Executive Licensing Panel - minutes

Centre 0006 (Lister Fertility Clinic)

Executive Update – Investigation into Media Allegations

Friday, 25 August 2017

HFEA, 10 Spring Gardens, London SW1A 2BU

Panel members	Hannah Verdin (Chair) Anna Coundley Howard Ryan	Head of Regulatory Policy Information Access and Policy Manager Report Developer
Members of the Executive	Bernice Ash	Secretary
External adviser		
Observers		

Declarations of interest

- Members of the panel declared that they had no conflicts of interest in relation to this item.

The panel had before it:

- 8th edition of the HFEA Code of Practice
- Standard licensing and approvals pack for committee members.

1. Background

1.1. The panel noted that on 2 May 2017, the Daily Mail newspaper published a report into the practices of some fertility clinics. There were several articles relating to, for example, the use of add-on treatments, medication pricing, egg freezing and in particular - egg sharing and the incentives offered to patients in this process.

1.2. The article suggests the fertility sector (or those parts subject to the investigation) is 'cashing in' on women desperate to have a child, on patients who cannot afford the costs of treatment, and that clinics are profiting unreasonably from patients. The panel noted these are serious allegations and have the potential to bring the sector in to disrepute and reduce public confidence in the integrity of the fertility sector, and the clinicians and other professionals working in licensed clinics.

1.4. The panel noted that the Lister Fertility Clinic featured in this newspaper report which made the following allegations, principally relating to egg freezing. Egg freezing is a method of fertility preservation, which allows women to freeze their eggs for later use. The article alleged that the Lister Fertility Clinic was exploiting desperate women by targeting them to freeze their eggs. It further alleged the clinic overstated the success of the treatment and underplayed the risks of it being unsuccessful.

1.3. The panel noted the HFEA's requirements for patients to be provided with information about treatments prior to it taking place, including egg freezing. The HFEA Code of Practice requires that 'before treatment is offered, a clinic should give the woman seeking treatment and her partner, if applicable, information about the likely outcomes of the proposed treatment (data provided should include the centre's most recent live birth rate and clinical pregnancy rate per treatment cycle, verified by the HFEA, and the national live birth rate and clinical pregnancy rate per treatment cycle)' (Guidance 4.2). In its information aimed at patients the HFEA states 'delaying parenthood techniques have low success rates so it is important (you) accept they may not work' and that egg freezing is 'not a quick fix for delaying motherhood'.

2. Consideration of Investigation

2.1. The panel considered the papers, which included a report of an investigation into media allegations and licensing minutes for the last three years.

2.2. The panel noted the report focuses on an investigation into the allegations including a meeting with key members of staff at the centre on 26 May 2017.

2.3. The panel noted the aim of the investigation was to:

- Discuss the newspaper article and review what happened from the centre's perspective.
- Investigate whether there has been a breach of the law (HF&E Act 1990 (as amended)).
- Review the centre's practices and procedures relating to egg freezing.

2.4 The panel noted the findings of the investigation and the following recommendations made in the report that the centre must;

- Review its practices, with attention to marketing and provision of information to prospective patients wishing to egg freeze and giving the potential patients accurate and relative statistical information.
- Review the verbal information given to patients to ensure it is like for like, up to date, relevant and complies with Code of Practice guidance.
- Ensure any prospective patients receive information that this is clear and additional literature is available for all intended patients to review at their leisure.

- Ensure any information based upon statistics are clear and are appropriate to practice and information given to prospective patients is clear and not misleading. This applies to presentations and any other patient information currently used for prospective patients.

3. Decision

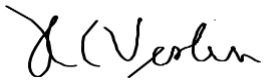
3.1. The panel noted the inspectorate's investigation and findings, regarding the media allegations. The investigation had focused on the statistics quoted for success rates following egg freezing and information provided to patients.

3.2. The panel noted the centre's thorough and detailed response to the allegations, within which, the Person Responsible (PR) did not accept the recommendations made in the report. The panel agreed to refer this case to the Licence Committee, for consideration of the inspectorate's recommendations and the suggestions made by the centre within its response.

4. Chair's signature

4.1. I confirm this is a true and accurate record of the meeting.

Signature



Name

Hannah Verdin

Date

5 September 2017

Report of an investigation into media allegations: The Lister Fertility Clinic, Centre 0006

Date of meeting: 26 May 2017

Location of meeting: The Lister Fertility Clinic

Investigation team: Grace Lyndon and Sharon Fensome-Rimmer

Present		
HFEA	Grace Lyndon Sharon Fensome-Rimmer	Centre Inspector Chief Inspector
The Lister	Safira Batha James Nicopoullos Julie Ivoska	Person Responsible (PR) Licence Holder (LH) Lead Consultant IVF Manager

1. Background:

1.1. On 2 May 2017, the Daily Mail newspaper published a report into the practices of some fertility clinics. There were several articles relating to, for example, the use of add-on treatments, medication pricing, egg freezing - in particular, egg sharing - and the incentives offered to patients in this process.

1.2. The article suggests the fertility sector (or those parts subject to the investigation) is 'cashing in' on women desperate to have a child, on patients who cannot afford the costs of treatment, and that clinics are profiting unreasonably from patients.

1.3. These are serious allegations and have the potential to bring the sector in to disrepute and reduce public confidence in the integrity of the fertility sector, and the clinicians and other professionals working in licensed clinics.

1.4. The Lister Fertility Clinic was featured in the press report. The article made allegations principally relating to egg freezing. Egg freezing is a method of fertility preservation, which allows women to freeze their eggs for later use. The article alleged that the Lister Fertility Clinic was exploiting desperate women by targeting them to freeze their eggs. It further alleged the clinic overstated the success of the treatment and underplayed the risks of it being unsuccessful.

1.5. In particular, the article alleges that at an open evening the lead consultant said that:

I) '15 or 20 eggs to have as an egg-freezing bank is the sort of number that would make me think you've got a reasonable insurance policy' and that 'we know how many fresh eggs would give you a possibility of having a baby'.

II) 'Although freezing doesn't guarantee pregnancy, it's an option that I think is a successful one' and asking his audience 'the key is, is freezing your eggs going to give you an alternative that could be better to where you are in the future? That's what you guys need to decide'.

III) 'Patients have a 40% chance of having a baby by freezing their eggs if they do so in their mid-30's and 38 year olds have a 30% chance, however egg freezing does not guarantee pregnancy, it's an option I think is a successful one'. The lead consultant also claimed that frozen eggs behave like fresh eggs so therefore gave the public information relating to achieving a pregnancy or live birth in relation to cycles of treatment using the patient's own fresh eggs.

IV) The Daily Mail also alleges that information used during patient open evenings possibly misconstrues information, notably the information given in a PowerPoint presentation and that egg freezing is being promoted for social reasons.

Context

Since 2005, the number of women storing their eggs has increased, with the most rapid growth occurring further to the introduction of egg 'vitrification' which became widely available around 2010. Vitrification is a cooling technique allowing the water inside and surrounding the egg to quickly cool into a solid state with no ice crystal formation at all, a problem with earlier, slow freezing, techniques. Despite growth of 25% to 30% year-on-year, egg storage cycles are still a relatively small proportion of fertility treatment performed in the UK. The live birth rate per thaw cycle started for women using their own thawed frozen eggs was 20.8% in 2012 and 13.9% in 2013, albeit the actual difference is represented by a small number of births due to the small numbers involved. This is lower rate than for fresh eggs or frozen embryo transfers (Fertility Treatment 2014 Trends and figures).

1.6. HFEA requirements

The HFEA requires patients to be provided with information about treatments prior to it taking place, including egg freezing. The HFEA Code of Practice requires that 'before treatment is offered, a clinic should give the woman seeking treatment and her partner, if applicable, information about the likely outcomes of the proposed treatment (data provided should include the centre's most recent live birth rate and clinical pregnancy rate per treatment cycle, verified by the HFEA, and the national live birth rate and clinical pregnancy rate per treatment cycle) (Guidance 4.2). In its information aimed at patients the HFEA states 'delaying parenthood techniques have low success rates so it is

important (you) accept they may not work' and that egg freezing is 'not a quick fix for delaying motherhood.

The Code of Practice guidance may not specifically target such audiences, but it could be considered in the spirit of the guidance should be followed to ensure any prospective patient is given balanced information about the treatments the potential patients are most interested in. However, it is recognised that further guidance is needed which the HFEA are considering and will be communicated with the sector in the near future.

2. Our investigation

This report focusses on an investigation into these accusations including a meeting with key members of staff at the centre on 26 May 2017.

2.1 Aim of the investigation

- To discuss the press article and review what happened from the centre's perspective.
- To investigate whether there has been a breach of the law (Human Fertilisation & Embryology Act 1990 (as amended)).
- To review the centre's practices and procedures relating to egg freezing.

2.2 Documents/papers reviewed or referred to during the investigation:

- Press accusations sent to centre and the centre's responses
- Sample of egg freeze notes
- HF&E Act 1990 (as amended)
- HFEA Code of Practice 8th Edition, revised May 2017
- Fertility Treatment 2014 Trends and figures

3. Findings:

3.1. Centre staff explained that the figures quoted at the open evening were generated directly from the centre's database of their own results for success rates following egg freezing. Furthermore the data excluded outliers, for example eggs vitrified before 2009; eggs that were subject to 'slow freezing'; and frozen eggs brought into the clinic from elsewhere, for patient use at the centre as they did not undertake their treatment to freeze at the centre. In short, the numbers relied upon by the clinic are very small and as a result subject to statistical variability due to the large role played by chance.

3.2. The lead consultant said that it is his approach to discuss the number of eggs necessary for freezing to act as an 'insurance policy' and that he considers this to be 15-20 eggs but he added that the numbers quoted to prospective patients is not documented in any of the information made available to the patients either in written form or on the clinic website.

3.3. This figure is derived other than from the clinic's experience. It is possible this could be seen as misleading due to the low numbers used to calculate the statistics which have

been used to set high expectations for some patients - where such an outcome may not be achievable. This may have the consequence of patients feeling pressured to undertake additional cycles to achieve the desired number of eggs, and incurring additional costs.

3.4. The clinic stated in their response to the allegation that 'one in 27 eggs thawed by the clinic led to a baby' this statement does not match the information given to the public at the information evening regarding the reasonable insurance policy which was clearly stated as being 15-20 eggs. This information can be seen as being misleading and confusing.

3.5. The lead consultant indicated that, in hindsight, he could have been clearer informing prospective patients that the number of eggs required is dependent on the specific circumstances of the patient, as there are a range of factors to take into consideration. For example, the patient's age and the maturity and quality of the eggs. He stated he utilised the 15-20 egg figure to be a broad indicator. He also stated he could have been clearer that individual and tailored assessments would need to take place in relation to each patient.

3.6. We also noted that attendees were not given information regarding egg freezing in written form to contemplate later. To provide this information in written form aids to minimise any misunderstanding and confusion regarding information.

3.7. We explored the claims made in relation to success rates. We noted the comment 'patients have a 40% chance of having a baby by freezing their eggs if they do so in their mid-30's and 38 year olds have a 30% chance, however egg freezing doesn't guarantee pregnancy, it's an option I think is a successful one'. It was also claimed that 'frozen eggs behave like fresh eggs.' It is clear that, in speculating as to success rates for treatments involving frozen eggs the clinic is relying on data relating to a usual cycle of IVF – where the patient's fresh eggs or (thawed) frozen embryos are used. This is likely to overstate the success rates of treatments where frozen eggs are used.

3.8. We were told (at the Lister) out of 31 women who have returned to use their frozen eggs ten achieved a pregnancy and have either delivered or are well into pregnancies – 'this is a very good result'. However, given the small numbers there is no statistical validity to this claim.

3.9. The inspection team recognises there is a dearth of reliable, statistically robust information available to provide good comparative information to patients, mainly because the numbers of women who have frozen their eggs and then returned for treatment using them to create an embryo is so small. In 2014 (the latest information available) there were 129 thawing cycles started (by 123 women) in the UK. 38 clinics reported thawing eggs for a patient's own treatment in 2014. Most of the clinics only do a handful of cycles each year. In 2014, only one centre performed more than 10 thawing cycles; and in 2013, none did. Of 80 egg thaw cycles started in 2013 (where 700 eggs were thawed) 12 babies were born, in 11 births.

3.10. During the open evening only two prospective patients attended of which one was a genuine patient the other being the undercover Daily Mail reporter. Due to the small numbers present there was more dedicated time for the lead consultant to answer

questions. This gave the patients the opportunity for more targeted and intense questions surrounding egg freezing.

4. Conclusion:

The inspection team conclude that:

- At this open evening, the centre did not emphasise the importance of each patient being different and the importance of individual assessments.
- Statements made by the clinic such as '15-20 eggs would make me think you would get a baby' and [frozen eggs] 'behave like fresh eggs' It is important to note that statistically reliable evidence to support these statements is currently not available.
- The information relating to the efficacy of treatment that was provided to prospective patients did not clearly define whether this was statistically derived from the centres own performance, or from nationally derived information such as the HFEA's, was being relied on. In any event the limitations of the performance information were not highlighted.
- Whilst it is noted in the centre's statement in response to the media allegations that it is: 'committed to ensuring patients are given transparent information and responsible medical advice to help them make informed decisions' it has not fulfilled this commitment to transparency on this occasion.
- From the information obtained and discussions held during the inspection; the review of the recordings of the lead consultant's comments made to the Daily Mail reporter could be misinterpreted. The centre's second patient information session on egg freezing was attended by the reporter in which only two people were present, one authentic prospective patient and one representative from the Daily Mail this small number of attendees allowed for more targeted and intense questions directed towards the lead clinician who was facilitating the open evening
- It could be said that the centre is promoting egg freezing as a scheme to enable patients to preserve their fertility to have treatment at a time of their choice, without fully explaining the limitations especially at open evenings.
- It is possible to conclude that the information provided at the open evening and information on the website are misleading due to the low numbers used to calculate the statistics.

5. Recommendations

5.1. The centre has a few improvements to make to ensure that it provides accurate and transparent information to prospective patients and it is compliant with Code of Practice guidance. Based on these findings we make the following recommendation: The centre must;

- review its practices, with attention to marketing and provision of information to prospective patients wishing to egg freeze and giving the potential patients accurate and relative statistical information.
- review the verbal information given to patients to ensure it is like for like, up to date, relevant and complies with Code of Practice guidance.
- ensure any prospective patients receive information, that this is clear and additional literature is available for all intended patients to review at their leisure.
- Ensure any information based upon statistics are clear and are appropriate to practice and information given to prospective patients is clear and not misleading. This applies to presentations and any other patient information currently used for prospective patients.

6. References:

1. Human Fertilisation and Embryology Authority (HFEA) Code of Practice 2017 8th edition.

2. Human Fertilisation and Embryology Authority: Fertility Treatment 2014 Trends and figures.

3. Egg Freeze Open Day PowerPoint 2016 The Lister Fertility Clinic

The Lister Fertility Clinic response to The Daily Mail report

Introduction

Following an article published in the Daily Mail on 2 May 2017, the Human Fertilisation and Embryology Authority ("HFEA"), met with The Lister Fertility Clinic ("LFC") on 26 May 2017 to discuss some of the allegations set out in the Daily Mail's article.

HFEA produced a report on 11 August 2017, which sets out its conclusions relating to the Daily Mail article.

It should be noted that Mr Sam Abdalla, the Person Responsible at The Lister Fertility Clinic, was not able to attend the meeting with HFEA on 26 May 2017, as he was recovering from an illness in hospital. He had made arrangements to attend the meeting on Skype, but HFEA did not accept his request to join the meeting.

Over thirty years we have established The Lister Fertility Clinic as a trusted and responsible facility. We have always worked closely with HFEA to ensure that the service we provide to our patients is of the highest standards. We have always been transparent and open with our patients and the public.

We do not believe that the HFEA report accurately reflects the service we provide to our patients. We ask that after reading our response below you consider revaluating your position and look to withdraw this report.

The report, both in its context and in its findings, appears to disregard the current scientific understanding and data available on egg freezing. We believe that this fundamental flaw underpins the report and can be highlighted in 4 key areas:

1. Comparison of vitrified oocytes and fresh oocytes
2. The number of eggs needed to freeze to give a chance of a livebirth and the importance of this discussion with patients
3. The importance and validity of presenting our data
4. The extent of the limitations of currently available HFEA data

Addressing these 4 areas in detail allows us to refute many of the allegations and comments made by HFEA's inspection report. Subsequently we will address the conclusions point by points.

1. Comparison of vitrified oocytes and fresh oocytes

The inspection report suggests that no reliable evidence is available to support the statement "*frozen [vitrified] eggs behave like fresh eggs*". LFC submits that the statement "*frozen [vitrified] eggs behave like fresh eggs*" can be supported by statistically reliable evidence. LFC refers to the following:

1. **The American Society of Reproductive Medicine (ASRM)** states in their Practice committee guideline on "Mature oocyte cryopreservation" of January 2013 (1) that *"There is good evidence that fertilization and pregnancy rates are similar to IVF/ICSI using fresh oocytes when vitrified/warmed oocytes are used as part of IVF/ICSI…..and evidence indicates that oocyte vitrification and warming should no longer be considered experimental".* The ASRM relied on a multitude of peer-reviewed and randomised and

observational trials. Below is the table that describes the 4 randomised trials comparing fresh and frozen oocytes, 2 of them utilising donor eggs and the other 2 comparing patients own and fresh frozen oocytes.

TABLE 1

Summary of randomized controlled trials comparing fresh versus vitrified oocytes.

	Cobo 2008 (24)	Cobo 2010 (26)	Rienzi 2010 (25)	Parmegiani 2011 (19)
Patient population	Oocyte donors	Oocyte donors	Infertile patients <43 years of age requiring ICSI with >6 mature oocytes	Infertile patients <42 years of age requiring ICSI with >5 mature oocytes
No. patients	30 vitrification 30 fresh	295 vitrification 289 fresh	40 vitrification 40 fresh	31 vitrification 31 fresh
Mean age at retrieval	26	26	35	35
No. oocytes	231 vitrification 219 fresh	3286 vitrification 3185 fresh	124 vitrification 120 fresh	168 vitrification NA fresh
No. oocytes per retrieval	18.2	11	13	NA
Survival	96.9%	92.5%	96.8%	89.9%
Fertilization rate	76.3 vitrification 82.2 fresh	74% vitrification 73% fresh	79.2% vitrification 83.3% fresh	71% vitrification 72.6% fresh
No. transferred vitrification vs. fresh	3.8 vitrification 3.9 fresh	1.7 vitrification 1.7 fresh	2.3 vitrification 2.5 fresh	2.5 vitrification 2.6 fresh
Day of transfer	3	3	2	2–3
Implantation rate	40.8% vitrification 100% fresh	39.9% vitrification 40.9% fresh	20.4% vitrification 21.7% fresh	17.1% vitrification NA fresh
CPR/transfer vitrification vs. fresh	60.8% (23 vitrification transfers) 100% (1 fresh transfer)	55.4% vitrification 55.6% fresh	38.5% vitrification 43.5% fresh	35.5% vitrification 13.3% fresh
CPR/oocyte thawed	6.1%	4.5%	12%	6.5%

Note: All used vitrification with Cryotop, 15% EG + 15% DMSO + 0.5M sucrose. CPR = clinical pregnancy rate.

Practice Committee. Oocyte cryopreservation. Fertil Steril 2013.

2. **The American College of Obstetrics and Gynaecology (ACOG)** have issued a committee opinion on Oocyte cryopreservation in 2014 (2), subsequently reviewed in 2016, that states:
    a. "Collectively, studies provide good evidence that fertilization and pregnancy rates using vitrified oocytes are similar to fresh IVF cycles or fresh ICSI cycles and are consistent with clinical experience with respect to the effect of the age of the oocyte when frozen or vitrified."
    b. "Both clinical trials and observational studies have compared reproductive outcomes after IVF and intra- cytoplasmic sperm injection (ICSI) with cryopreserved oocytes to IVF and ICSI with fresh oocytes. Outcomes of four published randomized controlled trials demonstrated that fresh and frozen oocytes yield similar pregnancy rates in IVF cycles, supporting the use of these technologies in well-selected patients aged 35 years and younger. In the two studies conducted in infertile couples (two trials were conducted in egg donors), implantation rates ranged between 17% and 41% and clinical pregnancy rates per transfer ranged from 36% to 65%. These data, the data in egg donors, and data from a recent meta-analysis suggest that specific outcomes of IVF and ICSI (fertilization and pregnancy rates) are similar between fresh oocytes and vitrified oocytes."

3. **The European Society of Human Reproduction and Embryology (ESHRE)** in their Ethics and Law Taskforce recommendations on Oocyte cryopreservation for age-related fertility loss of March 2012 (3) states that:
    a. "Oocyte cryopreservation should not just be available for women at risk of premature pathogenic or iatrogenic fertility loss, but also for those who want to protect their reproductive potential against the threat of time"
    b. "Fertility specialists should refrain from passing judgement on a woman's motives for postponing childbearing and requesting fertility preservation."

4. **A British Fertility Society (BFS) guideline** titled "Human Oocyte Cryopreservation: Evidence for Practice" of 2009 (4), due for review in 2013, but as of yet not updated, states:
    a. "Good survival, fertilisation, embryo development and comparable pregnancy rates can be achieved with vitrification" (Grade A evidence i.e. requires at least one RCT as part of a body of literature of overall good quality and consistency addressing the specific recommendation)
    b. "The ASRM Practice committee stated that livebirth per oocyte thawed of 4% for

vitrification….this may be a conservative figure and as more data is published this figure looks likely to increase"

5. **ACE consensus meeting report: oocyte and embryo cryopreservation Sheffield 2011 (5).**
   - **a.** The outcome of transferring embryos derived from vitrified and fresh donor oocytes appears similar.
   - **b.** For women with a partner, oocytes, embryos or both may be cryopreserved as a means of protecting fertility. Clinics should consider offering both options to couples routinely.
   - **c.** Egg donation: the banking of vitrified oocytes could now be used routinely for donated oocyte treatment cycles, with a mandatory quarantine period as for donated sperm. This is not routine practice in the UK but could now be considered.

6. **A systematic review and meta-analysis by Rienzi et al** (6) compared slow-freezing versus vitrification to produce evidence for the development of global guidance (6). Findings as below:
   - a. No evidence of a difference in ongoing CPR between fresh and vitrified oocytes per women randomised / per cycle or per oocyte (randomised trial)
   - **b.** No difference between cycles using exclusively vitrified oocytes versus fresh oocytes for LBR per cycle, LBR per oocyte or LBR per transfer (combined analysis of cohort studies and RCT)

7. **Numerous studies comparing the use of "sibling oocytes"** i.e. eggs from same donor collected at the same collection used either fresh of following vitrification.
   - **a.** Rienzi et al, Human Reproduction 2010 (7)
     - **i.** Prospective Randomised Study
     - **ii.** Fertilisation Rate 83% vs 77% (no sig difference)
     - **iii.** Top quality embryo rate 52% vs 52% (no sig difference)
   - **b.** Cobo et al, Human Reproduction 2010 (8)
     - i. Prospective Randomised Triple-blind study
     - **ii.** Implantation Rate 40% vs 41% (no sig difference)
     - **iii.** CPR/cycle 50% vs 50% (no sig difference)

8. **<u>Society of Assisted Reproductive Technology (SART) data</u>** from US to 2013 (9) outlines comparative nationwide data in donation cycles as below. This again highlights the success of the use of vitrified oocytes that also compares favourable to that with frozen embryos.

Donor Oocytes (all ages)

	Fresh Embryos	Banked Donor Eggs	Thawed Embryos	Donated Embryos
Number of Cycles	8921	2227	8172	1201
Percentage of recipient starts resulting in live birth	49.6	43.2	37.5	37.1
Number of Transfers	7875	2038	7553	1084
Percentage of transfers resulting in live births	56.1	47.1	40.5	41.0
Average number of embryos transferred	1.7	1.6	1.6	1.9

9. In view of the above many US clinics now offer the option of donor eggs as either fresh (synchronised) with a recipient or frozen-thawed from a donor egg bank with an example below:
   - **a.** **<u>Shady Grove (USA)</u>**

i. https://www.shadygrovefertility.com/treatments-success/donor-gestational-carrier/donor-egg

10. UK IVF clinic donor egg banks: Of note, this is now also happening in the UK with recipients offering patients the option of frozen-thawed eggs although data on success is not offered on the clinic websites.

a. Harley Street Fertility Clinic

i. http://hsfc.org.uk/fertility/egg-donation/

b. Manchester Fertility Clinic

i. https://www.manchesterfertility.com/blog/item/treatment-with-donor-eggs-frozen-eggs-vs-fresh/

In light of the above, ***LFC stands by its statement that "frozen [vitrified] eggs behave like fresh eggs".***

2. Number of Eggs

The inspection report suggests that no statistically reliable evidence to support a discussion of how many eggs to freeze to offer a realistic chance of future conception exists.

LFC believes that one of the most fundamental questions asked by patients in social media communication, open evenings and in consultation is how many eggs should they aim to freeze to guarantee (or to have a reasonable chance) of at least one live birth?

Therefore, as part of its responsibility towards patients and the public at large, it is important that this question is addressed directly by LFC. The implication in the report that there is a pre-determined marketing-style "approach", which leads to a clinician discussing the number of eggs to be frozen, is false.

Avoiding this question, rather than answering it based on the best available evidence as below (as we do), would be an abrogation of a major responsibility, deemed misleading, and in itself could leave us open to (inaccurate) accusations of overselling egg freezing.

For example, a patient with a reduced reserve at 33 having produced only 3 eggs to freeze may incorrectly feel confident that she now has a reasonable chance to have a baby in the future. In reality, her chances remain limited and subsequently (perhaps 10 years later) when this patient does not succeed with a successful pregnancy following an egg thaw, she may well be within her right to sue a clinic or clinician for not highlighting that having more eggs would have given her a significantly better chance.

In the absence of guidance from the HFEA, LFC relies on published data and its own experience and data to answer this question, as Lead Consultant, Dr James Nicopoullos, relied upon at the open evening.

1. In the randomised trials in Table 1 used for the ASRM committee opinion (1), the following CPR / oocyte are achieved.
    a. Cobo et al (2008) 6.1% (1 in 16)
    b. Cobo et al (2010) 4.5% (1 in 22)
    c. Rienzi et al (2010) 12.1% (1 in 8)
    d. Parmegiani et al (2011) 6.5% (1 in 15)

2. The Lister data of thawed oocytes used to the end of May 2017 suggest that:
    a. 1 in 19 thawed oocytes achieve a clinical pregnancy.
    b. 1 in 22 thawed oocytes achieve an ongoing pregnancy beyond 24 weeks.

c. The figure was 1 in 27 to the end of 2016 but is updated regularly

3. A British Fertility Society (BFS) guideline titled "Human Ooctye Cryopreservation: Evidence for Practice" of 2009 (4), due for review in 2013 but as of yet not updated states:
    a. ***"that livebirth per oocyte thawed of 4% for vitrification (i.e. 1 in 25)….may be a conservative figure and as more data is published this figure looks likely to increase"***

This question has been further addressed in recent publications that attempt to create an outcome model based on fresh oocytes in their programs. This methodology is used in these publications because the fact that cryopreserved oocytes behave like fresh is now an accepted fact.

4. Goldman et al, from Harvard Medical School (10) in an Original article published in Human Reproduction in 2017 developed a model to determine probability of livebirth from frozen oocytes based on data from:
    a. Women with normal ovarian reserve undergoing fresh ICSI from 2011-2015 (n=520)
    b. Modelling a determination of proportion of mature oocytes that fertilise and form blastocysts
    c. Age-specific probabilities of euploidy estimated from 14,500 PG embryos
    d. Assumed thaw survival rates adjusted by age
    e. Assumed 60% livebirth rates per transferred euploid blastocyst

According to this final model (see Figure 1 and Table S11 below):

- A woman of 34, 37 and 42, each with 20 mature oocytes frozen, would be expected to have a 90, 75 and 37% likelihood of having at least one live birth.
- A woman of 34, 37 or 42 would have to freeze 10, 20 and 61 oocytes, respectively, to have a 75% likelihood of having at least one live birth.
- An egg donor of average age 28.5 would be expected to have a 94% likelihood of having a live birth with 20 mature oocytes frozen.
- A woman of 34, 37 or 42, each with 20 mature oocytes frozen, would be expected to have a 66, 39 and 7% likelihood of having at least two live births respectively.

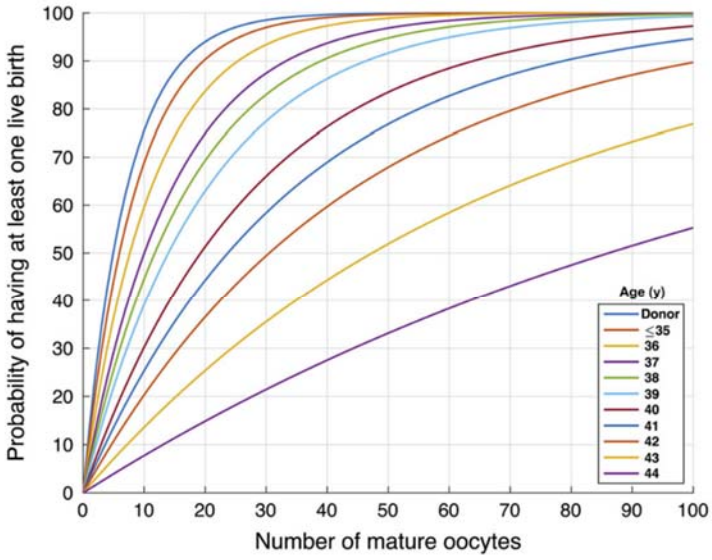


Figure 1 Live birth predictions by age and number of mature oocytes retrieved. Each curve shows the percent likelihood that a patient of a given age will have at least one live birth according to Equation 2, based on the number of mature oocytes retrieved and frozen.

Supplementary Table SII Live birth predictions (%) by age and number of mature oocytes for at least one live birth.

	Probability of at Least One Live Birth (%)										
No. Mature Oocytes	**Egg Donor**	**≤35 y**	**36 y**	**37 y**	**38 y**	**39 y**	**40 y**	**41 y**	**42 y**	**43 y**	**44 y**
1	13	11	9	7	6	5	4	3	2	1	1
2	25	21	17	13	11	9	7	6	4	3	2
3	34	30	24	19	16	14	10	8	7	4	2
4	43	37	30	24	21	18	13	11	9	6	3
5	51	44	36	29	26	22	16	14	11	7	4
6	57	50	42	34	30	26	19	16	13	8	5
8	68	61	52	42	38	33	25	21	17	11	6
10	76	69	60	50	45	39	30	25	20	14	8
12	82	75	66	56	51	45	35	30	24	16	9
14	86	80	72	62	56	50	40	34	27	19	11
16	89	85	77	67	61	55	44	37	30	21	12
18	92	88	80	71	65	59	48	41	34	23	13
20	94	90	84	75	69	63	51	44	37	25	15
25	97	95	90	82	77	71	59	52	43	31	18
30	99	97	93	87	83	77	66	58	49	36	21
35	99	98	96	91	87	82	72	64	55	40	25
40	>99	99	97	94	91	86	76	69	60	44	28
50	>99	>99	99	97	95	92	83	77	68	52	33
60	>99	>99	>99	98	97	95	88	83	74	58	38
70	>99	>99	>99	99	98	97	92	87	80	64	43
80	>99	>99	>99	>99	99	98	94	90	84	69	47
100	>99	>99	>99	>99	>99	99	97	95	90	77	55

5. Cobo et al in 2016 retrospectively reviewed outcomes of 137 women who returned to use vitrified oocytes that were either cryopreserved electively due to age or for a non-malignant medical conditions. Kaplan–Meier curves were created to estimate the live birth rate per oocyte as below (11):
    a. Women ≤35 who used 10 mature oocytes had a 60.5% likelihood of live birth
    b. Women ≥36 who used the same number of oocytes had a 29.7% likelihood of live birth.

6. Doyle et al in 2016 used outcomes from both fresh and frozen IVF cycles to estimate the oocyte-to-child efficiency for each retrieved oocyte after stratification by age group (12).
    a. Women aged 30-34 with 10 frozen mature oocytes were predicted to have approximately a 60% likelihood of having at least one live birth.
    b. Women aged 35 and 38 year with 20 frozen oocytes would have live birth rates of 80 and 60%, respectively.

In summary, in the absence of guidance from the HFEA, LFC has used raw data from its clinic and the data as suggested from the BFS guidelines as well as data based on fresh cycles and published studies and all suggest a figure of 20 to be a reasonable response to a question posed by this patient group, especially when the presentation at the open evening, and in written information given in clinic and on the website, all highlight how this is affected by other factors such as age. Dr Nicopoullos clearly used data from our fresh cycles to show that at ages <35, 35-40 and over 40 the number of oocytes for each livebirth was 15, 20 and 55 respectively. This both reiterated the effect of age on fertility, as well as helping act as an indicator of the number of oocytes required for a livebirth assuming that fresh and frozen oocytes achieve similar success.

Indeed it is reassuring that all the above is not dissimilar from what we mention in our patient information packs and on the website ***"From our egg thaw cycles themselves (up to May 2017) 1 in 22 achieves a live birth/ongoing pregnancy".***

3. Validity and presentation of LFC data

The inspection report suggests that the data provided has not fulfilled the clinic's commitment to transparency.

On its website, the HFEA advises prospective users of egg freezing to, **"make sure you choose a clinic that has plenty of experience and ask to see their most recent success rates for women your age."**

Yet, in the final conclusion of your report you state ***"It is possible to conclude that the information provided at the open evening and information on the website are misleading due to the low numbers used to calculate the statistics."***

LFC does not agree that it is misleading to provide statistics on its website, as these are provided with explanation.

LFC has provided patients with its own data on the 31 (now 35) cycles at the clinic, alongside national data, and refutes any suggestion that it could be misleading to the public when it is following the exact guidance offered by the HFEA. Indeed, LFC believes it would be detrimental to its communications with patients regarding egg freezing if this information was not provided.

Furthermore, we would like to draw your attention to 3 of a number of observational studies published in peer-reviewed journals describing success rates of oocyte cryopreservation with sample numbers (n= 19 to 22) significantly lower than ours (13-15). Such studies are relied upon to provide data for guidelines (1) as well as providing information to the medical establishment at large.

1. A retrospective cohort study of 19 women under 37 years of age undergoing either slow-freeze or vitrification of oocytes reported an oocyte survival rate of 89%, a fertilization rate of 78%, an implantation rate of 45%, and a live-birth rate per transfer of 58% (13*)*.
2. The same group previously reported the results of oocyte cryopreservation/thaw cycles in 22 infertile women and oocyte donors. Similar results (92% survival, 42% implantation rate, 57% clinical pregnancy

rate per transfer, and 4% CPR per oocyte thawed were demonstrated (14).

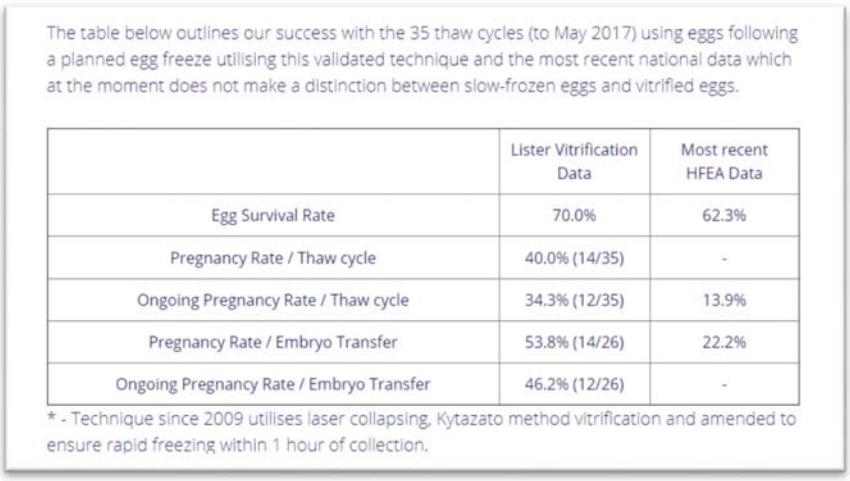
3. A study of oocyte vitrification in 19 fertile women at 35 or under with a prior tubal ligation demonstrated a survival rate of 81%, fertilization rate of 72.3%, implantation rate 45%, CPR of 80%, and LBR per transfer of 65%. Overall, the CPR per oocyte warmed was 5.1% in this study (15).

Four further points on the presentation and validity of our data:

1. Throughout the open evening presentation our data was not presented in isolation, but for complete transparency, in conjunction with HFEA data from website information, current HFEA data as per Fertility Treatment 2014 (16), as well as data from some scientific studies as above. This allows patients to put our data into context as it ensures they have the maximum amount of accurate information upon which to base decisions.

2. There is an implication that the elimination of "slow-freeze" or cycles with oocytes frozen elsewhere as supposed "outliers" is an attempt to artificially enhance outcomes. This is completely inappropriate. We are presenting data to those considering oocyte vitrification at LFC, so data on oocytes frozen elsewhere or frozen by slow-freezing methods that we no longer practice is irrelevant and not part of the dataset under discussion so therefore cannot be deemed "outliers". Our website clearly states the exact nature of the data being presented ***"Technique since 2009 utilises laser collapsing, Kytazato method vitrification and amended to ensure rapid freezing within 1 hour of collection"***

3. In point 1.6 of the report, you mentioned that the Code of Practice advises *"a clinic should give the woman seeking treatment and her partner, if applicable, information about the likely outcomes of the proposed treatment (data provided should include the centre's most recent live birth rate and clinical pregnancy rate per treatment cycle, verified by the HFEA, and the national live birth rate and clinical pregnancy rate per treatment cycle)" It may assist to note:*
    a. The HFEA has not published or verified any data for any specific centre regarding egg freezing.
    b. LFC has provided its own results and has provided the exact number of treatment cycles.
    c. On LFC's website, the HFEA data and its limitation is mentioned: *"Although, many thousands of eggs have safely been stored in the UK since 2001, according to the most recent data from the HFEA, fewer than 60 babies have been born to patients storing and thawing their own eggs. Initially, older less effective freezing techniques were utilised and many of the women who have undertaken egg freezing for social reasons have yet to use their eggs or didn't need to as they conceived naturally later in life"*.
    d. LFC has provided the national live birth rate of 13.9% alongside our data (see below).



The table below outlines our success with the 35 thaw cycles (to May 2017) using eggs following a planned egg freeze utilising this validated technique and the most recent national data which at the moment does not make a distinction between slow-frozen eggs and vitrified eggs.

	Lister Vitrification Data	Most recent HFEA Data
Egg Survival Rate	70.0%	62.3%
Pregnancy Rate / Thaw cycle	40.0% (14/35)	-
Ongoing Pregnancy Rate / Thaw cycle	34.3% (12/35)	13.9%
Pregnancy Rate / Embryo Transfer	53.8% (14/26)	22.2%
Ongoing Pregnancy Rate / Embryo Transfer	46.2% (12/26)	-

* - Technique since 2009 utilises laser collapsing, Kytazato method vitrification and amended to ensure rapid freezing within 1 hour of collection.

e. Criticism would be valid if we gave percentage outcomes without sample size, but as guided by the HFEA, we appropriately give cycle numbers. We provide the exact number of cycles and keep updating them as they further develop.
f. LFC is not aware of any instruction to clinics not to publish or talk about any results they have if the number falls below a certain point, especially if national data is also provided.

4. In point 3.6 of your findings, you mention *"We also noted that attendees were not given information regarding egg freezing in written form to contemplate later. To provide this information in written form aids to minimise any misunderstanding and confusion regarding information."* It may assist to note that on registering as a patient and in consultation, patients are given written information to support the verbal information as outlined in the Code of Practice. Of note, it has become common practice to refer to websites for further information. The HFEA itself once published a multitude of documents in paper format (such as the Code of Practice, Guide to Fertility Clinics etc.). These documents are now only available on the HFEA website only as PDFs.

4. HFEA and limitations of published egg freeze data

In its publication "Fertility treatment 2014, trends and figures" (16), the HFEA has for the first time reported data regarding egg freezing in isolation as a separate chapter which we welcome.

Some valuable information and insight is offered, most notably:

- **Confirmation of a significant rise in those seeking egg freezing (25% increase on 2013).**
- **Confirmation of a significant rise in those returning to use frozen-thawed oocytes (25% increase on 2013).**
- **Despite this rise, the number remains small in comparison with total number of other assisted conception procedures.**
    - **890 cycles of egg freezing in 816 women starting treatment**
    - **A small proportion of the over 60,000 treatment cycles in the UK.**
- **The HFEA mentions that women may want to consider egg freezing (among other reasons) if "***You're worried about your fertility declining but you're not ready to have a child or you haven't found the right partner – this is often called 'elective egg freezing*."
- A livebirth success rate of 13.9% is quoted for 2013 (20.2% for 2012) with a caveat that "*at the moment it's very hard to say as the number of women having treatment is so low. Since 2001 only 60 babies have been born from frozen eggs*".
- The HFEA advises prospective users of this service to, "*make sure you choose a clinic that has plenty of experience and* ***ask to see their most recent success rates for women your age*****."**

Nevertheless, because the way the data is collected

- The HFEA is as yet to produce accurate data for success rates of frozen oocytes based on age at cryopreservation rather than age at transfer.
- The HFEA remains unable to offer accurate data for success rates of frozen oocytes using vitrification

techniques alone (rather than slow freezing).

These are the two key parameters affecting outcome and without them analysis of nationwide data for use to counsel patients remains virtually impossible.

- A significant portion of data comes from units who perform too few freeze cycles to develop the required skill and experience, and as such negatively skew the data.

- HFEA has not published or verified any data for any specific centre regarding egg freezing.

- The HFEA data also fails to consider the increasing practice of egg freezing as a means of batching eggs for those with a poor prognosis before fertilisation (Cobo et al, 2012 (17)). In such scenarios, patients (primarily those with reduced ovarian reserve) undergo repeated egg collections and the small number of eggs they produce are cryopreserved, subsequently collectively thawed and fertilised as one with ICSI. The resulting embryos are observed and the best is transferred. We are aware that this approach is used by a number of clinics in the UK. This approach is controversial as it subjects the patient to two to three egg collections before she undergoes the IVF/ICSI part of the treatment, and it could be that the egg produced in the first egg collection would be the one that have resulted in live birth. Nevertheless, this technique could be especially valuable if PGD were to be performed, as in this case the cost of fertilisation and that of PGD is paid once, rather than added to each cycle with the number of eggs collected. <u>The important point is that such an approach would never be used or suggested unless the clinics believe that frozen-vitrified eggs behave as well as fresh ones</u>.

<u>5. HFEA's Conclusions</u>

For completeness, HFEA's conclusions are set out below, with LFC's responses beneath:

- **At this open evening, the centre did not emphasise the importance of each patient being different and the importance of individual assessments.**

LFC considers this conclusion to be factually incorrect.

Slides 11-55 of the presentation outline the physiology of ovarian reserve, how it is assessed and how it impacts on both natural fecundity and future fertility. Furthermore, the presentation outlined exactly how a patient would be individually assessed in clinic and how that would impact on any decisions made. LFC clearly stated that individualized assessments must be made before treatment.

The presentation also made it clear that the number of eggs required to achieve a live birth was dependent on patient age. Using the clinic's own data set, of over a decade of fresh cycles, demonstrated the difference in the number of "fresh" eggs required to achieve a livebirth i.e. 1 in 15 for those under 35, 1 in 20 for those between 35-40 and significantly more for those over 40. This re-iterated the effect of age on fertility, which is also an important part of the individual assessment.

- **Statements made by the clinic such as '15-20 eggs would make me think you would get a baby' and [frozen eggs] 'behave like fresh eggs' It is important to note that statistically reliable evidence to support these statements is currently not available.**

LFC disagrees with this conclusion. No such statement that "15-20 eggs would get a baby" were made and the presentation provided detailed and accurate data on the outcome of egg freezing from HFEA, in-house LFC data, and worldwide data sets, and highlighted on numerous occasions the limitations in terms of techniques, other

factors affecting outcome, and sample number. Section 1 above allows LFC to submit that the statement "*frozen [vitrified] eggs behave like fresh eggs*" can be supported by statistically reliable evidence and the LFC stands by this statement.

- **The information relating to the efficacy of treatment that was provided to prospective patients did not clearly define whether this was statistically derived from the centres own performance, or from nationally derived information such as the HFEA's, was being relied on. In any event the limitations of the performance information were not highlighted.**

LFC does not agree with the above conclusion.

To allow those present at the open evening to have all the information they required to make an informed choice, the following data was presented:

- HFEA data presented on website to 2012 demonstrating 20 livebirths from 160 thaw cycles (12.5% live birth rate);
- HFEA data received following a freedom of information request (FOI- 2015-00316);
- The scientific studies of the use of sibling oocytes (7-8), and those demonstrate a direct comparison of fresh versus vitrified oocytes;
- Raw LFC data of the outcome of frozen vitrified oocyte-thaw cycles; and
- Most recent HFEA data from Fertility Trends 2014 (16)

Furthermore:

- The sample number was presented on the slide of LFC's data and the limitations of the small numbers both in-house and nationwide reiterated.
- The table on the website which provides the data describes national and LFC's data separately.
- The limitation as regards to statistical validity is clear from the number of cycles reported which is what is required from the Code of Practice.
- We clearly referred to our data when we spoke about the number of eggs needed to achieve a livebirth "From our egg thaw cycles themselves (up to May 2017) 1 in every 19 eggs thawed has achieved a pregnancy and 1 in 22 a livebirth/ongoing pregnancy."

We reiterate that taking into account the limitations of HFEA data, as outlined in section 3 above, by providing its own data alongside the national data, LFC is providing patients with a fuller picture of egg freezing outcomes, and providing patients with greater transparency.

- **Whilst it is noted in the centre's statement in response to the media allegations that it is: 'committed to ensuring patients are given transparent information and responsible medical advice to help them make informed decisions' it has not fulfilled this commitment to transparency on this occasion.**

Please see the above responses and explanation. LFC considers that by providing clinical data about the experiences at its clinic, it is providing transparency to patients. This accords with HFEA's direction to prospective users of the service to a "*make sure you choose a clinic that has plenty of experience and ask to see their most recent success rates for women your age*."

LFC is not aware of any instruction to clinics not to publish or talk about any results they have if the number falls below a certain point, especially if national data is also provided.

LFC can be no more transparent than to offer patients all HFEA data as well as its own data.

- **From the information obtained and discussions held during the inspection; the review of the recordings of the lead consultant's comments made to the Daily Mail reporter could be misinterpreted. The centre's second patient information session on egg freezing was attended by the reporter in which only two people were present, one authentic prospective patient and one representative from the Daily Mail this small number of attendees allowed for more targeted and intense questions directed towards the lead clinician who was facilitating the open evening.**

LFC does not agree that any of its statements at the open evening could be misinterpreted.

LFC welcomes intense questioning at any open evening, whether two or twenty-two couples or patients attend.

LFC has highlighted the several inaccuracies in the Daily Mail article, and it is disappointed that this has not been discussed in HFEA's report. For example, the sensationalist statement in the article stating that the open evening was attended by "*half a dozen women, all single and some recently heartbroken*" bears no resemblance to the truth, but the report makes no comment regarding this falsehood that would be a valid indicator of the quality of facts offered in the article.

- **It could be said that the centre is promoting egg freezing as a scheme to enable patients to preserve their fertility to have treatment at a time of their choice, without fully explaining the limitations especially at open evenings.**

LFC does not agree with this statement. LFC does not promote egg freezing but, provides all relevant information regarding the procedure to women if they are considering the option of elective (social) egg freezing. LFC then refers all patients to its website for further information.

On our website, on the written information given to patients, and at open evenings (slides 74-81), we have been very careful to mention specific limitations of egg freezing.

To confirm at the open evening the following is discussed, for which you have written and visual confirmation in the form of slides and film images:

- Available data on long term safety of vitrification
- The risks of hormonal stimulation
- The risks of the operative procedure
- The risk of ovarian hyper stimulation
- The risks of pregnancy at the extremes of reproductive
- Informing patients that our consent forms state that ***"However, there is no guarantee of success with any number as other factors such as egg quality are also relevant. Some women may achieve a success with only a few eggs and some may be unsuccessful with over 20."***
- Informing patients that our consent forms state that ***"Similarly from a social perspective, freezing your eggs may allow you the peace of mind of a potential "fertility insurance policy" for the future if ever needed but there is never any guarantee of success. Freezing should never be seen as a definitive alternative to natural conception as it is not. Such a feeling of false reassurance may be in fact detrimental to overall chances of conception."***
- On our website is also stated *that* ***"one of the non intended social consequences is the false sense of security that may lead to a further detrimental delay in trying naturally for a baby. Should the frozen eggs prove unsuccessful, they may subsequently be faced with the prospect of trying for a baby with fresh eggs at an older age".***

LFC believes it has provided all relevant information on limitations to patients and is perplexed as to what further information it could provide.

- **It is possible to conclude that the information provided at the open evening and information on the website are misleading due to the low numbers used to calculate the statistics.**

LFC does not agree with this statement as discussed in detail in section 3 above.

Conclusion

Our priority is to provide patients with the accurate information and responsible medical advice that they need to make the best decision about their fertility.

It is important to note that, in our opinion, at the heart of our difference in views with the Inspector's report is the fact that the data that we present, and the questions that we are trying to answer, vary significantly from those provided by the HFEA. I hope that it is clear in this response how this variance does not translate into inaccurate or misleading information.

As the regulatory and expert body in the UK, people rightly turn to the HFEA when they have questions about a clinic's practice, and your role is invaluable to both patients and clinics. However, on this occasion, we believe that the limitations in the data that the HFEA is using, mean that patients do not get as full a picture as is available through critical analysis and examination of data and developments from around the world.

Our data is not at variance with the major body of published work in peer reviewed journals or with the recommendation of all the respectable bodies that guide fertility practice worldwide. The questions we are asking are the same as the answers provided from that body of work. Furthermore, and to reiterate, our data was not presented in isolation but - for complete transparency - in conjunction with HFEA data from website information, current HFEA data as per Fertility Treatment 2014 (16), as well as data from some scientific studies as above. This allows patients to put data into context, as it ensures that they have the maximum amount of accurate information upon which to base decisions.

The HFEA has a vital role to play in ensuring the highest possible standards of patient care and safety within assisted reproduction, as well as ensuring patients are provided with accurate information about treatment prior to it taking place, including egg freezing. Equally it is the role of the HFEA to regulate clinical practice, and it is the role of evidence-based research to drive clinical practice. The highest level of such evidence is based on randomized controlled trials and systematic reviews that both support the assertion that the outcomes of frozen/vitrified-thawed oocytes is superior to the data currently presented by the HFEA, and approaching that of fresh oocytes. The limitations of the HFEA data, in our view, prevents it from providing clinically applicable data on current practice. This, however, does not negate the quality of research and data available to drive best practice.

In order to move this forward for patients, we would like to suggest the establishment of a 'Task Force' group to examine the issue of Oocyte Cryopreservation at large, and to establish new methods for data collection that allows your great organisation to provide robust statistics in this area. We believe this would be of huge benefit to patients seeking detailed and current scientific research and evidence from responsible and well-informed clinicians.

We don't believe that we should be subject to a licensing committee meeting. The information that we provide our patients is not, in our view, misleading, but rather offers them the most current medical and scientific thinking. We provide patients with HFEA data, but also with a wider range of current information that is backed by scientific evidence and presented responsibly. We believe that this is what patients require, and that our

approach enables them to make informed decisions about their approach to fertility treatment.

Finally, The Lister Fertility Clinic has been in existence for almost 30 years and has operated within a regulatory framework with no previous concerns. Transparency and honesty are absolutely fundamental to us and, as one of the most trusted and well-established clinics in the UK, we believe that the report from the inspector is an inaccurate representation of The Lister Fertility Clinic. We very much hope that, after reading our robust response, you will consider withdrawing the report.

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