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 published this research. I have had no involvement in research on this procedure. Other (please comment): I have read and done bibliographic search on the topic previously.
3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	This is an innovative procedure that should be the standard of care for fertility preservation in young girls. The current standard of care is variable since the procedure is considered 'under research'. Many centres can provide this as 'standard of care', whilst others might not be able to. **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.

4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	This procedure has the potential to be the standard of care for appropriate patients.

Current management

5	Please describe the current standard of care that is used in the NHS.	This procedure is being offered as standard of care in the NHS, but considering it is provided by a few specialist centres, it might be that the standard of care provision is not equitable. Where this is not being offered, young girls would be at a disadvantage with regards to future fertility options.
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	No

Potential patient benefits and impact on the health system

7	What do you consider to be the potential benefits to patients from using this procedure/technology?	This procedure allows young cancer survivors to have the option of fertility preservation for future.
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Pre-pubertal/adolescent young girls diagnosed with cancer and likely to undergo gonado-toxic oncology treatment.
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Yes, it is likely to improve clinical outcomes for young oncology patients and benefit healthcare system. Yes, where appropriately selected, it would mean improved outcomes for fertility.
10 - MTEP	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	It would cost more for cryopreservation and re-implantation of the ovarian tissue. Performing the procedure itself would be the same as current standard of care in terms of staff, equipment, care setting- laparoscopic ovarian tissue removal.
11 - MTEP	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Although, staff training for laparoscopic ovarian tissue removal is not costly, resources will need to be considered in terms of theatre times/space/job plans and staffing. The procedure would need to be performed as an emergency or semi-elective as it would be time crucial to commence oncology treatment without delays. Centres for cryopreservation and re-implantation will need to be considered both in terms of logistics and costs.
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Clinical facilities are theatre time, staff, equipment, recovery post op ward, and provision of transportation of ovarian tissue to the appropriate cryopreservation facility.

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	It is important that any individual performing the procedure is trained for laparoscopic ovarian tissue removal. Cryopreservation of tissue and re-implantation in the future would be dependent upon the centres. Appropriate consent procedures to be followed for removal and storage of ovarian tissue.

Safety and efficacy of the procedure/technology

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Risks of performing an operative laparoscopic surgical procedure: immediate, early and late risks. Potential risk of removing ovarian tissue if oncology treatment is not gonado-toxic. Potential risk of malignant cells in the removed ovarian tissue. Transportation risk of ovarian tissue to suitable cryopreservation site. Risks of cryopreservation of tissue (standard risks with cryopreservation of any gametes). Fertility efficacy of re-implanted ovarian tissue. Malignant risk in the re-implanted ovarian tissue.
15	Please list the key efficacy outcomes for this procedure/technology?	Number of young oncology girls offered/been through this procedure for fertility preservation. Numbers who have had a baby following re-implantation of ovarian tissue (these numbers would be very low as it would be over a period of time).
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Uncertainties about how many use the cryopreserved ovarian tissue in the future. Space needed for cryopreservation.
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	None

18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please 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.

Abstracts and ongoing studies

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	There are publications such as: Transplantation of Transplantation of cryopreserved ovarian tissue in a series of 285 women: a review of five leading European centers. Fertil Steril 2021, 115:1102-1115 Marie-Madeleine Dolmans[1], Michael von Wolff[2], Catherine Poirot[3], Cesar Diaz-Garcia[4], Luciana Cacciottola[5], Nicolas Boissel[6], Jana Liebenthron[7], Antonio Pellicer[8], Jacques Donnez[9], Claus Yding Andersen[10]

Other considerations

21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Considering the incidence of lymphoma alone: over 400 young people aged 15 to 24 are diagnosed with lymphoma; will be atleast 80-100 cases per year who will be eligible for the procedure.
22	Are there any issues with the usability or practical aspects of the procedure/technology?	Resource impact as stated in number 10/11 above.
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	None
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	Keeping a National registry of all cases in the country would be helpful. I am aware the few centres currently doing research do keep their own data.
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late	Beneficial outcome measures: Short-term Number of young girls diagnosed with cancer and offered fertility preservation using ovarian tissue cryopreservation. Long-term Number of young girls subsequently rendered infertile post oncology treatment. Number of patients who use cryopreserved ovarian tissue to achieve pregnancy and their outcomes. Numbers who have premature menopause after removal of an ovary.

	complications. Please state the post procedure timescales over which these should be measured:	Adverse outcome measures: Short-term: surgical complications Long-term: 6 months and 1 year post completion of oncology treatment do fertility check with anti-mullerian hormone. Assess whether treatment offered was needed or not.
26	Is there any other data (published or otherwise) that you would like to share with the committee?	As above in number 20

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	None

NICE National Institute for Health and Care Excellence

Declarations of interests

Please state any potential conflicts of interest relevant to the procedure/technology (or competitor technologies) on which you are providing advice, or any involvements in disputes or complaints, in the previous **12 months** or likely to exist in the future. Please use the NICE policy on declaring and managing interests as a guide when declaring any interests. Further advice can be obtained from the NICE team.

Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Indirect	I do private practice in Reproductive Medicine and Gynaecology, however, none for offering fertility preservation patients/options.		
Non-financial professional	Planning to start the procedure locally.		
Choose an item.			

☒ I confirm that the information provided above is complete and correct. I acknowledge that any changes in these declarations during the course of my work with NICE, must be notified to NICE as soon as practicable and no later than 28 days after the interest arises. I am aware that if I do not make full, accurate and timely declarations then my advice may be excluded from being considered by the NICE committee.

Please note, all declarations of interest will be made publicly available on the NICE website.

Print name:	**Neelam Potdar**
Dated:	**15/11/22**

NICE National Institute for Health and Care Excellence

Professional Expert Questionnaire

Technology/Procedure name & indication: **IP1936 Removal, preservation and re-implantation of ovarian tissue to restore fertility**

Your information

Name:	Paul James Jean-Pierre Hardiman
Job title:	Consultant Gynaecologist and Director of Ovarian Tissue Cryopreservation Service
Organisation:	Royal Free London NHS Foundation Trust
Email address:	[redacted]
Professional organisation or society membership/affiliation:	General Medical Council
Nominated/ratified by (if applicable):	Click here to enter text.
Registration number (e.g. GMC, NMC, HCPC)	2635130

How NICE will use this information: the advice and views given in this questionnaire will form part of the information used by NICE and its advisory committees to develop guidance or a medtech innovation briefing on this procedure/technology. Information may be disclosed to third parties in accordance with the Freedom of Information Act 2000 and the Data Protection Act 2018, complying with data sharing guidance issued by the Information Commissioner's Office. Your advice and views represent your individual opinion and not that of your employer, professional society or a consensus view. Your name, job title, organisation and your responses, along with your declared interests will also be published online on the NICE website as part of the process of public consultation on the draft guidance, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate.

For more information about how we process your data please see our privacy notice.

x☐ I give my consent for the information in this questionnaire to be used and may be published on the NICE website as outlined above. If consent is NOT given, please state reasons below:

Click here to enter text.

Please answer the following questions as fully as possible to provide further information about the procedure/technology and/or your experience.

Please note that questions 10 and 11 are applicable to the Medical Technologies Evaluation Programme (MTEP). We are requesting you to complete these sections as future guidance may also be produced under their work programme.

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology?	I established the Ovarian Tissue Cryopreservation Service at the Royal Free Hospital and have been Director since it opened to referrals in February 2019. The laboratory protocols were developed in close collaboration with Professor Claus Andersen, Copenhagen, where the procedure has been in use since 2000. I supervised the laboratory studies required to obtain HTA approval. The Royal Free Trust has been hugely supportive of the service which is funded entirely by the NHS. We have contract with the North London Consortium and receive referrals from England and Wales. To date we have cryopreserved ovarian tissue from 31 patients and have laboratory capacity to expand ten-fold by recruiting additional scientific staff and a dedicated specialist nurse, once funding is secure. Three of our early patients are now ready for transplantation. Together with two surgical colleagues, including Mr Fevzi Shakir, I visited Aarhus earlier this year to observe three thawing and transplant operations. We are currently performing studies to assess the reproductive potential of tissue stored at the Royal Free and with HTA approval expect to perform the first transplant later this year. The clinical service operates in parallel and is supported by laboratory research designed to improve the efficiency (live birth rate) resulting from ovarian tissue cryopreservation and transplantation. This research is conducted in collaboration with Professor Barry Fuller, Department of Surgical Biotechnology UCL and the Centre for Cell Gene and Tissue Therapeutics, Royal Free Trust. And has been supported by the Royal Free Trust including a PhD fellowship.

	Have you used it or are you currently using it? – Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? – – – – – – – Is this procedure/technology performed/used by clinicians in specialities other than your own? – – – – – – – – – – – If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.	Based on the Danish experience where 13 cryopreservations are performed per million population each year, the need in England is around 845 cases. At least two large fully resourced centres would be required to treat these patients. The technique is used mainly in Denmark for patients with cancer so this estimate of need in the UK does not include procedures done for women with 1. sickle cell anaemia, thalassemia major, aplastic anaemia who require hematopoietic stem cell transplantation 2. autoimmune diseases which fail to respond to immunosuppressive therapy 3. genetic mutations that pose a high risk for premature ovarian failure and in whom no nexperimental fertility preservation procedures are contra indicated. 4. Benign gynaecological diseases which require ovarian surgery such as recurrent endometriomas or ovarian cysts At present oocycte cryopreservation is recommended in preference to tissue freezing in post pubertal girls and women on the basis that it is more efficient (higher live birth rate), the evidence used to support this opinion has been mainly drawn from the use of egg freezing performed for social reasons and compared to tissue freezing performed in cancer patients. This comparison fails to take into account the results of studies which show reduced fertility in female cancer patients compared to healthy controls. We recently published a systematic review and meta-analysis which showed no significant difference in live birth rate between egg and tissue freezing when used in cancer patients. If this finding is confirmed in future studies, post pubertal girls and women may request tissue freezing rather than egg freezing. even now, some centres offer women egg and tissue freezing or tissue freezing combined with in vitro maturation of antral ooctyes which is likely to give a higher probability of live birth than egg or tissue freezing used alone. The main source of referral is from paediatric oncologists but (as above) the procedure is applicable to patients with haematological, rheumatological and genetic conditions. The ovarian Tissue Cryopreservation Service at the Royal Free Hospital received referrals. I established a multi-disciplinary team including fertility specialists and oncologists to assess the suitability of complex cases

2	– Please indicate your research experience relating to this procedure (please choose one or more if relevant):	**I have done bibliographic research on this procedure**. • A literature search following PRISMA guidelines on Embase, Medline, and Web of Science. Studies included reported obstetric outcomes in cancer patients who completed cryopreservation of oocyte, embryo, or ovarian tissue. The total numbers of clinical pregnancies, live births, and miscarriages in women attempting pregnancy using cryopreserved reproductive cells or tissues were calculated. A meta-analysis determined the effect size of each intervention. No significant differences were found among groups. The live birth rates were 25.8%, 35.3%, and 32.3% for oocyte, embryo, and ovarian tissue cryopreservation, respectively, with no significant differences among groups. • A critical appraisal of elective oocyte and elective ovarian cortex cryopreservation cryopreservation for women who use it to mitigate the risk of age related fertility decline. **I have done research on this procedure in laboratory settings (e.g. device-related research).** • The effect of thawing protocols on follicle conservation in human ovarian tissue cryopreservation. Ovarian tissue biopsies from 11 patients were taken with informed consent and divided into four pieces, which were allocated to either fresh assessment or to one of several freeze-thaw protocols. The results showed greatest follicle conservation rates in fresh samples, followed by those thawed using a rapid thawing protocol. Tissue thawed using an ultra fast protocol and slow warming resulted in greater follicle loss. • A study was to test the level of phosphatidylserine phosphatidylserine (the phospholipid component which plays a key role in cell cycle signalling, specifically in regards to necrosis and apoptosis) translocation in frozen human medulla-contained and medulla-free ovarian tissue fragments. The results showed that the presence of medulla in ovarian pieces is beneficial for post-thaw development of cryopreserved human ovarian tissue. **I have published this research.** • Age-related fertility decline: is there a role for elective ovarian tissue cryopreservation? Hum Reprod. 2022 Aug 25;37(9):1970-1979. • A comparison of fertility preservation outcomes in patients who froze oocytes, embryos, or ovarian tissue for medically indicated circumstances: a systematic review and meta-analysis. Fertil Steril. 2022 Jun;117(6):1266-1276.

		• Morewood T, Getreu N, Fuller B, Morris J, Hardiman P. The effect of thawing protocols on follicle conservation in human ovarian tissue cryopreservation. Cryo Letters. 2017 Mar/Apr;38(2):137-144. • Isachenko V, Todorov P, Isachenko E, Rahimi G, Hanstein B, Salama M, Mallmann P, Tchorbanov A, Hardiman P, Getreu N, Merzenich M. Cryopreservation and xenografting of human ovarian fragments: medulla decreases the phosphatidylserine translocation rate. Reprod Biol Endocrinol. 2016 Nov 10;14(1):79.
3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	Ovarian tissue cryopreservation is the only method of fertility preservation for the majority of prepubertal children wo require gonadotoxic treatment for their cancer. Transplantation of cryopreserved ovarian tissue in the human was first performed in 1999 and the first birth in 2004. In 2019, based on many studies showing its effectiveness the American Society for Reproductive Medicine removed the term experimental and acknowledged this method as safe and clinically accepted. **Established practice and no longer new.**
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	The NHS already funds this procedure for many patients (including the local CCG contract with the Royal Free hospital) and by Individual Funding Requests from more distant CCG's but the funding is subject to geographical variation. In our experience some refuse to fund this.

Current management

5	Please describe the current standard of care that is used in the NHS.	The current standard of care is ad hoc funding for children with cancer. On a few occasions we have obtained funding for adults to have both egg and tissue freezing and on occasion tissue freezing for women undergoing repeat ovarian surgery for benign gynaecological disease.
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this?	Egg freezing much more commonly used in postpubertal girls and women facing gonadotoxic treatment but as above, the superiority to tissue freezing is challenged. An important advantage of tissue freezing over egg freezing, is that it restores endocrine function in 90% of cases, removing the need for exogenous hormone treatment.

	If so, how do these differ from the procedure/technology described in the briefing?	

Potential patient benefits and impact on the health system

7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Despite the proven effectiveness of ovarian tissue cryopreservation, around 50% of childhood cancer survivors and families do not recall conversations of fertility during their cancer care National guidelines suggest providers universally discuss fertility with their patients undergoing gonadotoxic treatments. Barriers to wider uptake include lack of awareness on the part of young people and their families, inadequate funding, lack of institution-specific fertility preservation guidelines, poor connections between oncologists, cancer surgeons and fertility specialists. NHS E funding and the establishment of nation centres for OCT will overcome many of these barriers.
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	OCT is the only method of fertility preservation available to prepubertal girls but as discussed above it is also applicable females with haematological diseases who require hematopoietic stem cell transplantation and some with autoimmune diseases, genetic mutations that pose a high risk for premature ovarian failure and those with benign gynaecological diseases which require ovarian surgery.
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Increased provision of OTC will allow more female cancer patients to avoid ovarian failure. It is reasonable to assume that this will result in reduced demand from this patient group for IVF with donor eggs.
10 - MTEP	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Provision of OCT to all female cancer patients for whom egg freezing is not possible, will require the establishment of a second centre in England. This will entail capital costs and ongoing funding. I have not performed a health economic evaluation of the procedure but these will be offset to some degree reduced expenditure on IVF. I suspect that national availability of OCT will have a cost implication for the NHS but I would argue that the current situation where around 400 girls each year undergo treatment leading to irreversible sterility, without their consent, should not be allowed to continue.
11 - MTEP	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about	As above, provision of OCT to all eligible patients who request the procedure, will involve additional cost to the NHS but I am concerned that the present patchy provision, whereby many girls/ women are not told of the risk of sterility or given the opportunity to avoid this complication is unsustainable.

	same-in terms of staff, equipment, and care setting)?	
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Establishment of a OCT second centre in England. This will require an HTA licenced laboratory and an approved Product Preparation Document (PPD) for ovarian tissue cryopreservation, storage and thawing
13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	The procedure requires scientific staff trained to process ovarian tissue. This training would require visit to a centre with experience in OCT, with initial use of animal tissue before human. After completion of the training, the HTA will require validation experiments to show the reproductive potential of tissue processed according to the PPD in the new centre. Clinical staff will need training in the range of fertility preservation procedures so they can give information needed for patients/ families to select the most appropriate method for their circumstances.

Safety and efficacy of the procedure/technology

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	The procedure is not associated with a high risk of harm to the patient. The small risks are associated with the laparoscopy and ovarian cortical biopsy or oophorectomy, subsequent laparoscopy (ies) for transplantation and general anaesthesia.
15	Please list the key efficacy outcomes for this procedure/technology?	1) Endocrine function after transplantation 2) Pregnancy rate after transplantation. 3) Live birth rate after transplantation.
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	More than 200 births have been reported worldwide using OCT. Reported pregnancy and live birth rates are around 50 and 40% respectively but these rates are likely to increase with refinements in laboratory and surgical protocols.

17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	The American Society of Reproductive Medicine, removed the caveat of experimental, for OCT in 2019
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please 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.** Based on practice in many European countries and the USA, laparoscopic tissue retrieval can be carried out by surgeons (with prior training) in hospitals close to the patient. The tissue can be transported without degradation to the specialist laboratory for cryopreservation and storage. When required, the tissue can be transported to a hospital for transplantation but to maximise the chance of pregnancy, the surgical technique of transplantation has to be individualised depending on the patient anatomy, number and size of cortical pieces. For this reason, transplantation should be performed by a team of surgeons with training and ongoing experience. Cannot predict at present.

Abstracts and ongoing studies

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Numerous publication report outcomes of OCT in various centres or networks (which include transport of tissue) worldwide. There are very few publications which compare outcomes of OCT with other methods of fertility preservation. This is important because patients who are suitable for egg freezing are generally advised that the pregnancy rate is higher than with OCT. In my experience, doctors base this advice on results obtained with social egg freezing (in healthy patients) rather than those with cancer (as in report of OCT). The following study (of which I am a joint author) provides a more meaningful comparison and found no difference in outcome between egg freezing and OCT. *Ní Dhonnabháin B, Elfaki N, Fraser K, Petrie A, Jones BP, Saso S, Hardiman PJ, Getreu N. A comparison of fertility preservation outcomes in patients who froze oocytes, embryos, or ovarian tissue for medically indicated circumstances: a systematic review and meta-analysis. Fertil Steril. 2022 Jun;117(6):1266-1276.*

20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	I am not aware of any but there may be some.

Other considerations

21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	840 (based on 13/ million population)
22	Are there any issues with the usability or practical aspects of the procedure/technology?	OCT has applications beyond children with cancer but the efficiency and cost effectiveness in these situations are less well established.
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	The current barriers relate to patient and clinician awareness, variability of funding between CCG's and lack of laboratory capacity
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	The efficacy of OCT could be increased by in vitro-maturation of immature oocytes collected during ovarian tissue preparation prior to ovarian cortex cryopreservation (OTO-IVM). The first live births from ovarian tissue oocytes were reported after monophasic OTO-IVM, showing the ability to achieve mature OTO-IVM oocytes. However, fertilisations rates and further embryological developmental capacity appeared impaired. The introduction of capacitation, has been a significant improvement of the oocytes maturation protocol. However, studies are required including follow-up of OTO-IVM children.
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most	Beneficial outcome measures: Graft survival (longitudinal endocrine data). Pregnancy rates with OCT alone and with OTO-IVM Live birth rates with OCT alone and with OTO-IVM x

	appropriate method of measurement for each and the timescales over which these should be measured. – Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured:	Adverse outcome measures: OCT alone and with OTO-IVM
26	Is there any other data (published or otherwise) that you would like to share with the committee?	None in addition to that on this form or in the public domain.

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	I have been researching Oct since 2015. I obtained authority from the HTA, developed the protocols in collaboration with Professor Andersen and Dr Kristensen in Copenhagen and established the NHS funded OCT service at the Royal Free Hospital which opened in February 2019. I am Director of this service which receives referrals from CCG's in England and Wales.

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Declarations of interests

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Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Choose an item.	None		
Choose an item.			
Choose an item.			

X☐ I confirm that the information provided above is complete and correct. I acknowledge that any changes in these declarations during the course of my work with NICE, must be notified to NICE as soon as practicable and no later than 28 days after the interest arises. I am aware that if I do not make full, accurate and timely declarations then my advice may be excluded from being considered by the NICE committee.

Please note, all declarations of interest will be made publicly available on the NICE website.

Print name:	**Paul Hardiman**
Dated:	**14/11/2022**

NICE National Institute for Health and Care Excellence

Professional Expert Questionnaire

Technology/Procedure name & indication: IP1936 Removal, preservation and re-implantation of ovarian tissue to restore fertility

Your information

Name:	Richard Anderson
Job title:	Professor of Clinical Reproductive Science
Organisation:	University of Edinburgh
Email address:	[redacted]
Professional organisation or society membership/affiliation:	BFS
Nominated/ratified by (if applicable):	BFS
Registration number (e.g. GMC, NMC, HCPC)	GMC 3353567

How NICE will use this information: the advice and views given in this questionnaire will form part of the information used by NICE and its advisory committees to develop guidance or a medtech innovation briefing on this procedure/technology. Information may be disclosed to third parties in accordance with the Freedom of Information Act 2000 and the Data Protection Act 2018, complying with data sharing guidance issued by the Information Commissioner's Office. Your advice and views represent your individual opinion and not that of your employer, professional society or a consensus view. Your name, job title, organisation and your responses, along with your declared interests will also be published online on the NICE website as part of the process of public consultation on the draft guidance, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate.

For more information about how we process your data please see our privacy notice.

☒ I give my consent for the information in this questionnaire to be used and may be published on the NICE website as outlined above. If consent is NOT given, please state reasons below:

Click here to enter text.

Please answer the following questions as fully as possible to provide further information about the procedure/technology and/or your experience.

Please note that questions 10 and 11 are applicable to the Medical Technologies Evaluation Programme (MTEP). We are requesting you to complete these sections as future guidance may also be produced under their work programme.

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it? − Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? − Is this procedure/technology performed/used by clinicians in specialities other than your own? − If your specialty is involved in patient selection or referral to another specialty for this	I have been involved in this procedure for 25 years Currently using. We are the only centre doing this in Scotland. There is very limited availability in the NHS.

	procedure/technology, please indicate your experience with it.	
2	– 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. I have published this research. Other (please comment)
3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	There is no comparable standard of care Definitely novel and of uncertain safety and efficacy.
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	

Current management

5	Please describe the current standard of care that is used in the NHS.	n/a as not generally available

6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	For adult women egg/embryo freezing is available

Potential patient benefits and impact on the health system

7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Only option for pre/peripubertal girls Offers option of natural conception Provides hormone replacement
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Prepubertal girls
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	n/a
10 - MTEP	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	n/a
11 - MTEP	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	More, as no really comparable current option
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Overall it involves patient assessment/surgical procedure/tissue storage/2nd surgical procedure thus operating theatres and a tissue bank are the key aspects, in addition to normal clinical facilities.

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	As with any surgical procedure. Also the whole approach will require multidisciplinary review/discussion of potentially appropriate patients.

Safety and efficacy of the procedure/technology

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Surgical risk Unnecessary intervention Replacement of malignant cells-recurrence of cancer
15	Please list the key efficacy outcomes for this procedure/technology?	Successful tissue storage Successful replacement: ovarian function, pregnancy Patient assessment: prevalence of ovarian function/fertility after tissue removal
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Unknown efficacy in prepubertal girls
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	As 16; appropriate patient selection
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	A minority of hospitals, but at least 10 in the UK: yes for removal Fewer than 10 specialist centres in the UK: yes for replacment

Abstracts and ongoing studies

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	

Other considerations

21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Several hundred per year across UK
22	Are there any issues with the usability or practical aspects of the procedure/technology?	Need for licensed tissue bank
23	Are you aware of any issues which would prevent (or have prevented) this	

	procedure/technology being adopted in your organisation or across the wider NHS?	
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	Lots! Relating to appropriate patient population, the procedures themselves, optimising tissue freezing.
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured:	Beneficial outcome measures: Procedure completion rates Time interval from referral Reimplantation: ovulation, pregnancy, duration of function (up to years) Adverse outcome measures: Surgical complications Lack of return of ovarian function/fertility
26	Is there any other data (published or otherwise) that you would like to share with the committee?	

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	We have been undertaking this for many years for highly selected patients, mostly girls/adolescents, with some adults. We have had 1 successful pregnancy.

NICE National Institute for Health and Care Excellence

Declarations of interests

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Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Choose an item.	None		
Choose an item.			
Choose an item.			

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Please note, all declarations of interest will be made publicly available on the NICE website.

Print name:	**Richard Anderson**
Dated:	**4/11/22**

NICE National Institute for Health and Care Excellence

Professional Expert Questionnaire

Technology/Procedure name & indication: IP1936 Removal, preservation and re-implantation of ovarian tissue to restore fertility

Your information

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Nominated/ratified by (if applicable):	British Fertility Society
Registration number (e.g. GMC, NMC, HCPC)	GMC 3442201

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x☒ I give my consent for the information in this questionnaire to be used and may be published on the NICE website as outlined above. If consent is NOT given, please state reasons below:

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Please answer the following questions as fully as possible to provide further information about the procedure/technology and/or your experience.

Please note that questions 10 and 11 are applicable to the Medical Technologies Evaluation Programme (MTEP). We are requesting you to complete these sections as future guidance may also be produced under their work programme.

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology?	I have been involved with the development of the Oxford Fertility programme for children and young adults since 2008. I became the Programme Lead in 2014. This amazing programme offers fertility advice to children and young adults at risk of infertility. We also offer reproductive tissue storage and use to patients who are at high risk of infertility but are too young or are unable to store mature gametes. We launched the full programme in 2013. The programme offers treatment to young people across England , Wales and Northern Ireland via a Hub and Spoke Model. This enables patients to have surgery to remove tissue as local to home as safely possible and for the knowledge base and tissue storage to occur centrally. In Oxford my surgical colleges, Professor Kokila Lakhoo (Paediatric Surgeon) and Professor Christian Becker (Young Adult Gynaecologist) perform the surgery for removal of tissue. Since 2013 we have stored tissue for around 1000 young girls. Most of the young people are too young to have a wish to start a family but we have re-implanted tissue for 5 patients. $ have regained their hormone function and we have had one live birth and two on going pregnancies. My colleague professor Becker is the surgeon who auto transplants tissue in Oxford
	Have you used it or are you currently using it? – Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake?	The Oxford Programme is the main fertility preservation programme in the UK. We work closely with colleagues in Edinburgh who have run a fertility preservation research programme for children and young adults since 1997. We participate in National and International meetings, and research programmes and have close ties with leaders of similar programmes in Europe, Scandinavia, Israel, and USA.

	− Is this procedure/technology performed/used by clinicians in specialities other than your own? − If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.	All referrals for tissue storage from centres across the country are reviewed in Oxford to ensure that we are offering tissue storage to patients who fall within the programme eligibility criteria.. Alongside colleagues from Scotland, I have authored the UK CCLG Onco fertility Guidelines and been part of the Group that wrote the Oncofertility Guidance for adults Professor Becker and I run a bi-weekly clinic in which we see any child or young adult who is at risk of infertility and advise on potential options. This clinic is where we see patients when they wish to have tissue auto transplanted and discuss the risks and benefits and organise all investigations.
2	− 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 co supervised 2 research PhD students in work related to this area. I have co-authored chapters for several books on fertility preservation for children and young adults and have around 50 peer reviewed publications in this area. I am co PI on three research projects with international funding .
3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	Ovarian Tissue cryopreservation and auto-transplantation of tissue is no longer considered an experimental procedure. The first live birth from auto transplanted tissue occurred in 2004 in Belgium and since then there have been many more births. Whilst egg and embryo freezing are still first line treatment ,where this is not possible due to age or the urgency to start treatment , storage of ovarian tissue offers a very good alternative treatment option. Established practice and no longer new.
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	It would compliment the existing treatments of egg and embryo storage

Current management

5	Please describe the current standard of care that is used in the NHS.	The current standard of fertility preservation treatment for adult patients who have time prior to starting gonadotoxic treatment would be storage of eggs and embryo. Ovarian tissue storage is only offered in a few centres with Oxford being the main centre in England, Wales and Northern Ireland. Care is offered in a hub and spoke model with surgery to remove tissue being done as local to home as possible. Tissue re-implantation is mainly offered through Oxford . NHSE funding is currently being negotiated
6	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	For children and young adults who either due to age or the urgency to start cancer treatment cannot store eggs or embryos there is no alternative treatment options

Potential patient benefits and impact on the health system

7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Fertility preservation so that they can have a family when they become adults Hope for a future and that the future will be as as normal as possible post cancer treatment Reduces the stigma and mental health issues associated with infertility at a very young age Reduces the need for hormone replacement therapy as hormone function is restored
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Children and young adults with cancer prior to high dose chemotherapy or pelvic radiotherapy Children receiving a stem cell transplant for cancer and non-cancer reasons eg sickle cell disease Children with chromosomal abnormalities that lead to early premature ovarian insufficiency
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	The procedure most definitely changes the current pathway and clinical outcomes and has direct and indirect health care benefits. Patients who have had tissue stored are more able to see a positive future, have less mental health problems , make friendships and relationships. They are more able to meet their potential in life and to need less support and help
10 - MTEP	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	NHSE Commissioning work is currently underway to look at this area
11 - MTEP	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	NHSE Commissioning work is currently underway to look at this area

12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	The collection, storage and distribution of reproductive tissue is regulated by the Human Tissue Authority. To obtain an HTA licence for this work requires a site offering this treatment to have facilities to process the tissue that comply to the HTA safety and quality standards and who hold a Human Sector HTA Licence. It is envisaged that there will be 2 or 3 Hub sites that process and store tissue and each hub site will have a number of spoke/satellite sites where tissue is collected. This work needs to be based in a main NHS facility as it requires surgery under GA for children and young adults.
13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	The removal and auto-transplantation of ovarian tissue uses standard laparoscopic procedures that should be available in all children's hospitals and main gynaecology units. Processing of tissue requires laboratory skills and pathology facilities

Safety and efficacy of the procedure/technology

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	The procedures require laparoscopic surgery under general anaesthetic. The patients must be carefully assessed to ensure that they are fit for a general anaesthetic and that any marrow disfunction can be managed. Laparoscopic surgery carries a small (1 in 100 – 1000) risk of internal organ damage and with all surgery there is the risk of bleeding and infection Delay to the start of cancer treatment but this is much less of a problem with tissue storage that egg or embryo storage Risk of micro-metastatic contamination of the ovarian tissue from the original malignancy
15	Please list the key efficacy outcomes for this procedure/technology?	Live birth rate Pregnancy rate Endocrine function restoration

16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	The loss of follicles that occurs during auto-transplantation In adults whether the whole ovary or strips would be the best technique – in children the ovary is very much smaller than in adults and so whole ovary removal is the favoured option Size and number of strips to be stored The surgical technique across the country is not standardised and the thermal coagulation equipment used will cause variable amounts of damage to the tissue
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Established technology across the world
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Children and TYA centres are equipped to remove tissue – there are 14 such centres across the UK. 2/3 Hub centres to coordinate policy and standards and to store tissue 2/3 Hub auto transplant sites

Abstracts and ongoing studies

19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	There is extensive literature International Society for Fertility preservation biannual Conference Brussels Nov 10 12th 2022 – Most up to date information on all aspects of the subject 1.Mulder RL, Font-Gonzalez A, Hudson MM, van Santen HM, Loeffen EAH, Burns KC, et al. Fertility preservation for female patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. The Lancet Oncology. 2021 Feb;22(2):e45–56. 2.Anderson RA, Amant F, Braat D, D'Angelo A, Chuva de Sousa Lopes SM, Demeestere I, et al. ESHRE guideline: female fertility preservation†. Human Reproduction Open. 2020 Oct 3;2020(4). 3. Donnez J, Dolmans MM Fertility Preservation in Women. New England Journal of Medicine. 2017 Oct 26;377(17):1657–65. 4. Dolmans MM, Manavella DD. Recent advances in fertility preservation. Journal of Obstetrics and Gynaecology Research. 2019 Feb;45(2):266–79.

20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	UK Store is a registry being set up in UK for children and young adult tissue storage

Other considerations

21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Estimated to be around 500 female patients per year for storage – the auto transplantation will build up over time as more of the children become of child bearing age.
22	Are there any issues with the usability or practical aspects of the procedure/technology?	The Programmes need to be centralised. Storage must be in Grade A air quality facilities under an HTA licence
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Money – we need NHSE specialised funding as this should be seen as an integral part of cancer care . The Oxford prograqmme has been possible through charitable monies
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	It is essential that any programme for storage of tissue is linked to an active research programme. The patient s donate up to 10% tissue for research and ther are many areas where future advances will significantly improve the treatment
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: – Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most	Beneficial outcome measures: Live birth rates Endocrine restoration rates Quality of life questionnaires Surgical technique improvement Processing technic improvement

	appropriate method of measurement for each and the timescales over which these should be measured. – Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured:	Potentially vitrification of tissue rather than slow freezing Adverse outcome measures: Intra operative complications Infections/bleeding post op Delay in chemotherapy due to surgical complications Tissue usability due to adverse risk factors
26	Is there any other data (published or otherwise) that you would like to share with the committee?	n/a

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	This programme has already made a significant difference to many young people who have hope that they will not only survive cancer but that life after cancer will be of good quality , full of the same opportunities as their peers – the programme and this technology has been lifesaving – about 20% cancer patients that develop premature ovarian failure contemplate suicide and serious mental health problems. Without tissue storage they have no self-worth, feel they are 'un-loveable' and some go on to take their own lives.

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Declarations of interests

Please state any potential conflicts of interest relevant to the procedure/technology (or competitor technologies) on which you are providing advice, or any involvements in disputes or complaints, in the previous **12 months** or likely to exist in the future. Please use the NICE policy on declaring and managing interests as a guide when declaring any interests. Further advice can be obtained from the NICE team.

Type of interest *	Description of interest	Relevant dates	
		Interest arose	Interest ceased
Choose an item.			
Choose an item.			
Choose an item.			

☒ I confirm that the information provided above is complete and correct. I acknowledge that any changes in these declarations during the course of my work with NICE, must be notified to NICE as soon as practicable and no later than 28 days after the interest arises. I am aware that if I do not make full, accurate and timely declarations then my advice may be excluded from being considered by the NICE committee.

Please note, all declarations of interest will be made publicly available on the NICE website.

Print name:	**Dr Sheila Lane**
Dated:	**09/11/2022**