# Background to the novel process application for Anecova AneVivo Intrauterine device

<table>
<thead>
<tr>
<th>Strategic delivery:</th>
<th>Safe, ethical, effective treatment</th>
<th>Consistent outcomes and support</th>
<th>Improving standards through intelligence</th>
</tr>
</thead>
</table>

## Details:

- **Meeting**: Scientific and Clinical Advances Advisory Committee (SCAAC)
- **Agenda item**: 5
- **Paper number**: SCAAC (08/06/2020) 005
- **Meeting date**: 08 June 2020
- **Author**: Victoria Askew, Policy Manager

## Output:

- For information or recommendation? For recommendation
- **Recommendation**: Member are asked to consider:
  - whether the process outlined in this application is sufficiently different from the processes currently authorised as to be considered ‘novel’
  - whether there is evidence that this process is not effective
  - whether there is evidence that this process is not safe

- **Resource implications**: N/A
- **Implementation date**: N/A
- **Communication(s)**: N/A
- **Organisational risk**: ☒ Medium

- **Annexes**
  - Annex A: Novel process application – IVF using the AneVivo device in interpartner and standard egg donation
  - Annex B: Supporting information
  - Annex C: Novel processes authorisation decision tree
1. **Background – authorised processes and the role of SCAAC**

1.1. A list of authorised processes, approved by the Authority, are available on the HFEA Clinic Portal, organised under licensable activities permitted by the HFE Act 1990 (as amended). Fertility clinics that hold a license with the HFEA are permitted to undertake the appropriate authorised processes, in accordance with their licence, as part of their clinical practice. If a centre wishes to use a 'novel process' which does not appear on the authorised list, they need to apply to the HFEA to seek permission to use it in clinical practice.

1.2. The Authority has delegated the authorisation of novel processes to the Statutory Approvals Committee (SAC), who are advised on the matter by SCAAC (Annex C). The role of the SCAAC is to review the novel process applications and provide an opinion to the SAC on the following questions:

- whether there is evidence to suggest the process is not safe; and
- there is evidence to suggest that the process is not effective.

1.3. SAC can make the following decision options:

- Refuse authorisation
- Adjourn decision in order to seek further information
- Authorised for use at all centres
- Authorised for use at named centres only
- Refer to the Authority for final decision

1.4. On approval, the process is labelled as ‘recently approved’ for the first two years and centres that would like to use the process have to inform the HFEA. At the end of the two years all centres using the process should submit an outcome report to the HFEA on safety and efficacy.

1.5. An application (Annex A) has been received for the extension of the use of the current authorised process intrauterine culture to allow the device to be used between different women. This would allow the eggs donated by a partner or donor to be inserted into a second partner or recipient for incubation. The process is currently only authorised for use in a single woman.

2. **Executive Summary – previous information relevant to this application**

2.1. In June 2015, a novel processes application for the intrauterine culture of gametes and embryos (including insertion and removal of device, followed by transfer of embryo(s) to the same woman) was discussed by SCAAC. SCAAC made the following comments:

- Due to the limitations of the data provided the Committee felt that they could not make an assessment of the efficacy of the process. However, the Committee noted that Anecova AneVivo intrauterine device has been used in for treatment in three European countries resulting in a number of live births, suggesting that it is sufficiently effective to give successful IVF outcomes some of the time.
The Committee agreed that insufficient evidence was provided in the application to determine whether intrauterine culture of gametes and embryos in a device such as the Anecova AneVivo intrauterine device is safe.

2.2. This meeting was followed up by a teleconference between the applicant and SCAAC to provide further evidence on the process. SCAAC made the following conclusions:

- there is no evidence to show that the device is not unsafe; and
- that the clinical data on the device is too limited to demonstrate its efficacy, but there is no evidence to indicate that the process is not effective.

2.3. In July 2015, further data was submitted by the applicant to reassure SCAAC of retrieval rates of the embryo used during this process.

2.4. In August 2015, the SAC considered the application and noted that SCAAC’s consideration was as follows:

- The use of intrauterine culture devices did constitute a novel process;
- The process applied for falls within two licensable activities: processing gametes and processing embryos;
- The evidence provided gave no indication that the process is unsafe;
- SCAAC did not see any evidence to suggest that intrauterine culture of gametes/embryos using a device such as the Anecova AneVivo would not be effective. However, it did not feel that there was sufficient clinical data to say whether the process has a greater or lesser efficacy than that of traditional IVF methods.

The SAC approved the application for the intrauterine culture of gametes and embryos (including insertion and removal of device, followed by transfer of embryo(s) to the same woman) by majority and the process was subsequently added to the authorised processes list. In agreeing to authorise the novel process, the SAC agreed with SCAAC’s observation that, as it is possible that the process might offer no improvement in efficacy and might add an unnecessary cost to patients, any patient information provided by clinics should highlight this. In addition, information on the HFEA website should draw attention to the fact that the process has not yet been subject to a clinical trial, and its efficacy is therefore not known.

2.5. In line with Authority’s standard operating procedure for reviewing novel processes, in February 2018, SCAAC reviewed an outcomes report provided by the applicant two years after the process’s initial approval. SCAAC were asked to provide an opinion as to whether they had any concerns that intrauterine culture should be removed from the authorised process list. In agreeing to authorise the novel process, the SAC agreed with SCAAC’s observation that, as it is possible that the process might offer no improvement in efficacy and might add an unnecessary cost to patients, any patient information provided by clinics should highlight this. In addition, information on the HFEA website should draw attention to the fact that the process has not yet been subject to a clinical trial, and its efficacy is therefore not known.

2.6. In October 2018, Professor Nick Macklon attended the SCAAC meeting to update the Committee on activity since the novel process application was approved in 2015. Prof Macklon and the Committee made the following comments:
• Prof Macklon stressed that the treatment is not currently offered to improve pregnancy rates or to benefit the embryo, rather the claimed benefits to the woman are psychological as she can be more physically involved in the process.

• Two factors led to the introduction of the intrauterine culture technique being deprioritised. Training took place before the procedure was ready to be offered to patients. Prof Macklon at that point left the centre and the Trust then began the process of selling the clinic to a private investor.

• Data from use of the device in Spain will be presented at Fertility 2019. Prof Macklon asked the Committee to consider whether there is sufficient data to allow continued use of the device in the UK subject to further review in 2 years’ time from now once there is more data. This outcome report is due to be submitted to the HFEA by the end of 2020. It is intended that this report will be presented to SCAAC for consideration at the October 2020 meeting.

• A member asked about pre-clinical experience with the device using human embryos donated to research. Prof Macklon addressed that this has not progressed due to the lack of embryos donated for research for this purpose.

• SCAAC concluded that the Executive will follow up with Prof Macklon to review the patient information relating to intrauterine culture.

2.7. In January 2019, the applicant shared slides on new data regarding the technique that had been presented at the Fertility 2019 conference, however the SCAAC suggested that this was not sufficient and additional data would still be needed for SCAAC to review whether intrauterine culture should remain on the list of approved novel processes.

2.8. In December 2019 it was reported in the press that a same sex couple undergoing partner donation during their IVF treatment had used intrauterine culture. Reported as ‘shared motherhood’ this allowing both partners to ‘carry’ the pregnancy at some point during their treatment. This did not fall under the authorised process, which only allowed intrauterine culture to take place in a single women. Due to concerns over infection risk the centre were contacted by their HFEA inspector about their misuse of this authorised process.

2.9. In January 2020, a novel processes application was received for intrauterine culture of gametes and embryos (including insertion and removal of device, followed by transfer of embryo(s) between different women). This would extend the use of the intrauterine device to lesbian couples undergoing partner donation and to recipients of donor eggs.

2.10. Of note, the applicant has made no claim that this treatment is intended to increase live birth rate. It is instead intended to mimic a more ‘natural’ environment, reduce the exposure to synthetic in vitro culture media and give some psychological benefits to patients. However, SCAAC have previously commented that the device does not mimic ‘natural’ development as the embryo would usually be in the fallopian tubes in the early stages of development, rather than the womb.

3. Conclusion

3.1. An application has been received for the extension of the use of the current authorised process intrauterine culture to allow the device to be used between different women. This would allow the eggs donated by a partner or donor to be inserted into a second partner or recipient for incubation. The process is currently only authorised for use in a single woman.
3.2. SCAAC has previously raised concerns about the lack of available data on the effectiveness and safety of intrauterine culture

4. Recommendations

4.1. Members are asked to consider:
- whether the process outlined in this application process is sufficiently different from the processes currently authorised as to be considered ‘novel’; and
- whether there is evidence that this process is not effective; and
- whether there is evidence that this process is not safe.
Annex A (Application form)

Human Fertilisation & Embryology Authority

Application to carry out a licensed activity using a novel process

1. Introduction

The HFEA publishes a list of authorised processes on its website (https://portal.hfea.gov.uk/knowledge-base/other-guidance/authorised-processes/), with the processes arranged under each of the licensable activities permitted by the Act.

In order for a centre to carry out a process which does not appear on the list, it must apply to the Authority for permission to perform the novel process.

This application from should be used by centres that wish to carry out a licensed activity using a process that has not previously been authorised by the Authority.

Note: Please note if you plan to implement this novel process as part of a clinical trial.

The authorisation process

Applications will be reviewed by the HFEA’s Scientific and Clinical Advances Advisory Committee (SCAAC) who will:

- consider whether the process is novel;
- provide a view on which licensed activity/activities the process should fall under;
- consider whether there is evidence to suggest that the process is not effective; and
- consider whether there is evidence to indicate that the process is unsafe (either to patients or embryos).

It is therefore important that applications contain sufficient evidence to allow the committee to make an assessment of the safety and efficacy of the process. If the committee has not been provided with sufficient evidence they may adjourn their decision until additional information has been provided, which will delay processing of the application.

Once SCAAC has made an assessment of the application, the committee will provide advice on the safety and efficacy of the process to our Statutory Approvals Committee (SAC).

The Statutory Approvals Committee will then decide whether or not to add the process to the authorised processes list. If it decides that it should, any clinic or laboratory may use the process, provided they are licensed to carry out the associated licensed activity.

It is important that the language used in this application is clear and as far as possible, understandable to non-specialists. All abbreviations should be explained.
2. **Novel process details**

2.1. What is the name of the process?

   In-vivo fertilization using the AneVivo device in inter-partner and standard egg donation

2.2. To which cell type(s) is the process applied?

   Gametes and embryos

2.3. Please provide a description of the process and its intended purpose/application

The process is that originally approved by the HFEA in 2015, which permits the use of the AneVivo device to allow the process of fertilization of eggs to take place in the uterus rather than in the IVF laboratory. The current approval is restricted to the following clinical context: ‘Intrauterine culture of gametes and embryos (including insertion and removal of device, followed by transfer of embryo(s) to the same woman’.

This application is to request that the technique may also be employed in the following two clinical contexts:

1. Lesbian couples in whom one partner donates her eggs to the other. In order to increase the involvement of the egg donor in the creation and nurturing of their embryo, the device would be used to enable the donor’s eggs to undergo fertilization and early embryo development in her uterus. The wording of the current approval excludes this, requiring that in-vivo fertilization take place in the uterus into which the embryos will be transferred

2. Recipients of donor eggs who wish to use the device to allow fertilization and early embryo development to take place in their uterus rather than in the IVF laboratory.
3. **Licensed Activity**

Please indicate which licensed activity the new/novel process is applicable to.

**Activity**

- Procuring gametes
- Keeping gametes
- Processing gametes
- Distribution of gametes
- Use of gametes
- Storage of gametes
- Storage of embryos
- Creation of embryos in vitro
- Procuring embryos
- Keeping embryos
- Embryo Testing
- Processing embryos
- Distribution of embryos
- Placing any permitted embryo in a woman

4. **Evidence to support application**

4.1. Please explain why the process is necessary or desirable for carrying out the licensed activity.
The process in question was the subject of a successful application to the HFEA in 2015 and following further review in October 2018 remains listed as an approved procedure. However, the current wording of the approval excludes its use from two patient groups with a particular interest in accessing the technique.

The primary reason for carrying out the AneVivo process is to increase the physiological and psychological participation of women undergoing IVF treatment in the creation of embryos. It is not currently offered in the UK with any claim to increase success rates, despite being listed on the HFEA Add-ons webpage.

The importance of participation is well established in lesbian couples for whom the ability for one partner to carry a pregnancy derived from the egg of the other is considered by many to be highly desirable and has been reported by our group to be effective (Bodri et al, RBMO 2018). Removing the current qualification that excludes these women from accessing the AneVivo technique will allow the donor partner not only to provide eggs but to be involved in the creation of the couples' embryos. This would address the presumably unintended inequity in access that the current wording of the approval creates.

Another group that has expressed an interest in using the device are donor egg recipients. Indeed, several clinics elsewhere in the EU are currently offering the technique to this group. Many women who require donor eggs in order to conceive regret their lack of involvement in the creation of the embryos that will be transferred to their uterus. Indeed, for some, this can be a reason to decide not to undergo the procedure. The AneVivo device enables recipients of donor eggs to have a direct physiological and psychological role in the creation of their embryos. However, the current wording of the approval for intra-uterine fertilization and embryo culture excludes them from using this, while women who do not require donor eggs may use it.

It is therefore proposed that these inequities be addressed by removing the current qualification to the wording of the approval from:

'Intrauterine culture of gametes and embryos (including insertion and removal of device, followed by transfer of embryo(s) to the same woman'.

'Intrauterine culture of gametes and embryos (including insertion and removal of device)'

Safety

4.2. Please provide a summary of the evidence that demonstrates that this novel process is safe. Include copies of any relevant published and/or unpublished data as appendices to this form. For example you may wish to include data from animal studies, research on human embryos, CE marking assessments or clinical trials data.
I would refer to the attached document provided to the SACC in 2018 that summarised data from a matched controlled cohort study carried out by the IVI Clinics in Spain and subsequently presented an oral communication to the British Fertility Society at its annual meeting in 2019 and to the Minutes of the SACC meeting that considered these data.

While we are not aware of any further publications reporting its safety, we are advised that to date no complications from using this CE marked device affecting either the woman or the babies born have been reported.

Our own experience of using the device is consistent with this, with one healthy live birth and one ongoing pregnancy from just three cycles of treatment.

4.3. Please list all reagents and materials used in the new process that come into contact with patients, gametes or embryos, providing details of the supplier and quality/safety specification.

Please expand this table as necessary. If authorised, this process may be used by other licensed centres and it is acknowledged that there may be variations in the reagents used however any clinic using the process will be expected to show that they are using reagents of similar specification to those referenced below.

<table>
<thead>
<tr>
<th>Reagent/material</th>
<th>Manufacturer or supplier</th>
<th>Product code</th>
<th>Specification e.g. CE marked, clinical grade, reagent grade, etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kitazato Catheter</td>
<td>Kitazato</td>
<td>213325</td>
<td>CE marked</td>
</tr>
<tr>
<td>ANECOVA-d5</td>
<td>Anecova</td>
<td>T4MC6</td>
<td>CE marked, approved for use by HFEA</td>
</tr>
<tr>
<td>C SCM</td>
<td>Biocare Europe</td>
<td>90165</td>
<td>CE marked</td>
</tr>
<tr>
<td>Oil</td>
<td>Vitrolife</td>
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<tr>
<td>G MOPS</td>
<td>Vitrolife</td>
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<td>CE marked</td>
</tr>
<tr>
<td>Stripper tips (275um)</td>
<td>Origio</td>
<td>MXL3-275</td>
<td>CE marked</td>
</tr>
<tr>
<td>Embryoscope dish</td>
<td>Vitrolife</td>
<td>16450</td>
<td>CE marked</td>
</tr>
</tbody>
</table>
Efficacy

4.4. Please provide a summary of the evidence that demonstrates that this novel process is effective. Include copies of any relevant published and/or unpublished data as appendices to this form. For example, you may wish to include data from animal studies, research on human embryos, or clinical trials data.

I again refer to the study data provided to the SACC in 2018 and subsequently presented at the BFS Meeting in 2018 (see appendices).

In our own hands, two out of three patients in whom the device was used have conceived, one has delivered a healthy term pregnancy and the other pregnancy is ongoing.

4.5. Please note that clinics using this process will be expected to be able to show that they have:

- provided suitable information to patients about the nature of the treatment including any consequences and risks arising as a result of the use of this process;
- that staff have been suitably trained in the application of the new process and can provide evidence of the assessment of their competence;
- that the process and any equipment used in the process has been fully validated;
- there are mechanisms in place for monitoring the effectiveness of the process through regular audit

Please provide brief details of your plans, with timelines, to ensure that these requirements are met.
If approval is given to enable lesbians undergoing inter-partner egg donation and donor egg recipients to be able to access the device in the same way that other women who undergo transferred with embryos created with their own eggs currently can, then the extended availability will be announced on our website. This will mean that the pages relating to our egg donation program and our Shared Motherhood program will refer to the technique as means of increasing biological and psychological participation in the creation of embryos in ART.

While their may be a biological rationale to anticipate that using this technique may be of benefit to the embryos, both in terms of viability and safety compared with the synthetic and non-dynamic environment in which they are currently normally cultured, it will not be presented as a means of increasing success rates after IVF. In that sense, it will not meet the current criteria used by the HFEA to describe an ‘Add-on’.

5. Declaration

The information provided on this form is to the best of my knowledge true and accurate. Check the box to confirm acceptance of the above statement ☒

Signature: [Signature]

Date: 22/01/2020

This must be completed by the person responsible of the licensed centre applying for authorisation of the novel process. The form should then be submitted, with any associated papers and information to your inspector.
Annex B (Supporting information)

Anecova AneVivo Report

Report for HFEA of clinical experience and outcomes using the AneVivo device for in-vivo fertilization since 2015.

Background

Concern is growing that in-vitro culture may impact on epigenetic regulation of birthweight, growth and long-term cardiovascular health in babies born after IVF. The challenge is therefore to minimize the exposure of human gametes and embryos to synthetic conditions in this critical pre-implantation phase of development. A novel porous device (AneVivoTM, Anecova SA, Switzerland) allows gametes and embryos to be placed into the uterine cavity, thus offering a natural and dynamic in-vivo environment for fertilization and early embryo development.

In 2015, the AneVivo device was introduced into clinical practice by IVI Bilbao and then IVI Barcelona. In this document, the experience gained with the device is summarized and outcomes in this cohort are described.

Prior to offering the device, both clinical sites were trained and certified on the full AneVivo clinical procedure. No other specific directive nor recommendation was given to the clinical sites and all patients followed the standard care of the IVI group when undergoing ART in general and the AneVivo procedure in particular.

Clinical Procedures

Patients wishing to undergo the AneVivo procedure underwent clinicaassessment to confirm the absence on ultrasound examination of intra-uterine anatomic anomalies, and a trial placing of the device was carried out before embarking on a treatment cycle. As part of their new technology introduction procedures, both clinics decided from the outset to fertilize some of the oocytes obtained in-vitro, while they gained experience and reassurance as to the efficacy of the AneVivo approach. In practice, this meant putting half of the oocytes (selected at random) into the AneVivo device, and half into the standard in-vitro environment for fertilization. The device containing injected oocytes was inserted into the uterine cavity under transvaginal ultrasound monitoring for in-vivo culture from ICSI to 18 hours after ICSI.

After the 18-hour period, the AneVivo device was retrieved from the uterine cavity and fertilization was assessed for both in-vivo and in-vitro cultured embryos. The in-vivo embryos were further cultured in vitro with the other half of the embryos until selection for transfer. The morphological quality of the embryos and their development were assessed at Day 2 and Day 3 and classified into 4 grades (A, B, C and D) with A being of good quality and D of poor quality depending on the number of blastomeres, fragmentation, multinucleation and symmetry. At Day 5, Day 6 and Day of transfer, the classification of the blastocysts was based on the internal cell mass, the trophectoderm and the degree of expansion of the blastocoel. Gardner's classification was used.
At time of transfer, the embryos underwent the standard selection process. An embryologist selected the best quality embryos regardless of whether it was derived from the AneVivo fertilization process or in the in-vitro procedure, which made it possible to compare data between the AneVivo and standard treatment procedure. The required number of embryos – according to medical criteria and patient preferences - were transferred into the uterine cavity using the standard transfer procedure.

Patients were followed up until pregnancy tests: chemical and clinical pregnancies were defined respectively with an hCG blood pregnancy test 10 days post ET/FET (± 2 days) and an ultrasound exam 2 ± 1 weeks later, according to the routine follow-up of both clinical sites.

Clinical Outcomes

A retrospective study of the clinical data generated at the two IVI clinics between June 2015 and August 2018 was undertaken to further assess, on an observational basis, the performance and safety of the CE-marked AneVivo intra-uterine culture device under normal conditions of use when exposed to a representative population of users and patients suffering from subfertility issues and undergoing assisted reproductive medical treatments.

Outcome data were available from fresh cycles but also from follow on frozen thaw cycles. The study described outcome from 69 such cycles. Outcomes analysed included fertilization, loss and degeneration of oocytes, embryo quality and pregnancy.

Below, a summary of the study findings is presented. These data have been submitted for presentation at an international conference.

STUDY RESULTS

Although numbers were limited, no significant difference in in-vivo versus in-vitro fertilisation rates (66% vs 71%), oocyte degeneration rates (11% vs 13%) or percentage of top quality embryos (29% vs 35%). The proportion of fertilized oocytes that generated blastocysts after in vitro and in vivo fertilization was 60% and 53% respectively. Paired t testing revealed no statistically significant difference (p=0.09)

Clinical pregnancy rates

Clinical pregnancy rates were higher after the transfer of an in-vivo fertilized embryo: 81% vs 56%, but statistical significance testing by chi-square was not demonstrated (p=0.156) most likely reflecting the cohort size. The relative risk (chance) of getting pregnant was = 1.5 times (CI 0.9 -2.6) greater in the vivo than the vitro group.

No adverse events were reported.

Study Conclusion

These preliminary data following the introduction of the AneVivo device into clinical practice indicate that this approach may provide an effective alternative to current in-vitro techniques for generating embryos in the IVF setting. However, larger properly powered studies will be required to confirm these initial findings.

Patient experience and implementation
The device remains popular as means of providing a more natural means of performing IVF and increasing patient involvement in the process. In 2018 the first baby born as a result of using the device in an egg recipient was announced in a press release from a clinic in Poland (see attached). The IVI group of clinics in Spain have approved AneVivo for use, and it is currently being introduced into practice in Italy (SISMER) and into the UK (CARE and LWC).

Anecova
Lausanne
October 2018

SCAAC minutes – October 2018 meeting
Minutes as referred to in the novel process application – IVF using the AneVivo device in interpartner and standard egg donation. Provided by the applicant as additional supporting information to this application.

Scientific and Clinical Advances Advisory Committee (SCAAC)

15 October 2018 11:00am – 4:00pm
Derwent Room, HFEA Offices, 10 Spring Gardens, London SW1A 2BU

| Authority Members | Present | Yacoub Khalaf (Chair)  
|                  |         | Kate Brian  
|                  |         | Andy Greenfield  
|                  |         | Anne Lampe  
| Apologies        | Tony Rutherford  
|                  | Gudrun Moore  
| Members of the Executive | Anna Quinn (lead)  
|                  | Rasheda Begum  
|                  | (secretary)  
|                  | Laura Riley  
|                  | Clare Ettinghausen  
|                  | Nick Jones  
|                  | Mhairi West  
|                  | Julia Katsaros  
|                  | Victoria Askew |
5. **Intrauterine culture**

5.1. Intrauterine culture is a procedure that was reviewed by SCAAC and approved by the Statutory Approvals Committee as a novel process in 2015. When a centre wishes to carry out a process which does not appear on the list of authorised processes, it must apply to the Authority for permission. It involves placing fertilised eggs into an intrauterine culture device, which is inserted into the woman’s womb. The device stays in place for several hours during the initial stages of embryo development within the womb instead of an incubator as would be done in conventional IVF. When the device is removed, the embryos are removed from it and put in an incubator until they are ready to be transferred back to the womb (without the device) or to be frozen for use in future treatment. After a novel process is approved, the applying clinic is required to submit an outcomes report to the HFEA two years after the initial approval for review by SCAAC. The outcomes report for intrauterine culture from the applying clinic was considered by SCAAC in February 2017. The Committee agreed that more information and data was required from the centre and suggested that a representative from any clinics planning to implement the technique should be invited to SCAAC.

5.2. The Committee was joined by Professor Nick Macklon, Medical Director at London Women’s Clinic who had been invited to provide insight into clinical experiences and outcomes using the AneVivo device which is used for intrauterine culture. A report on clinical outcomes of the AneVivo device from clinics in Spain and Poland had been circulated to the Committee in confidence for commercial reasons in advance of the meeting.

5.3. Prof Macklon explained that a device that could allow human embryos to be placed in the uterus and then removed offered a unique opportunity to research the impact of the embryo on the endometrium and vice versa. Prof Macklon became involved in advising the company and saw it through development to being offered for use in patients. Prof Macklon stressed that the treatment is not currently offered to improve pregnancy rates or to benefit the embryo, rather the claimed benefits to the woman are psychological as she can be more physically involved in the process. Prof Macklon said that he is interested in this technique as an alternative to *in vitro* culture as it may reduce the impact of exposure of the embryo to synthetic in vitro culture media.
5.4. Prof Macklon updated the Committee on activity since the novel process application was made on behalf of Complete Fertility Centre to the HFEA for use of the device and approved in 2015, from which point the Complete Fertility Centre was required to collect data on outcomes for reporting back to the HFEA. Training took place before the procedure was ready to be offered to patients. Prof Macklon at that point left the centre and the and the Trust then began the process of selling the clinic to a private investor. These two factors led to the introduction of the intrauterine culture technique being deprioritised. The technique has been used in a clinical context in Spain and Poland via the AneVivo device. Prof Macklon felt that the technique is ready to be offered to patients at London Women’s Clinic.

5.5. The company’s aim for the AneVivo device is that it could potentially replace in vitro culture up until blastocyst stage by using the uterus as an alternative to a laboratory incubator and synthetic culture media. Data from use of the device in Spain will be presented at Fertility 2019. Prof Macklon asked the Committee to consider whether there is sufficient data to allow continued use of the device in the UK subject to further review in 2 years' time from now once there is more data. During this time period, Prof Macklon anticipates the device will become available for longer term intrauterine culture up to blastocyst stage.

5.6. The Committee were asked for questions and comments. One member commented that the device does not mimic ‘natural’ development as the embryo would usually be in the fallopian tubes in the early stages of development. Prof Macklon agreed, however as pregnancies still occur when early embryos are placed in the uterus, this indicates that the uterus is not a hostile environment.

5.7. A member asked how much patients would be charged for using the device as an add-on and whether the device could harm the patient. Prof Macklon commented that some people may consider the procedure to be quite invasive as patient will undergo egg collection as well as having the device placed in the uterus and removed some hours later therefore the market will be small. However there has been interest from patients who view the procedure as providing less embryonic exposure to in vitro culture. In terms of pricing, Prof Macklon was not able to confirm the price in UK clinics, however, he did note that patients in clinics overseas may be charged approximately 700 Euros.

5.8. One member asked whether there has been research into the psychological benefits described for the device. Prof Macklon commented that there have been focus groups, which highlighted that some patients found using the device empowering, whereas others felt concerned about taking responsibility for the embryos instead of a laboratory. In Spain and Poland, there has been particular interest and enthusiasm in the psychological impact on donor egg recipients. Some donor egg recipients have reported that they decided to use the donor eggs with the device because the device made them feel like they have contributed to the process.

5.9. Prof Macklon was asked what evidence he wants to see before the device can be introduced into routine use in the UK as a method of incubation. Prof Macklon responded that the device should be evidenced as being as safe as standard in vitro culture procedures, as well as presenting ongoing pregnancy rates comparative to standard procedures. Longer term follow-up needs to show that babies born from using the device are as healthy as those born from standard in vitro fertilisation and vice versa. It will take a
long time to collect this data, however there are other approaches which could give some information in the shorter term such as carrying out epigenetic analysis on embryos.

5.10. A member asked about pre-clinical experience with the device using human embryos donated to research. Prof Macklon addressed that this has not progressed due to the lack of embryos donated for research for this purpose. Another question was on whether ICSI needs to be used with this method. Prof Macklon explained ICSI was not in principle required, however ICSI has been used to ensure the sperm got into the device.

5.11. Prof Macklon raised that there is some evidence to suggest that the constituents of embryo culture media may have an impact on children born from ART associations have been made on birth weight and that IVF children show some cardiovascular differences to naturally-conceived children. Due to the possible negative impacts of *in vitro* culture, Prof Macklon felt it was justified to explore methods which would reduce the time spent in these conditions.

5.12. One member commented on the cost of the device of ~700 Euros, noting that as the technique is still in experimental phase it seemed unreasonable to charge patients.

5.13. The Chair commented that the biological plausibility of the technique is lacking. Prof Macklon highlighted that the technique is being investigated to see whether the uterine environment is better than *in vitro* culture.

**Action**

5.14. The Executive will follow up with Prof Macklon to review the patient information relating to intrauterine culture.