HFEA Licence Committee Meeting

10 July 2014

Finsbury Tower, 103-105 Bunhill Row, London, EC1Y 8HF

Minutes – Item 5a

Centre 0094 (Barts and the London Centre for Reproductive Medicine) – Whistleblower Report

Members of the Committee:	Legal Adviser:
Andy Greenfield (lay) (Chair) David Archard (lay) Debbie Barber (professional) Jane Dibblin (lay)	Tom Rider, Fieldfisher Committee Secretary: Lauren Crawford

Declarations of Interest: members of the Committee declared that they had no conflicts of interest in relation to this item.

The following papers were considered by the Committee:

- HFEA's additional licensing report
- Independent review report

The Committee also had before it:

- HFEA Protocol for the Conduct of Licence Committee Meetings and Hearings
- 8th edition of the HFEA Code of Practice
- Human Fertilisation and Embryology Act 1990 (as amended)
- Decision trees for granting and renewing licences and considering requests to vary a licence (including the PGD decision tree); and
- Guidance for members of Authority and Committees on the handling of conflicts of interest approved by the Authority on 21 January 2009.
- Guidance on periods for which new or renewed licences should be granted
- Standing Orders and Instrument of Delegation
- Indicative Sanctions Guidance
- HFEA Directions 0000 – 0012
- Guide to Licensing
- Compliance and Enforcement Policy
- Policy on Publication of Authority and Committee Papers

Background

1. Barts and the London Centre for Reproductive Medicine has held a treatment and storage licence with the HFEA since 1992 and provides a full range of fertility services, including storage of gametes and embryos. The inspection team is satisfied that the activities carried out at the centre are necessary or desirable in order to provide licensed treatment services.

2. The centre provided 1,084 cycles of treatment (excluding partner intrauterine insemination) in the 12 months to February 2014. In relation to activity levels this is a large centre.

Discussion

3. The Committee noted that in January of this year the CQC forwarded a file of papers to the Head of Inspection regarding concerns raised by a whistle-blower about this centre. Following a review of the paperwork a meeting was held between the two regulatory bodies. The whistle-blower drew attention to various aspects of the centre's clinical practices from 2012 to 2013. The main areas of concern are set out below:
    - Issues around the centre's monitoring and stimulation regimes for patients undergoing in-vitro fertilisation (IVF) thus increasing the risk of patients developing Ovarian Hyperstimulation Syndrome (OHSS).
    - Incorrect information provided by the centre to the HFEA regarding OHSS incidents including deliberately underestimating the severity grading and under reporting of OHSS incidents.
    - Issues around what patients from outside the catchment area are entitled to by way of surgical referrals and what constitutes a cycle of IVF (in relation to commissioning body funding).
    - Fertility theatre lists changed at short notice to accommodate general gynaecology patients.
    - Lack of feedback regarding the Trust's internal incident reporting system.
    - Employment issues.

4. The Committee noted that it was concluded that the issues related to OHSS were within the remit of the HFEA to investigate as this was the main area of concern potentially impacting directly on patient safety. An investigation comprising an independent review of the centre's clinical protocols around treatment regimes, OHSS management and OHSS incident reporting to the HFEA should be conducted. This report outlines the finding of the review.

5. The Committee noted that terms of reference were drawn up and an external clinical expert was recruited to undertake an independent review of the centre's practices. To ensure there was no perception of bias the HFEA identified a relevant cohort of patient records for the clinical expert to review; this included a random sample of patient notes as well as 22 sets of notes relating to patients that developed OHSS.

6. The Committee noted that the clinical expert carried out the review in late April and provided a copy of the findings to the HFEA in June 2014. The clinical expert concluded that the protocols in use at the centre from July 2012 – April 2013 were appropriate.

7. The Committee noted that the report stated that the centre was not *required* to report cases of moderate OHSS to the HFEA but did so nevertheless. A few of the moderate cases turned out to be severe but it is likely that the initial grading was mostly correct. Part of the issue is that most of the patients, when calling the centre with symptoms of OHSS, were advised to attend their local hospital's emergency department for review. The clinical expert suspects that in a number of cases the patient was admitted for OHSS by an emergency department clinician without experience of the condition. This also meant that there was limited information about the presenting symptoms and signs. However, it is likely that some of the moderate cases that were not seen by an IVF clinician were actually severe. Therefore the external assessor suggests that the centre encourages patients to attend the unit where possible.

8. The Committee noted that the clinical expert made the following suggestions for improvement:

    - consideration should be given to cross-referencing the main IVF and OHSS protocols to reduce the risk of possible confusion;
    - the IVF protocol should be updated in line with the OHSS protocol.

9. The Committee noted that the Person Responsible (PR) has given verbal assurances to the HFEA that these recommendations will be implemented.

10. The Committee noted that, in summary, the clinical expert does not believe that there are any concerns over practice as regards OHSS during the time period in question or currently.

11. The Committee noted that the Executive's next steps in this matter will be to hold a meeting with the CQC and Trust Senior Management to share the findings of our investigation and to ensure that concerns that fall outside of the HFEA's regulatory remit are and/or have been addressed. If findings of any CQC or Trust investigations are pertinent to the centre's licence the HFEA Executive will provide a further update to the Licence Committee.

Decision

12. The Committee were satisfied with the actions and reactions of the centre in regards to OHSS protocols.

13. The Committee were satisfied that the Executive and the Centre had worked well together on this issue.

14. The Committee would like to see the findings of any CQC or Trust investigations.

Signed: Date: 23/07/2014

Andy Greenfield (Chair)

COVER SHEET

Licence Committee

Centre Name: Barts and The London Centre for Reproductive Medicine

Centre Number: 0094

Person Responsible: Ms Bonnie Collins

Additional licensing report regarding a whistle-blower's concerns

Papers Enclosed:

- HFEA's additional licensing report
- Independent review report

Additional Licensing Report

Centre Name: Barts and The London Centre for Reproductive Medicine

Centre number: 0094

Date of Licence Committee meeting: 10 July 2014

Purpose of the report

The report summarises the findings of a body of work carried out by the HFEA Executive regarding a whistle-blower's concerns about this centre. It is primarily written for the Authority's Licence Committee.

Brief background to the HFEA'S involvement with the whistle-blower's concerns:

In January of this year the CQC forwarded a file of papers to the Head of Inspection regarding concerns raised by a whistle-blower about this centre. Following a review of the paperwork a meeting was held between the two regulatory bodies. The whistle-blower drew attention to various aspects of the centre's clinical practices from 2012 to 2013.

The main areas of concern are set out below:

- Issues around the centre's monitoring and stimulation regimes for patients undergoing in vitro fertilisation (IVF) thus increasing the risk of patients developing Ovarian Hyperstimulation Syndrome (OHSS).
- Incorrect information provided by the centre to the HFEA regarding OHSS incidents including deliberately underestimating the severity grading and under reporting of OHSS incidents.
- Issues around what patients from outside the catchment area are entitled to by way of surgical referrals and what constitutes a cycle of IVF (in relation to commissioning body funding).
- Fertility theatre lists changed at short notice to accommodate general gynaecology patients[1].
- Lack of feedback regarding the Trust's internal incident reporting system.
- Employment issues[2].

It was concluded the issues related to OHSS were within the remit of the HFEA to investigate as this was the main area of concern potentially impacting directly on patient safety. An investigation comprising of an independent review of the centre's clinical protocols around treatment regimes, OHSS management and OHSS incident reporting to the HFEA should be conducted. This report outlines the finding of the review.

Methodology

Terms of reference were drawn up and an external clinical expert was recruited to undertake an independent review of the centre's practices.

To ensure there was no perception of bias the HFEA identified a relevant cohort of patient records for the clinical expert to review; this included a random sample of patient notes as well as 22 sets of notes relating to patients that developed OHSS.

The clinical expert carried out the review in late April and provided a copy of the findings to the HFEA in June 2014.

Independent Review Findings:

The clinical expert concluded that the protocols in use at the centre from July 2012 – April 2013 were appropriate.

[1] Including, on occasion the absence of patient records to review prior to starting the theatre list.
[2] The whistle-blower was informed this issue did not fall within the remit of either regulator and the contact details of " Public Concern at Work" the whistle-blowing charity were provided

The report noted that the centre was not required to report cases of moderate OHSS to the HFEA but did. A few of the moderate cases turned out to be severe but it is likely that the initial grading was mostly correct. Part of the issue is that most of the patients, when calling the centre with symptoms of OHSS, were advised to attend their local hospital's emergency department for review. The clinical expert suspects that in a number of cases the patient was admitted for OHSS by an emergency department clinician without experience of the condition. This also meant that there was limited information about the presenting symptoms and signs. However it is likely that some of the moderate cases which were not seen by an IVF clinician were actually severe. Therefore the external assessor suggests that the centre encourages patients to attend the unit where possible.

The clinical expert made the following suggestions for improvements:

- consideration should be given to cross-referencing the main IVF and OHSS protocols to reduce the risk of possible confusion:
- the IVF protocol should be updated in line with the OHSS protocol.

The Person Responsible has given verbally assurances to the HFEA that these recommendations will be implemented.

In summary, the clinical expert does not believe that there are any concerns over practice as regards OHSS during the time period in question[3] or currently.

Next Steps:

To hold a meeting with the CQC and Trust Senior Management to share the findings of our investigation and to ensure that concerns that fall outside of the HFEA's regulatory remit are and/or have been addressed. If findings of any CQC or Trust investigations are pertinent to the centre's licence the HFEA Executive will provide a further update to the Licence Committee.

[3] July 2012 – April 2013.

INDEPENDENT REVIEW OF ST BARTHOLOMEW'S HOSPITAL IVF UNIT WITH REGARDS TO PRACTICE SURROUNDING OVARIAN HYPERSTIMULATION SYNDROME

REQUESTED BY: Paula Nolan, Clinical Governance Lead, HFEA

UNDERTAKEN BY: Mr. Tim Child MA MD MRCOG, Consultant Gynaecologist and Subspecialist in Reproductive Medicine, University of Oxford; Medical Director and Person Responsible, Oxford Fertility Unit.

DATE OF VISIT TO BARTS IVF: 17 April 2014

DATE OF REPORT: 13 June 2014

'The terms of reference for the independent review are:

- Were the stimulation regimens and monitoring protocols of a reasonable standard at the time the whistle blower first raised his concerns within the unit (July 2012 – April 2013)?
    - To review protocols in use between July 2012 – April 2013.
    - To review a random sample of the notes of patients undergoing stimulation in this time period to assess compliance with the protocols. The sample size is to be at your discretion depending on the findings of the review (perhaps starting with five sets of notes – if no discrepancy stop at this point, however if discrepancies found you may want to examine a further cohort to ascertain if this was a systematic problem rather than a potential one off).
- Have protocols been changed in the time since the concerns were raised and are they currently of a reasonable standard?
    - To review current protocols.
    - To review a random sample of the notes of patients undergoing or having recently undergone stimulation using current protocols to ascertain compliance with the protocols (sample size at the

reviewer's discretion).

- Was information provided to the HFEA regarding OHSS incident reporting accurate?
    - To review the severity grading decisions made by the centre in relation to submitted OHSS incidents (for OHSS incidents reported from July 2012 – April 2013).
    - To review the information submitted by the centre regarding follow up reports (case reviews) in relation to severe OHSS.
- Any further comments or observations you have (positive or negative) in relation to clinical practices in general, stimulation and management of OHSS practices in particular.'

PART 1- BACKGROUND

Ovarian Hyperstimulation Syndrome (OHSS) is the main iatrogenic risk to a woman's health during IVF/ICSI. Women who develop OHSS may experience nausea, vomiting, diarrhoea, abdominal distension and pain (due to ascites), and shortness of breath due usually to splinting of the diaphragm by the distended abdomen, though sometimes due to a pleural effusion. The syndrome occurs when fluid moves from the circulatory system into the 'third space' ie into the abdominal cavity, lungs, or other tissues. This movement of fluid out of the circulatory system leads to the woman's blood becoming concentrated and in addition the clotting system is activated- both of these can potentially lead to renal failure and/or venous thromboembolism which may be fatal. Treatment is supportive and for women with Severe OHSS hospital admission with intravenous rehydration and the use of anti-thrombotic regimes such as TED stockings and heparin are used. If the ascites is extensive and causing severe symptoms then it may be drained transabdominally. Occasionally a pleural effusion will require a tap.

Recognised pre-treatment risk factors for OHSS include younger female age, lower BMI, previous OHSS, the presence of one or more ovaries of polycystic appearance

on scan (PCO), or PCO combined with anovulatory cycles (polycystic ovarian syndrome (PCOS)), or a raised blood AMH level. In order to reduce the risk of developing OHSS a lower starting dose of FSH may be used and also an antagonist (rather than long protocol agonist) regime.

Per-treatment risk factors include high numbers of follicles and/or estradiol. Management options include lowering the dose of FSH or stopping it all together for one or more days ('coasting'), using a lower hCG trigger dose, or cancelling the cycle before hCG. The only way to absolutely prevent OHSS is by not giving the hCG trigger. Unfortunately, it is usually difficult to predict who is going to go on and develop OHSS and so the 'number needed to cancel' IVF cycles to prevent one OHSS case will be quite high. Once the egg collection has taken place then management approaches include freezing all embryos (FAE) which will prevent 'late onset' OHSS which occurs secondary to embryo implantation. FAE will not prevent 'early onset OHSS which occurs secondary to the hCG trigger.

There are a number of OHSS classifications though none are universally accepted. Barts IVF opted for the widely used Golan et al (1989) Classification in which Mild OHSS is essentially abdominal distension with possibly some nausea/vomiting/diarrhoea. Moderate OHSS is mild plus ultrasound evidence of abdominal ascites. Severe OHSS is moderate OHSS plus clinical evidence of ascites or pleural effusion, or blood changes such as haemoconcentration, coagulation abnormalities or renal dysfunction. Around 1% of IVF cycles result in Severe OHSS.

PART 2

Were the stimulation regimens and monitoring protocols of a reasonable standard at the time the whistle blower first raised his concerns within the unit (July 2012 – April 2013)?

- To review protocols in use between July 2012 – April 2013.
- To review a random sample of the notes of patients undergoing stimulation in this time period to assess compliance with the protocols. The sample size is to be at your discretion depending on the findings of the review (perhaps starting with five sets of notes – if no discrepancy stop at this point, however if discrepancies found you may want to examine a further cohort to ascertain if this was a systematic problem rather than a potential one off).

A. To review protocols in use between July 2012 – April 2013.

I was supplied the documents 'ART (IVF/ICSI) Controlled Ovarian Hyper Stimulation (COS) [issue date January 2007]' and 'Management of ovarian hyperstimulation syndrome (OHSS) [issue date 1/06/2011]' which appear to have been the protocols in use between July 2012 and April 2013.

The 2007 document describes IVF protocols for use in all patients and includes recommended FSH stimulation doses. The protocol is rather dated (5 years old by 2012) in that it does not suggest the use of antagonist cycles to reduce the risk of OHSS in women with PCOS. However, the 2011 OHSS document augments the 2007 protocol and covers prevention (identifying those at risk pre and per treatment) and management of OHSS and includes a section on classification. This document is clear, well written and (as far as is possible with OHSS) evidence-based and describes the use of multiple strategies to reduce risk including antagonist cycles. In summary, the protocols in-place were appropriate.

B. To review a random sample of the notes of patients undergoing stimulation in this time period (July '12 – April '13) to assess compliance with the protocols.

I asked the HFEA to select 10 random names of patients undergoing IVF during the time period of concern and also the period since and requested that Barts IVF pulled the notes. I assessed the 9 available records (6 treated July '12 to April '13 and 3 subsequent) for compliance against the above protocols.
In all 9 sets of notes the appropriate treatment regime, drug dose, decision to hCG trigger and other aspects of treatment were undertaken as per the two protocols. Importantly, 6 of the patients had a dose reduction and 2 were coasted as per protocol to reduce the risk of OHSS. No patients developed OHSS. In summary, the random sample of 9 patients showed no concerns and treatment was as per protocol.

PART 3

Have protocols been changed in the time since the concerns were raised and are they currently of a reasonable standard?

- To review current protocols.
- To review a random sample of the notes of patients undergoing or having recently undergone stimulation using current protocols to ascertain compliance with the protocols (sample size at the reviewer's discretion).

A. To review current protocols.
I was supplied with the relevant documents 'IVF and ICSI treatment [issue date 02/10/2013]'; 'Management of ovarian hyperstimulation syndrome (OHSS) [issue date 02/10/2013]' and 'Prevention and treatment of ovarian hyperstimulation syndrome (OHSS) [issue date 20/03/2014]' which replaced the 02/10/2013 version.

The current OHSS document is clear, well written and, where possible, evidence based. The 'IVF and ICSI treatment' document only suggests the use of antagonists for 'Low Responders' which is at odds with the co-existing OHSS document and could lead to some confusion. It's very similar to the 2007 protocol. I think it should be

revised to fit-in properly with the current OHSS protocol. However, the OHSS document should allow for the identification and management of at-risk patients as it is very clear. In summary, whilst improvements can and should be made, the current protocols are suitable for safe management of patients.

B. To review a random sample of the notes of patients undergoing or having recently undergone stimulation using current protocols to ascertain compliance with the protocols (sample size at the reviewer's discretion).

As described above, 3 sets of notes were audited against the current protocols and were found to be correct. No concerns though only 3 records were reviewed.

PART 4

Was information provided to the HFEA regarding OHSS incident reporting accurate?

- To review the severity grading decisions made by the centre in relation to submitted OHSS incidents (for OHSS incidents reported from July 2012 – April 2013).
- To review the information submitted by the centre regarding follow up reports (case reviews) in relation to severe OHSS.

A. To review the severity grading decisions made by the centre in relation to submitted OHSS incidents (for OHSS incidents reported from July 2012 – April 2013).

I undertook a detailed review of the notes of 22 patients reported to the HFEA for OHSS between July '12 and April '13. In particular I looked at pre- and per-treatment risk factors for OHSS and their management. Pre-treatment factors included female age, BMI, PCOS, antral follicle count, IVF cycle number and whether there was a history of OHSS. Treatment factors included the regime (agonist or antagonist), starting FSH dose and alterations including coasting,

maximum serum estradiol and serum FSH levels, number of follicles, number of oocytes collected, whether all embryos were frozen ('FAE'), whether OHSS developed and, from the notes, the apparent grade, whether an abdominal drain was inserted after hospital admission, the grade of OHSS reported to the HFEA and whether overall treatment was as per the protocols in-place. The anonymised data were entered onto an Excel database for analysis.

Of the 22 cycles 15 patients had risk factors for developing OHSS including PCOS, ovaries of polycystic morphology, or previous OHSS. Four of the patients had a full diagnosis of PCOS. In only 3 of the 22 cycles was an antagonist regime used (which is recognised to significantly reduce the rate of OHSS). However, this low rate of antagonist use is in keeping with the protocol in use at the time (issue date 1/06/2011) which states that for women at risk of OHSS (PCOS, young, thin, multifollicular (PCO) ovaries, previous OHSS or high response) then *Consider antagonist cycle of stimulation* ie its use was not strongly recommended.

During the stimulation phase of treatment the monitoring, FSH dose and changes, and decision re hCG timing were as per protocol in 17 of the 22 reported cycles. In 4 of the 5 cycles that were not as per protocol this is because the starting FSH does was slightly higher than in the protocol. In 2 cycles the decision to give hCG was not as per protocol. It is important to recognize that there always needs to be some leeway for clinicans to act outside of a protocol/guideline as the clinical scenario dictates. In my opinion the deviations from the protocol were fairly minor and within acceptable clinical practice.

Six of the cycles resulted in FAE. 21 of the cycles resulted in the patient being admitted for OHSS, and for one cycle admission was suggested but declined by the patient. Of the 22 reported cycles the OHSS was graded as moderate in 19, severe in 2, and ungraded in one (though the patient appears to have had a drain inserted so would be severe, though this was probably inserted after the cycle had already been reported). It is difficult to determine whether the actual grade of OHSS suffered by the patient was the same as that reported to the HFEA. In part this is because many of the patients were not reviewed at the IVF Unit but,

instead, were seen and admitted through their local Emergency Department. Information in the Barts notes from the admitting hospital was often limited, or gained from the patient or her partner. The OHSS protocol uses the Golan 1989 classification of OHSS in which ultrasonic evidence of ascites equates to Moderate OHSS and clinical ascites (ie able to detect on manual examination) equates to Severe OHSS. Since reporting to the HFEA happened within the first day of the Unit being aware of the diagnosis it is entirely possible that what was thought to be Moderate OHSS then developed into Severe over the subsequent days. Also, according to the HFEA code of practice Unit's are required to report Severe OHSS, not Moderate, as an adverse incident. Therefore, even if a few of the 'Moderate' OHSS cases turned out to be Severe it would appear that a number of the 'true' Moderate OHSS cases needn't have been reported to the HFEA in the first place.

B. To review the information submitted by the centre regarding follow up reports (case reviews) in relation to severe OHSS.

I reviewed the 2 submitted case reports regarding the Severe OHSS cases and found these summaries to be appropriate and correct.

PART 5- OBSERVATIONS AND SUMMARY

In my opinion the protocols in place were and are appropriate though do need to be more cross-referenced (eg the main IVF and OHSS protocols) to reduce the risk of possible confusion. The IVF protocol should be updated in line with the OHSS protocol.

Treatment occurred as per protocol in the majority of cases and deviation from the protocols were relatively minor.

The Unit was not required to report cases of Moderate OHSS to the HFEA but did. A few of the moderate cases turned out to be severe but it likely that the initial grade was mostly correct. Part of the issue is that most of the patients, when calling the IVF unit with symptoms of OHSS, were advised to attend their local hospital's Emergency Department for review. Sometimes the hospitals were not too far from Barts. I suspect that in a number of cases the patient was unnecessarily admitted for OHSS by an ED clinician without experience of the condition. This also meant that there was limited information about the presenting symptoms and signs. I suggest that the Unit encourage patients to attend Barts for review where possible. The 'true' rate of OHSS requiring reporting to the HFEA will, I suspect, be less than the actual rate reported. However, it is likely that some of the Moderate cases which were not seen by an IVF clinician were actually severe.

There are now regular minuted monthly Unit meetings in which clinical and other issues are discussed with the team.

In summary, I do not believe that there are any concerns over practice as regards OHSS during the July 2012 – April 2013 time period in question or currently.

Tim Child MA MD MRCOG
OXFORD 18 JUNE 2014