NICE National Institute for Health and Care Excellence

Professional Expert Questionnaire

Technology/Procedure name & indication: **IP1804 Removal, preservation and subsequent re-implantation of ovarian tissue to delay the menopause**

Your information

Name:	Yousri Afifi
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Nominated/ratified by (if applicable):	Click here to enter text.
Registration number (e.g. GMC, NMC, HCPC)	4707497

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interests will also be published online on the NICE website as part of the process of public consultation on the draft guidance, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate.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 am familiar with the procedure and currently provide the procedure within its recommended aspects It is used for cancer patient in reproductive age all over the world My speciality are dealing with selection and performing the 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. I have done clinical research on this procedure involving patients or healthy volunteers. 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):	Established practice for certain group of patients with known efficacy. Extension of the existing technology to be used other group of patient with shared decision making process
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?	yes

Current management

5	Please describe the current standard of care that is used in the NHS.	No provision of protection from early menopause (1%) HRT only for management of menopause (10-20% lack of compliance)
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?	HRT as above

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?	Prolong the ovarian function using the abundant ovarian reserve without compromise the fertility or natural ovarian age. This is for fertility restoration and hormonal restoration. Opportunity to change the women fifty to be similar to her thirty or forty.
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Patient less than 40 years of age
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 can reduce the need of clinical support to manage the menopause and its clinical implications.
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)	With the consideration of long term benefits it will cost less
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)?	Provide the procedure in the opportunistic model during other surgery with access to abdominal cavity will be very cost effective
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Tissue freezing lab

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Lab training and surgical training

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	Risk of laparoscopy in primary procedure Risk of bleeding (rare) Risk of infection (uncommon) Risk of adhesions (minimal as the surgery is unilateral)
15	Please list the key efficacy outcomes for this procedure/technology?	Fertility and hormonal restoration
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Persistent function for enough time
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Graft survival
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. 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.	We did a systematic review that has been accepted for publication in Human Reproduction
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Our service is on annual audit

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)?	It depends on inclusion
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?	Just that it is a novel concept

24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	Keep the audit for prospective evaluation
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: Complication of the retrieval process Fertility outcome Hormonal restoration and quality of life Adverse outcome measures: 6 month following the retrieval 5 years following the grafting

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	The technology is used currently clinically proven technology for fertility preservation as it is biologically impossible for fertility to be restored without hormonal restoration

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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.	I am the CMO of ProFaM a company that offer private ovarian tissue freezing	**2020**	
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:	**Click here to enter text.Yousri Afifi**
Dated:	**Click here to enter text.17/1/2022**

NICE National Institute for Health and Care Excellence

Professional Expert Questionnaire

Technology/Procedure name & indication: **IP1804 Removal, preservation and subsequent re-implantation of ovarian tissue to delay the menopause**

Your information

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Job title:	Consultant Gynaecologist; Honorary Associate Professor
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Professional organisation or society membership/affiliation:	British Menopause Society; elected to Medical Advisory Council 2015-2018, re-elected 2018-2021. British Fertility Society; Chair of special interest group for Fertility Preservation, co-opted member of Executive Committee
Nominated/ratified by (if applicable):	n/a
Registration number (e.g. GMC, NMC, HCPC)	GMC 2497138

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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? 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.	I am familiar with the technology of ovarian tissue removal, preservation and subsequent reimplantation. The technology is currently used in the context of fertility preservation for young women and girls undergoing treatment for medical conditions which may impair fertility. Ovarian tissue removal is undertaken before treatment for cancer (eg intensive chemotherapy or pelvic radiation) or less commonly for benign disease (eg bone marrow transplant for thalassaemia major). Regrafting tissue aims to restore fertility. The technology is not currently used in healthy women. It is not used to delay the menopause. As a consultant gynaecologist with a particular interest in oncofertility, I am personally involved in advising clinicians and counselling patients on the value of ovarian tissue storage. In the past I have undertaken laparoscopic procedures for removal of ovarian tissue, and I now work very closely with colleagues to offer this service. The procedure is not commonly performed in the UK and few units have the necessary HTA licence to process and store tissue. There are two leading cryostores in the UK, the largest in Oxford which is charitably funded, and the other in Edinburgh which is MRC funded. Both are dedicated to fertility preservation. NHS funding for this procedure is extremely limited; in 2020 we surveyed clinical commissioning groups in England and only 9 of 129 funded ovarian tissue cryopreservation (referenced below). It is under consideration by NHS England. Scotland provides funding for cryopreservation of gametes, embryos, ovarian and testicular tissue for medical reasons. Provision of a service for ovarian tissue storage requires collaboration between oncologists, fertility specialists, gynae laparoscopic surgeons and laboratory scientists.

		The procedure is not undertaken by clinicians in other specialties.
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 took part in research appraisal to assess the value of this procedure for fertility preservation, as a member of the guideline group producing *Fertility preservation for medical reasons in girls and women: British Fertility Society policy and practice guideline* https://www.tandfonline.com/doi/full/10.1080/14647273.2017.1422297 Please note the conclusion of the BFS guideline (2018): "OTC is still not an established treatment and as such, should only be offered by units with relevant clinical and laboratory expertise, protocols and HTA licensing or associated with an established unit using a third-party arrangement. NHS trusts also require local governance requirements to be satisfied before a new procedural technique is introduced." I am involved in research on treatments for menopause symptoms. I also took part in research appraisal as a member of the NICE guideline group *Menopause: diagnosis and management* https://www.nice.org.uk/guidance/ng23 In my opinion there is no adequate research base to support the claim that this technique will 'delay the menopause'. There are no data in healthy women. In the context of fertility preservation, we know that reimplanting ovarian tissue will lead to successful regrafting in most cases, with resumption of ovulation and endocrine function, removing the need for hormone replacement therapy. However, this is often short-lived. Duration of function relates to the number of follicles in the tissue. Ovarian follicle number declines as women age, in addition, there is substantial follicle loss during freeze-thaw-regraft (loss of about 40% of follicles) which impacts ovarian reserve. Efficacy therefore depends on age at the time of storage.
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 reimplantation of ovarian tissue with the aim of delaying menopause is novel. 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?	In my opinion it neither has the potential to replace current standard care nor would be used as an addition to standard care.

Current management

5	Please describe the current standard of care that is used in the NHS.	There is no treatment to “delay the menopause”. Advice can be given on environmental and lifestyle factors (eg smoking) which play a small part. Women experiencing menopausal symptoms can access a range of treatments, both pharmacological and non-pharmacological. Hormone replacement therapy is the most effective. HRT is available through the NHS in primary and secondary care.
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?	As explained above, potential benefits of endogenous hormones are similar to exogenous HRT.
8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Not applicable – this proposal is not targeted at patients
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?	No
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)	More – it requires at least two surgical procedures and long-term cryostorage in a specialist facility. Most women undergoing menopause do not engage with health services, and for those that do, HRT requires only outpatient attendance, usually in a community setting.
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)?	As 10 above
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	As 1 above

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Yes

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 complications during laparoscopy: infection, bleeding, venous thromboembolism, damage to bowel / bladder / blood vessels which may require further surgery. Minor complication rate is estimated at 1-2:100 and major complication rate 1:1000 Anaesthetic complications Risk of unintended pregnancy (depending on the graft site), need for contraception Restoration of menstrual periods – some women may consider this an unwanted outcome
Quire lapair	Please list the key efficacy outcomes for this procedure/technology?	In the current proven use of this technology for fertility preservation, outcome is assessed by pregnancy. In the proposed use 'to delay menopause', I suppose the outcome measure would be physiological levels of ovarian hormones
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Undertaking invasive surgical procedures in a healthy woman seems inappropriate when there is no evidence of benefit. There are no data in healthy women. There is very little information on endocrine outcomes in the current context of young cancer patients. The implications of removing ovarian tissue in healthy women need to be considered. Given the degree of follicle loss, it is likely that tissue removal would need to be done aged <35,

		preferably earlier, and a whole ovary would need to be removed rather than small biopsies. This is particularly challenging before completion of family.
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	This is a highly controversial proposal put forward by a commercial clinic. It has been introduced without supportive data. There has been no endorsement from professional societies, and indeed the proposal was met with a highly critical response. The company's website promotes tissue storage 'to provide your own, natural hormones … for an additional 10 or 20 years'. There is no documentation as far as I am aware of any ovarian tissue graft lasting 20 years, so this statement is misleading. '…your own, natural hormones' is an attractive concept, but there is no information given on the alternative, i.e. exogenous hormone replacement therapy, for women to make an informed choice. HRT is highly effective and has been extensively studied, so the risks and benefits are well documented; it is far cheaper than private surgery and cryostorage.
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	n/a

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	Abstract (oral presentation) on NHS funding for ovarian tissue storage referenced in question 1: https://fertilityconference.org/wp-content/uploads/2021/01/Fertility-2021-Abstract-book_with-deleted-ones.pdf SP1.1 page 7 Pre-print article on ovarian graft longevity (case series) https://pubmed.ncbi.nlm.nih.gov/33078972/#&gid=article-figures&pid=fig-1-uid-0

	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.	n/a There are registries of ovarian tissue storage for fertility preservation eg FertiProtekt

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)?	As menopause is universal there is a large target population
22	Are there any issues with the usability or practical aspects of the procedure/technology?	As 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?	As above
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	As above. Further work is needed on the endocrine outcomes of ovarian tissue regrafting, the adequacy of endogenous hormone production, the duration of endocrine function, and the optimal protocols for pre-procedure assessment / biopsy size / regrafting technique and site.
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: See above

	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: See above for risks of procedure

Further comments

26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	The media have extensively reported this proposal. It may be enlightening for the committee to access some of these articles eg Sunday Times 4 Aug 2019 contains several pieces and a number of readers' comments. I have been approached on several occasions to contribute on behalf of professional societies / Science Media Centre. In my opinion, it is inappropriate to undertake this procedure currently outside a research setting, and it is unethical to charge women for unproven procedures.

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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.

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Print name:	**MELANIE DAVIES**
Dated:	**28 Dec 2021**