Scientific and Clinical Advances Advisory Committee Paper

Paper title	**Novel process application: Anecova AneVivo intrauterine device**
Paper number	SCAAC(06/15)05
Meeting date	10 June 2015
Agenda item	05
Author	Sarah Testori (Scientific and Clinical Policy Manager)
Information/decision	Decision
Resource implications	None
Implementation	None
Communication	SCAAC's recommendations will be presented to the Statutory Approvals Committee to inform their decision about whether or not to authorise this novel process.
Organisational risk	Low
Committee recommendation	Members are asked to: • Consider whether the Anecova AneVivo intrauterine device is a novel process. • Provide a view on which licensed activities it considers are addressed by the device. • Provide a view on whether the device is effective and there is any evidence to indicate that the device is unsafe.
Evaluation	None
Annexes	**Annex A** – Completed application form **Annex B** – Supporting evidence **Annex C** – Blockeel, C et al. (2009). An in vivo culture system for human embryos using an encapsulation technology: A pilot study. Human Reproduction, 24(4), 790–796. **Annex D** – Novel process decision tree **Annex E** – CE marking certification, and additional evidence

1. Background

1.1. The Authority publishes a list of authorised processes on its website (http://www.hfea.gov.uk/139.html), with the processes arranged under each of the licensable activities permitted by the Act. If a centre wishes 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. If approved, the novel process is placed on the approved process list so that it can be performed by all centres. The Authority has delegated the authorisation of novel processes to the Statutory Approvals Committee (SAC), who are advised on the matter by SCAAC (Annex D).

1.2. This paper asks the Committee to provide an opinion as to whether the use of intrauterine culture devices should be approved as a process for carrying out the licensed activities of 'keeping gametes', 'processing gametes', 'keeping embryos' and/or 'processing embryos'.

1.3. As part of its consideration, the Committee should discuss whether the intrauterine device is sufficiently different from the processes currently authorised as to be considered 'novel'.

1.4. The Committee should provide a view on whether the Anecova AneVivo intrauterine device is effective and whether there is any evidence to indicate that the device is unsafe.

1.5. The Committee should provide a view as to which licensed activities are achieved through the use of the Anecova AneVivo intrauterine device.

2. Executive summary

2.1. The Anecova AneVivo intrauterine device is an *in vivo* embryo culture device for use during IVF treatment that allows fertilisation and embryo development to occur in the patient's uterus within the natural tubal and uterine fluids, rather than in an incubator and artificial medium.

2.2. The intended use of the device is the placement and retrieval of gametes or embryos into and from the uterine cavity, with the objective of their culture within the device while inside the uterine cavity. This enables fertilization and early embryo development to take place *in-vivo*, reducing the exposure of embryos to synthetic in-vitro conditions during this crucial early phase of the development, but also exposing the endometrium to biochemical produced by the developing embryos.

2.3. Information in support of the safety of the device is presented in Blockeel et al's 2009 paper, 'An in vivo culture system for human embryos using an encapsulation technology: A pilot study', which can be found in Annex C. Information in support of the efficacy and safety of the device can be found in the same publication (Blockeel et al., 2009) and also in the supplementary information found in Annex B. This information includes CE mark certification for the device.

2.4. The Executive notes that the proposed use of the Anecova AneVivo intrauterine device for gamete and embryo culture could be considered to contribute to the following licensed activities: ‘keeping gametes’, ‘processing gametes’, ‘keeping embryos’ and/or ‘processing embryos’. HFEA licences defining ‘keeping gametes/embryos’ as ‘any authorised process by which gametes/embryos are maintained prior to their use, storage or in the course of carriage’; ‘processing gametes/embryos’ is defined as ‘any authorised operation involved in the preparation, manipulation or packaging of embryos’.

3. Recommendation to the committee

3.1. The Committee is asked to provide a view on whether the Anecova AneVivo intrauterine device is effective and whether there is any evidence to indicate that the device is unsafe.

3.2. The Committee is asked to provide a view on which licensed activities (‘keeping gametes’, ‘processing gametes’, ‘keeping embryos’ and/or ‘processing embryos’) it considers are addressed by the use of the Anecova AneVivo intrauterine device.

3.3. In providing its view, the Committee is asked to note that, if authorised, the Authority would allow centres licensed for ‘keeping gametes’, ‘processing gametes’, ‘keeping embryos’ and/or ‘processing embryos’, to culture embryos using any intrauterine device, providing the centre had undertaken to validate all processes used to carry out licensed activities and that the device was CE marked, and CE marked reagents were used where available.

4. Next steps

4.1. The opinion of the Committee, together with any additional information submitted by licensed centre, will be presented to the Authority’s Statutory Approvals Committee for decision, and their applying clinic(s) will be informed of their views.

5. References

Blockeel, C., Mock, P., Verheyen, G., Bouche, N., Le Goff, P., Heyman, Y., … Simón, C. (2009). An in vivo culture system for human embryos using an encapsulation technology: A pilot study. *Human Reproduction*, *24*(4), 790–796. doi:10.1093/humrep/dep005

ANNEX A – Application for authorisation of a novel process

Application to carry out a licensed activity using a new process

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

It is important that the language used in this application from is clear and understandable to non-specialist lay members and staff. All abbreviations should be explained.

Centre details

Centre Name	Complete Fertility Centre
Centre Number	0307
Person Responsible	Prof. N.S. Macklon

New/Novel process

What is the new/novel process?

Name of the process	In vivo fertilisation of oocytes as part of ART using the Anecova AneVivo intra-uterine medical device.
Description of the cells to which this preparation process is applied.	Sperm, oocytes, inseminated / injected oocytes
Please provide a brief description or a flowchart of the process	1) Patient follows the traditional course of ART treatment up to OPU, including ovarian stimulation with exogenous gonadotrophins, avoidance of premature luteinisation by either GnRH agonist or antagonist, and triggering of final oocyte maturation by hCG or GnRH agonist. 2) Egg retrieval and fertilisation preparation a. Oocyte retrieval using standard procedures b. Standard sperm preparation for fertilisation c. Standard oocyte preparation for fertilisation d. Fertilisation with a co-incubation of oocytes and spermatozoa in vitro to initiate fertilisation (2 hours) or with ICSI e. Loading of the Anecova device with cells 3) Anecova device placement in utero under ultrasound guidance. 4) Anecova device retrieval after 18 hours. 5) Fertilisation assessment (PN), embryos placed into in

	vitro culture according to standard procedures 6) Embryo selection, transfer and selection for cryo preservationaccording to standard criteria and procedures. 7) Luteal phase support according to standard procedures

Licensed Activity

Please indicate which licensed activity the new/novel process will be used to carry out

Activity	State YES if the novel process will be used to carry out the activity
Procuring gametes	
Keeping gametes	
Processing gametes	
Distribution of gametes	
Use of gametes	YES
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	

Evidence to support application

1) Please explain why the process is necessary or desirable for carrying out the licensed activity.

In-vivo fertilisation reduces exposure of gametes to the synthetic environment provided by in-vitro culture conditions during this crucial phase of early development.
The use of this intra-uterine device for fertilization will also increase direct involvement of women in their ART treatment.

2) Please provide evidence (e.g. copies of available published studies), that the new process is safe – e.g. from animal studies or research on human embryos

An in vivo culture system for human embryos using an encapsulation technology: a pilot study. Blockeel et al, Hum Reprod, 2009:24;790-796. (see attached pdf)

Please see Appendix 1

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.

Reagent/material	Manufacturer or supplier	Product code	Specification e.g. CE marked, clinical grade, reagent grade, etc.
Titanium grade 2	Pierval	Titanium Grade 2	USP – Class 6 - Certified
Stainless steel	Heraeus	AISI 302 FPRO-00037	316 LVM – Class 6 - Certified
Human grade silicone	Speciality Silicone	SSF-METN-750 USP CLASS VI 29407	USP class 6 certified
Polycarbonate vessel	IT4IP / Dow Chemicals	Calibre 201-6	USP class 6 certified
Polyamide monofilament	G.KRAHMER GmbH	Polyamide monofilament	CE mark, USP and EU conformity

		12H0140R	

4) Please provide evidence (e.g. copies of available published studies), that the new process is effective.

See attached Appendix 1.

The use of the medical device for the proposed purpose has been approved by a number of European Competent Authorities, including:
Denmark (Sundhedsstyrelsen)
Czech Republic (Ministerstvo Zdravotnictví České Republiky)
The Danish Competent Authorities have considered that the use of this medical Device should not be regarded as a new treatment methodology and that as the intended use of the healthcare product was similar to established technologies of the ART sector there was no further need for limitations or obligations by healthcare personnel.

The device has already been introduced into clinical practice in these countries and is currently undergoing regulatory approval prior to clinical introduction in Spain, Hungary and Finland.

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

Can you provide brief details of your plans, with timelines, to ensure that these requirements are met.

The clinical team at Complete Fertility Centre has undergone preliminary training in the use of the device, and this will be completed and certified prior to commencing clinical use.

The following information will be provided to patients prior to start the treatment of patients:
Patient Information Leaflet, Patient Consent form. The option of using the device, and details regarding its use, pros and cons will also be explained during patient information evenings.
The device has already been presented to our patient support group and feedback from this will inform the preparation of patient information resources.

Instruction for the use of the AneVivo Device:
Detailed Standard Operation Procedures for a step-by-step guidance of the use of the AneVivo Device will be provided by the company and adapted to fit those of the Complete Fertility Centre Southampton.

When completed, please submit this application form and any associated papers and information to your centre's inspector.