Incident Report

Date of Licence Committee: 28 March 2013

Purpose of the incident report
The report summarises the findings of an incident review conducted by the HFEA. It is primarily written for the Authority's Licence Committee.

Centre details

Centre Name	Glasgow Royal Infirmary
Centre Number	0037
Centre Address	Assisted Conception Services Unit Walton Building 84, Castle Street Glasgow, G4 0SF
Person Responsible	Dr Helen Lyall
Licence Holder	Professor Scott Nelson

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Report to Licence Committee

Brief description of the centre and its licensing history

The Glasgow Royal Infirmary Assisted Conception Services Unit has held a licence with the HFEA since 1992. The centre provides a full range of fertility services and delivered 1178 cycles of treatment (excluding partner intrauterine insemination (IUI)) in the 12 months to 30 April 2012. In relation to activity levels this is a large centre.

The centre's licence was last renewed in 2008 when a licence was issued for a period of five years with no additional conditions.

An interim inspection of the centre was carried out in July 2012 when recommendations for improvement were made as follows:

'Critical' areas of non compliance:

- **the PR to ensure that personnel in the centre are available in sufficient numbers and are qualified and competent for the tasks they perform**

'Major' area of non compliance:

- the PR to submit a revised multiple births minimisation strategy to the executive which demonstrates how the revised strategy aims to meet the current 15% target and the timescales required
- the PR to perform a risk assessment of the state of repair of the cryostore and inform the executive of the outcome and resulting actions taken by the centre
- the PR to ensure that the outstanding registration of a number of donors is completed.

When the report was considered by the Executive Licensing Panel (ELP), it was noted that there were no outstanding recent donor registrations and that the Person Responsible (PR) had given a commitment to fully implement the remaining recommendations. In October 2012, the ELP agreed to the continuation of the centre's licence with no additional conditions.

In responding to this draft incident report, the PR confirmed that the recommendations relating to the cryostore premises have been fully implemented (see section "Additional information from the Person Responsible") and improvements have been completed to ensure the on-going suitability of the cryostore facilities. The centre also submitted a revised multiple births minimisation strategy within the timescale prescribed in the report.

Brief background to incident review

It was reported to the HFEA that on 6 November 2012, the treatment of five patients undergoing treatment at Glasgow Royal Infirmary had been affected by unexplained failed or reduced fertilisation rates. The centre reported that it had initiated a full investigation into the circumstances of the incident but was continuing to provide further treatment as fertilisation rates were normal on 7 November 2013.

On 8 November 2012 the centre reported that the treatment of a further six patients had been affected by unexplained failed or reduced fertilisation and that as a result of this the centre were closing its laboratory with immediate effect pending further investigation.

As a result of these events, the centre implemented its contingency plans and all on-going patient treatments were transferred to another HFEA licensed facility.

Summary for licensing decision

The Licence Committee is asked to note that on the basis of the investigation of an incidence of failed fertilisation in November 2012 that has been attributed to the conduct of building works in the vicinity of the fertility clinic, it is concluded that the laboratory premises of the Glasgow Royal Infirmary are not suitable for the conduct of HFEA licensed activity.

Recommendation to the Licence Committee

It is recommended that a condition is applied to the licence of Glasgow Royal Infirmary (centre 0037) prohibiting the clinic from undertaking licensed activity other than storage of gametes and embryos and distribution of gametes and embryos.

When the Person Responsible is able to provide the inspectorate with evidence of the suitability of the laboratory premises this will then be presented to a licence committee.

It is noted that the centre has voluntarily ceased licensed activity other than storage of gametes and embryos and that this condition represents a formalisation of the voluntary actions undertaken by the centre.

It is noted that the Authority may revoke a licence if it ceases to be satisfied that the premises specified in the licence are suitable for the licensed activity (1990 Human Fertilisation and Embryology Act (as amended, S. 18(2)). In circumstances where the Authority has the power to revoke a licence then S.18A(3) states that the Authority may vary a licence without an application under subsection (2) if it has the power to revoke the licence under section 18(2). S.18A(5) provides that the Authority may vary a licence without an application under this subsection by adding a condition to the licence.

The draft incident report also recommended that the centre should reconsider the evidence that that led them to conclude that only treatments provided since September 2012 were compromised as a result of building work being carried out in the vicinity of the laboratory. In responding to the draft report, the PR provided evidence of having reconsidered the evidence (see section “Additional information from the Person Responsible”). The HFEA executive is not able to form a conclusion of whether trends in pregnancy rates seen earlier in 2012 were the result of normal fluctuations or whether they may have been impacted by environmental factors. The Committee is asked to review the evidence provided by the PR and consider whether to recommend that the centre should seek to have the evidence reviewed by an independent expert.

Incident review

On 6 and 8 November 2012 the Glasgow Royal Infirmary Assisted Conception Services Unit submitted incident reports to the HFEA reporting that the treatment of a total of 11 patients had been affected by unexplained failed fertilisation or reduced fertilisation[1] and that as a result the centre was closing its laboratory with immediate effect pending further investigation. The centre's contingency arrangements were also implemented immediately and all on-going patient treatments were transferred to another HFEA licensed facility.

A summary report and timeline of events was submitted to the HFEA in response to the incidents on 19 December 2013 and a meeting was held on 22 January 2013 with senior members of the Glasgow Royal Infirmary staff and representatives of the HFEA executive.

The summary report noted that the investigation of potential causes for the deteriorating success rates (including *inter* alia review of staff competence, procedures, equipment and reagents) had not identified an explanation for the declining success rates. In the absence of a local explanation, the centre concluded that external factors were a possible cause.

Evidence of environmental monitoring of air quality submitted to the HFEA showed that required standards for air quality continued to be met throughout 2012 but that monthly monitoring showed some fluctuations (albeit within the limits required to maintain Grade C air quality) in the levels of small particles detected in June, July, September, October and November 2012. The centre's report noted that the fluctuations observed in June and July were attributed to deep cleaning and maintenance activities being undertaken in the unit at the time.

The timeline and report submitted by the centre also show evidence of fluctuations in success rates at various times from May 2012. Similar trends identified in monitoring undertaken by the HFEA were also communicated to the centre in relation to success rates for treatments provided in May, June and July 2012.

The centre did not make any association between success rate trends and fluctuations in air quality monitoring before September 2012: there appeared to be clear reasons for the fluctuations in air quality in June and July 2012 (cleaning and maintenance) and trends in success rates were not sustained, leading the centre to conclude that the variations observed in success rates had arisen as a result of the treatment of a number of patients with poor prognosis and the introduction of a single embryo transfer protocol to reduce the centre's clinical multiple pregnancy rate in line with the requirements of HFEA standard licence conditions.

Following the incidence of failed fertilisation in November 2012 however, in the absence of any other likely causes it was concluded by the centre that building works being undertaken in the vicinity of the fertility unit were impacting on fertilisation rates and immediate action was taken to close the laboratory and move patient treatments to alternative licensed premises.

[1] Fertilisation is said to have failed when a sperm fails to penetrate an egg and no embryo is created

In the course of the meeting held with the HFEA executive, the Glasgow Royal Infirmary team explained that following the closure of the laboratory, all treatments provided on the alternative licensed premises were being provided exclusively by Glasgow Royal Infirmary staff, using unchanged procedures and protocols and using the centre's own reagents and laboratory consumables. The team was able to confirm that outcomes had returned to those usually observed in the course of the centre's monitoring.

The HFEA consider that this supports the conclusion that the incidents in November were caused by an unidentified environmental contaminant affecting the laboratories of the Glasgow Royal Infirmary. Building works being undertaken in the vicinity of the laboratories are considered the likely source of the contamination.

It is noted that the centre made considerable efforts to anticipate the risks of the building works and liaised closely with contractors to mitigate these risks: these efforts are documented in the timeline that was provided by the centre (see attached). It is also noted that the centre was proactive in the implementation of contingency arrangements when a second incidence of failed fertilisation was observed.

The PR and Licence Holder confirmed that there is no intention to resume laboratory activity in the immediate future. Representatives of the Trust present at the meeting with the HFEA confirmed that plans are being drawn up for a comprehensive refurbishment of the facilities at Glasgow Royal Infirmary within the next 6-9 months. Pending completion of the refurbishment, the Trust is seeking to tender a contract to permit the on-going treatment of patients under similar arrangements to those in operation at the time of the meeting.

It is concluded however, that the laboratory premises of the Glasgow Royal Infirmary are not currently suitable for the following activities:

- Procuring gametes
- Keeping gametes
- Processing gametes
- Use of gametes
- Creation of embryos in vitro
- Procuring embryos
- Keeping embryos
- Embryo Testing
- Processing embryos
- Distribution of embryos
- Placing any permitted embryo in a woman
- Using embryos for the purpose of training persons in embryo biopsy, embryo storage or other embryological techniques

The premises are considered suitable for the following activities:

- Distribution of gametes
- Storage of gametes
- Storage of embryos

The centre has concluded that only treatments provided since September 2012 were compromised. The HFEA acknowledges that it may have been reasonable for the centre to attribute fluctuations in success rates and air quality seen between May and July 2012 to

what appeared to be known causes, but with hindsight, the centre should reconsider the evidence that supports this conclusion.

Areas of practice that require the attention of the Person Responsible

The section sets out matters which the Inspection Team considers may constitute areas of non compliance. These have been classified into critical, major and others. Each area of non-compliance is referenced to the relevant sections of the Acts, Regulations, Standard Licence Conditions, Directions or the Code of Practice, and the recommended improvement actions require are given as well as the timescales in which these improvements should be carried out.

Critical areas of non compliance and concern

A critical are of non compliance is an area of practice which poses a significant direct risk of causing harm to a patient, donor, embryo or to a child who may be born as a result of treatment services. A critical area of non-compliance requires immediate action to be taken by the Person Responsible.

Area of practice and reference	Action required and timescale for action	PR Response	Executive Review
The laboratory premises of the Glasgow Royal Infirmary are no longer suitable for the conduct of HFEA licensed activity	It is recommended that a condition is applied to the licence of Glasgow Royal Infirmary (centre 0037), that the centre should not resume licensed activity other than storage of gametes and embryos and distribution of gametes and embryos until the HFEA have been satisfied that the laboratory premises are suitable and that a report documenting the evidence considered in support of this conclusion has been presented to a licensing committee of the Authority. It is noted that the centre has already voluntarily ceased activity and that this condition represents a formalisation of the actions already undertaken by the centre.		

Additional information from the Person Responsible

I will address each of the points outlined in your e mail of 8th March in turn[2]:

Number of patients affected

The incident reports submitted to the HFEA on 7th and 9th November related to fertilisation rates from 6 patients who had undergone oocyte retrieval on 5th November and 5 patients who had undergone oocyte retrieval on 7th November, 11 patients in total. The fertilisation checks on 6th November and 8th November revealed the significant problem which led to the decision to invoke the contingency arrangements for the Unit.
The decision to invoke the contingency was taken on the 8th November. There were 6 patients due to have embryo replacement on 9th and 10th November. As at that point we had no clarity regarding the source of the problem, a clinical decision was taken to freeze the embryos from these patients rather than proceed to fresh embryo transfer. These patients were all contacted by myself in the evening on 8th November and informed of the situation. I explained that following investigation of the incident a decision would be taken to advise either leaving the frozen embryos in storage and proceeding to a fresh cycle of ovarian stimulation, or proceeding to frozen embryo transfer. I also indicated that whatever the outcome a complimentary cycle would be offered. These patients have subsequently been advised that a fresh cycle would be preferable to a frozen cycle using the embryos stored at the time of the incident.

Fair and equitable treatment for our patients was of paramount concern to us and we took some time to consider how to identify those patients whose treatment had been potentially compromised by the incident. As fertilisation in the IVF programme was the parameter affected we looked to our mean fertilisation rate, warning (2 standard deviations below the mean) and control (3 standard deviations below the mean) limits. As the IVF fertilisation rate breached the warning limit for the first time in September we identified all those patients in the IVF programme who had exhibited fertilisation rates below the warning limit from 1st September 2012 to 8th November 2012 when the contingency was invoked. These patients were all contacted by letter and offered a complimentary cycle of treatment. It should be noted that during the period from the 1st of Sep to the 31st Oct 2012 the IVF fertilisation rate did not breach the control limit. However, early indications form 1st -8th November 2012 indicated that the IVF

[2] In an email on 8 March 2013 the PR was asked to clarify the number of patients who were affected by the incident.

fertilisation rate would drop below the control limit if we failed to take action in November.
The total number of patients affected is 42. This number comprises 6 patients who had embryo freezing rather than a fresh transfer and 36 patients who exhibited fertilisation rates below the warning limit for that period. All 42 patients have been contacted and offered a complimentary cycle of treatment.

"The HFEA acknowledges that it may have been reasonable for the centre to attribute fluctuations in success rates and air quality seen between May and July 2012 to what appeared to be known causes, but with hindsight, the centre should reconsider the evidence that supports this conclusion."

I have reviewed the KPIs relating to activity from 2009 to 2012 inclusive. This has confirmed the observation, with which we have always been familiar, that the KPIs for clinical activity in the Unit exhibit wide fluctuation. However, over this time period the fluctuations have been observed in unrelated patterns and have neither been sustained nor of sufficient magnitude to warrant a decision to invoke contingency arrangements.

Review of the KPIs has revealed a number of occasions where the clinical pregnancy rate has declined. These months were always both preceded and followed by substantially superior rates. During 2009 to 2011 inclusive these changes could not have been attributed to building work as the latter commenced on 6th January 2012.

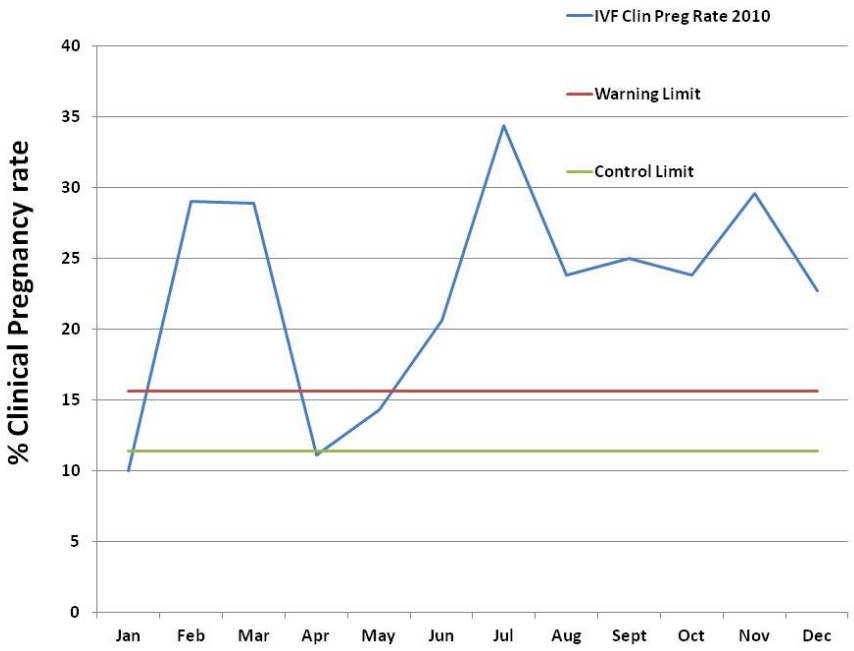
As the Unit has been asked to reflect on the cause of fluctuations in success rate prior to the incident and the latter has already been the subject of a detailed report, I have discontinued the x axis for 2012 in September of that year.
The graphs below illustrate clinical pregnancy rates in the IVF programme for 2010, 2011 and 2012, graphs A, B and C respectively. It should be noted that as KPIs exhibited fluctuation the y axis differs in these graphs.

The report submitted to the HFEA on 19th December 2011 explained that review of staff competence, procedures, equipment and reagents had not identified an explanation for the declining success rates at points observed during 2012. The decline in clinical pregnancy rate in May 2012 was immediately followed by an elevated rate, the fluctuation up to August being similar to patterns observed in previous years.

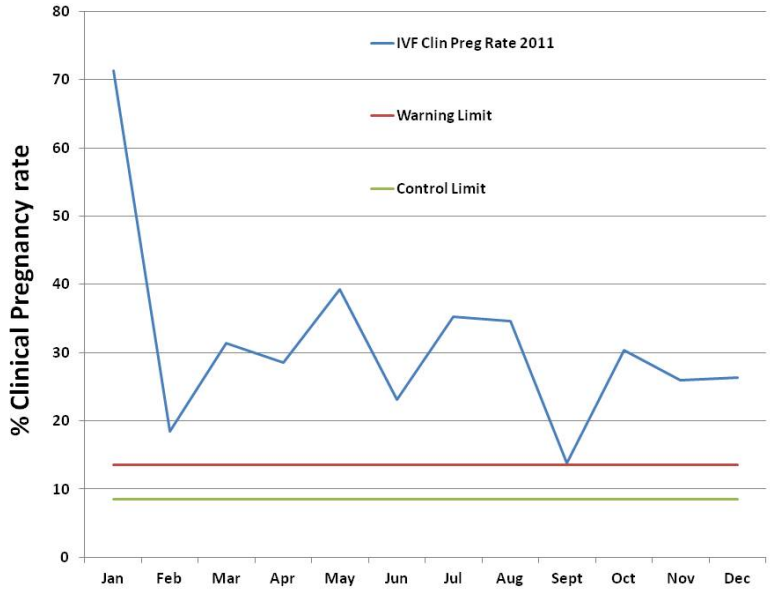
Our review of available evidence also took cognisance of the fact that in May 2012 the standards for air quality had been met. There

were some fluctuation in the levels of small particles detected in June, July, September and October. However until September 2012 we observed the same pattern of peaks and troughs in clinical pregnancy rate which had been observed in previous years. It is worthy of note that there were clear reasons for the fluctuations in air quality in June and July (cleaning and maintenance) however this occurred after the fall in clinical pregnancy rate in May and coincided with a rebound elevated clinical pregnancy rate. A similar pattern is observed in the ICSI clinical pregnancy rates for 2012 (graph E).

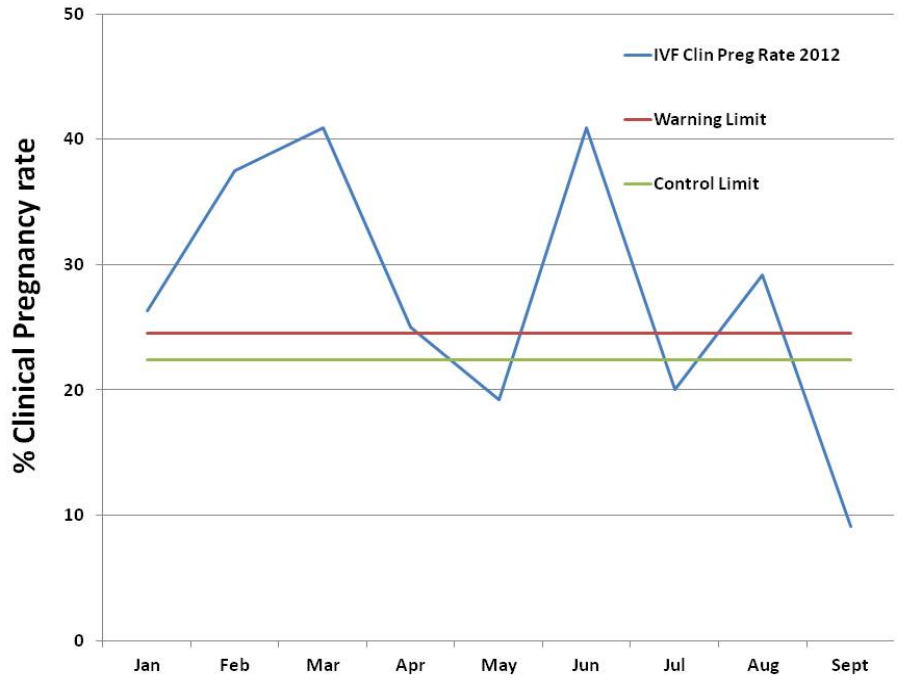
This led to our conclusion that at this time point we could not establish a causal link between air quality and clinical pregnancy rate. Further evidence in support of this conclusion is that at that time the building work was not immediately adjacent to the ACS laboratory.


IVF Clin Preg Rate 2010
Warning Limit
Control Limit
% Clinical Pregnancy rate
40
35
30
25
20
15
10
5
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sept
Oct
Nov
Dec

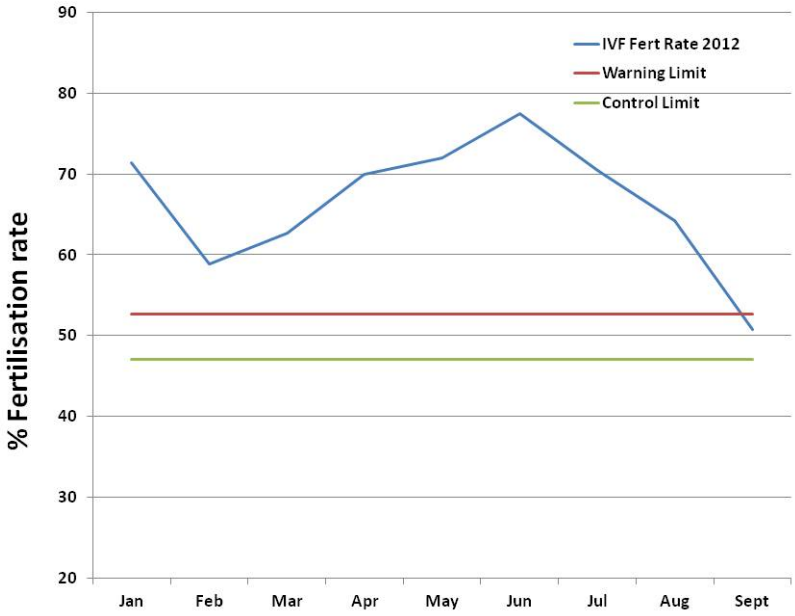
Graph A


% Clinical Pregnancy rate
80
70
60
50
40
30
20
10
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sept
Oct
Nov
Dec
IVF Clin Preg Rate 2011
Warning Limit
Control Limit

Graph B

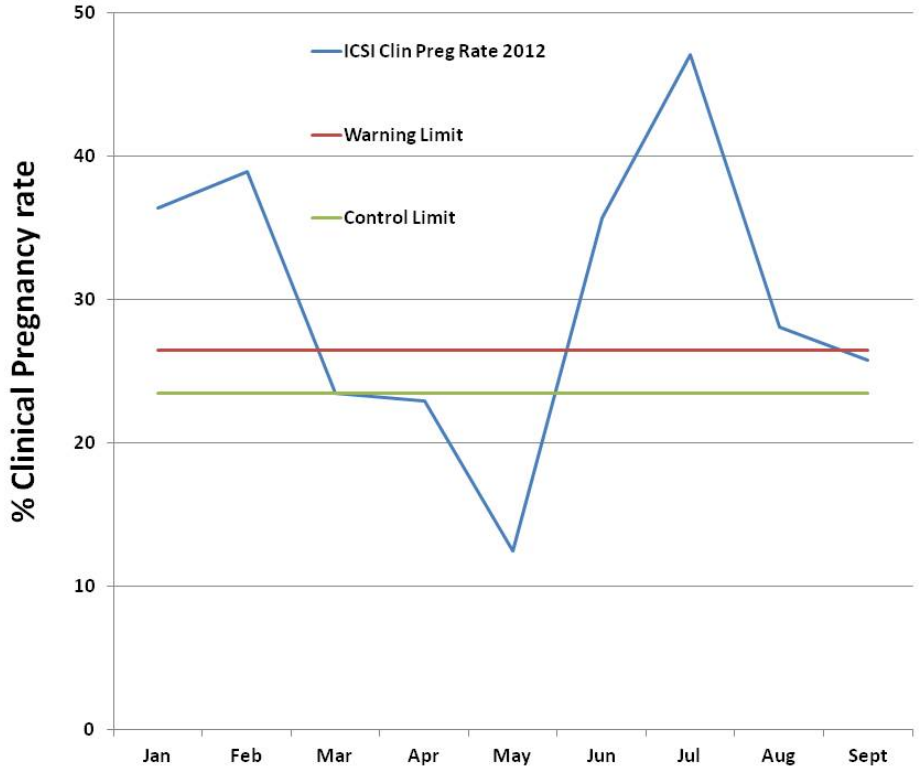

% Clinical Pregnancy rate
50
40
30
20
10
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sept
IVF Clin Preg Rate 2012
Warning Limit
Control Limit

Graph C



Graph D

Graphs C and D illustrate the clinical pregnancy rate and fertilisation rates for IVF respectively in 2012. These both show that for the first time the KPIs exhibited a sustained declining trajectory rather than a fluctuating one which coincided with the building works moving closer to the laboratory and is further support for the decision to invoke contingency arrangements. By changing the clinical environment and maintaining all other parameters we have already reassured the HFEA that this trend has been reversed.



Graph E

Although the evidence for a causal link between the incident in late 2012 and adjacent building work is indirect there are a number of congruent factors in support of this. Building work moving closer to the laboratory, deteriorating air quality, downward trajectory of KPIs and the fact that a changed environment has alleviated the problem.
Our review has failed to identify a similar set of congruent parameters at any earlier points in the year to explain the fluctuations in

clinical pregnancy rates. The latter did not at that point maintain a sustained downward trajectory but exhibited the same unrelated pattern of fluctuation we have observed over some time. We therefore contend that it is impossible to conclude beyond reasonable doubt that the fluctuations in clinical pregnancy rate earlier in 2012 were connected to the laboratory environment in the same way as the events which occurred later in the year.

Progress on the safety of the cryostore

Work on the new cryostore facility commenced in February 2013. The cryostore is now complete with the exception of the nitrogen extraction system and the low level oxygen alarm. To avoid a repeat of the issues surrounding the current cryostore floor due to nitrogen damage, we have undertaken a radical redesign of this facility which now consists of a 5mm thick aluminium checker plate floor and 10mm aluminium welded skirting. This flooring design will significantly reduce the damage routinely caused in vinyl floor coverings when exposed to LN2 at -190°C by virtue of the resistance offered by the use of metal flooring. Furthermore we have included in this project provisions for a 500 litre external liquid nitrogen storage tank to further reduce the wear on the floor from the moving of the existing mobile filler tank which is housed internally. From a health and safety perspective we are implementing a state of the art LN2 extraction and alarm system which will consist of low level ducting around the perimeter of the cryostore coupled with a three stage fan which increases its extraction velocity in line with the levels of LN2 detected through the alarm system. This aspect of the project has not been completed due to a supply issue for the three stage fan. As yet the contractors do not have a confirmed date for delivery of this unit. As soon as this information is made available to us by the contractors we will provide a confirmed date for validation and handover of the new cryostore facility.

HFEA Licence Committee Meeting

28 March 2013

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

Minutes – Item 7

Centre 0037 (Glasgow Royal Infirmary) – Incident Review Report

Members of the Committee:	Committee Secretary:
Sue Price (professional) Chair Debbie Barber (professional) Jane Dibblin (lay) Andy Greenfield (lay)	Lauren Crawford Legal Adviser: Stephen Hocking, Beachcroft LLP

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

- Cover sheet
- Incident Review Report (including the Person Responsible's response)
- Timeline provided by the centre
- Previous licencing history:
    - Executive Licensing Panel minutes for an interim inspection held on 22/10/2012
    - Executive Licensing Panel minutes for an interim inspection held on 29/06/2011

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. The Committee noted that this report summarises the findings of an incident review conducted by the HFEA.

2. The Committee noted that the Glasgow Royal Infirmary Assisted Conception Services Unit has held a licence with the HFEA since 1992. The centre provides a full range of fertility services and delivered 1178 cycles of treatment (excluding partner intrauterine insemination (IUI)) in the 12 months to 30 April 2012. In relation to activity levels this is a large centre. The centre's licence was last renewed in 2008 when a licence was issued for a period of five years with no additional conditions.

3. The Committee noted that an interim inspection of the centre was carried out in July 2012 when recommendations for improvement were made as follows:
   'Critical' area of non compliance:
   • the PR to ensure that personnel in the centre are available in sufficient numbers and are qualified and competent for the tasks they perform

   'Major' areas of non compliance:
   • the PR to submit a revised multiple births minimisation strategy to the executive which demonstrates how the revised strategy aims to meet the current 15% target and the timescales required
   • the PR to perform a risk assessment of the state of repair of the cryostore and inform the executive of the outcome and resulting actions taken by the centre
   • the PR to ensure that the outstanding registration of a number of donors is completed.

4. The Committee noted that when the report was considered by the Executive Licensing Panel (ELP), it was noted that there were no outstanding recent donor registrations and that the Person Responsible (PR) had given a commitment to fully implement the remaining recommendations. In October 2012, the ELP agreed to the continuation of the centre's licence with no additional conditions.

5. The Committee noted that in responding to this draft incident report, the PR confirmed that the recommendations relating to the cryostore premises have been fully implemented (see section "Additional information from the Person Responsible") and improvements have been completed to ensure the on-going suitability of the cryostore facilities. The centre also submitted a revised multiple births minimisation strategy within the timescale prescribed in the report.

Discussion

6. The Committee noted that an incident was reported to the HFEA that on 6 November 2012, the treatment of five patients undergoing treatment at Glasgow Royal Infirmary had been affected by unexplained failed or reduced fertilisation rates. The centre reported that it had initiated a full investigation into the circumstances of the incident but was continuing to provide further treatment as fertilisation rates were normal on 7 November 2013.

7. On 8 November 2012 the centre reported that the treatment of a further six patients had been affected by unexplained failed or reduced fertilisation and that as a result of this the centre were closing its laboratory with immediate effect pending further investigation. As a result of these events, the centre implemented its contingency plans and all on-going patient treatments were transferred to another HFEA licensed facility.

8. The Committee noted that on the basis of the investigation of an incidence of failed fertilisation in November 2012 that has been attributed to the conduct of building works in the vicinity of the fertility clinic, it is concluded that the laboratory premises of the Glasgow Royal Infirmary are not suitable for the conduct of HFEA licensed activity.

9. The Committee noted the Executive's recommendation that a condition is applied to the licence of Glasgow Royal Infirmary (centre 0037) prohibiting the clinic from undertaking licensed activity other than storage of gametes and embryos and distribution of gametes and embryos.

10. The Committee noted It is noted that the Authority may revoke a licence if it ceases to be satisfied that the premises specified in the licence are suitable for the licensed activity (1990 Human Fertilisation and Embryology Act (as amended, S. 18(2)). In circumstances where the Authority has the power to revoke a licence then S.18A(3) states that the Authority may vary a licence without an application under subsection (2) if it has the power to revoke the licence under section 18(2). S.18A(5) provides that the Authority may vary a licence without an application under this subsection by adding a condition to the licence.

11. The Committee noted further that in responding to the draft report, the PR provided evidence of having reconsidered the evidence (see section "Additional information from the Person Responsible"). The HFEA executive is not able to form a conclusion of whether trends in pregnancy rates seen earlier in 2012 were the result of normal fluctuations or whether they may have been impacted by environmental factors. The Committee is asked to review the evidence provided by the PR and consider whether to recommend that the centre should seek to have the evidence reviewed by an independent expert.

Decision

12. The Committee noted all the actions taken by the Executive and PR to ensure the safety of patients and note that the response has been appropriate.

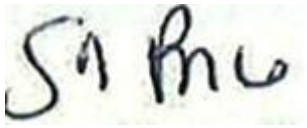
13. The Committee noted that the statistical information was not clear, as there were none given for any other centres for a comparison or any information or direction from the Executive to suggest whether the rates were outside of normal range.

14. The Committee asks the Executive to clarify the arrangements for the patients whose treatment may have been affected.

15. The Committee endorsed the Executives recommendation and add the condition that '**no licensed activities other than 'storage of gametes and embryos' and 'distribution of gametes' may take place at the Centre**.

16. The Committee agreed that the condition should remain on the licence until such time as the Person Responsible is able to provide the inspectorate with evidence of the suitability of the laboratory premises. It is then open to the PR to apply to have the licence varied to remove the additional condition, if he so wishes. If such an application is made the Committee directed that the matter should come back to the Licence Committee.

Signed: Date: 30/04/2013



Sue Price (Chair)