Device Incident Report : Medical Devices Branch - Device Vigilance and Monitoring

DIR : 41 - ID : 510535

16/10/2020
UNSIGNED

Released by [redacted] on 19/11/2020 14:40:19

Report #:	Records Management #:	Reporter's Reference #:	Report Type:
65968	E20-373384	RM4949	Final

ARTG:

Document Container URL

Report Information Section

Report Status:	Sponsor's Reported Category:	Date of Adverse Event:	Date of In tial Report:
Active	Trend	25/09/2020	16/10/2020
Date of Final Report:	**Date of In tial TGA Action:**	**Reviewed by Team:**	**Date Response Received:**
30/06/2021	16/10/2020	27/10/2020	
Date Completed:	**Operator at Time of Event:**	**If 'Other' Operator Selected:**	**Reporter consents to contact by sponsor:**
			N/A
Source of Report:	**If 'Other' Source Selected:**	**Type of In tial Act on:**	
Sponsor		For Team Meeting	

Event Description for Website Publ cat on:

Clin cal Event Informat on:

The outcome following a surveillance aud t on Repromed SA Genet cs laboratory's cell free (non-invasive) PGT-A program that has triggered a detailed internal investigation.
Whilst our investigation has not been completed, irregular ties have been found in the Val dation document that supported the implementation of this test and the accred tat on granted by NATA. Consequently, Repromed have decided that the test will cease to be offered clin cally to its patients, or any patients it performed the test for in the broader Monash IVF Group's network of clin cs. NATA have been informed accordingly, and a repeat of the val dation study performed as a matter of urgency.
Monash IVF Group will work through a process of Open disclosure w th our clin cians and patients wh ch will include remediation where found to be appropriate.
I have also included below a sample of the sort email that has been sent to patients, this one is for patients w th aneuploidy only embryos.

Background
Monash IVF's NI PGT program was launched following an almost four-year long process of research and Val dation trials. The program was approved by Monash IVF GMAC and had human eth cal trials approval from an accred ted HREC.
The research and validat on, led by [redacted], focussed on whether the genet c results from NI PGT systems were as accurate as those from gold standard PGT-A with trophectoderm b opsy.
[redacted]
The val dation data was obtained on a cohort of 121 embryos, and showed the two methods were very similar in their outcomes of detecting aneuplo dy. There was a correlation of 98% between invasive PGT and NI-PGT; consequently the test was subm tted for NATA accred tation. The NATA accred tation audit with peer review from a techn cal expert and review of val dation report occurred in early 2019. Monash IVF Group launched the NI PGT-A program across New South Wales, Northern Territory, Queensland, South Australia, Tasmania and V ctoria in May 2019. The test has also been performed on behalf of [redacted] in [redacted]

Findings
As part of our routine surveillance program, a review of the NI-PGT outcomes was undertaken in June 2020. This review cons dered not only how accurately the two alternatives performed in terms of detecting abnormality, but also in clinical pregnancy rates. In add tion, the post launch surveillance sample size was considerably larger (n = 805) than the val dation studies (n = 121). This review highlighted some variat ons of the performance of the test in clinical use, as compared to the validat on results:
- Failed DNA amplif cation rates were pleasingly lower than the validat on study (2.6% Surveillance vs 5.0% Val dation).
- There was an increase in inconclusive rates compared to val dation study (6.3% Surveillance vs 1.6% Validat on); however both outcomes were within parameters experienced in routine clinical practice.
- The significant unexpected finding, was that there was a signif cant increase in aneuplo dy rates in the NI PGT tested embryos when compared to the current invasive PGT tested embryos. This was evident across all ages and for non-delayed and delayed embryos. The increase in aneuploidy was 20-30% higher in the NI PGT group.
- This implies a higher false positive rate compared w th PGT-A w th b opsy, indicating that more embryos may have been called abnormal when in fact they may be normal, compared w th b opsy PGT-A.

The discordant results between Biopsy PGT and NI PGT prompted a full interrogation of the validation study data files to try and better understand these unexpected outcomes. This review revealed some discrepancies in the val dation data that are not yet fully understood, but bring into quest on its scientific and clinical val d ty.

Next Steps
Monash IVF Group are working with clinicians to prior tise patient communications and support programs, as we notify patients that the test is being suspended and the impact that our findings have on any stored aneuplo dy embryos.
A further val dation study is underway, under the supervision of a multidisciplinary Steering Committee, to assess the possibil ty of continuing to prov de the test.
NATA have been advised of our decision to suspend the test and we will work with them in the event that we are in a position to repeat the accred tation process in the coming months.
If you have any quest ons regarding any of the informat on or would like further information, please do not hes tate to call me.

Number of Inc dents in Report:	Contact:	Alternative Person Title:	Alternative Person First Name:
1			
Alternative Person Surname:	**Alternative Person Phone:**	**Alternative Person Fax:**	**Alternative Person Email:**

Recorded Problems Observed

Recorded Problems Observed:

Output Problem -> Incorrect, Inadequate or Imprecise Result or Readings -> False Positive Result

Clin cal Signs, Symptoms and Condit ons

Recorded Clin cal Signs, Symptoms and Conditions:

Others -> Insufficient Information ->

Health Impact

Recorded Health Impacts:

Delay to Treatment/ Therapy -> ->

Patient Information

Sex:

Weight:

Age:

Patient Focused Corrective Action Taken:

Patient History:

Patient Outcome/Consequences:

Addit onal Event Description:

Describe any test (Lab, xray, etc.):

Injured - Extent of Injury:

Other med cal devices currently using/implanted:

Med cal Problem Device Used For:

Addit onal Patients Added:

0

Submitting Reporter Sect on

Search Reporter By Surname:

Reporter #:

Preferred Contact Method:

Reporter Title:

First Name:

Surname:

Pos t on:

Company/Institut on:

Monash IVF Group

Address 1:

Monash IVF Group, 21-31 Goodwood Street

Address 2:

Town/Suburb:

Richmond

State:

VIC

Country:

Australia

Postcode:

3121

Phone:

Fax:

Mobile:

Email:

Last External Submiss on By:

104241_65620 - 16/10/2020 17:03

Initial Reporter Sect on

As Above?:

No

If No, fill out the following:

Initial Reporter Confidential:

Yes

Search Reporter By Surname:

Initial Reporter #:

Preferred Contact Method:

T tle:

First Name:

Surname:

Pos t on:

Company/Institut on:

79 631 193 489

Address 1:

Address 2:

Town/Suburb:

State:

Postcode:

Country:

Phone:

Fax:

Mobile:

Email:

Allow the device company to contact you about the inc dent:

Device Informat on Section

Product Exempt *(Note: If not exempt, enter ARTG No)*:	Search Device ARTG:	Device ARTG #:	Therapeut c Licence Type:
No	DV-2017-IVI-10175-1		
Product L cence Category:	**Device Class:**	**GMDN / UMDN Code:**	**GMDN / UMDN Text:**
Brand Name:	**Initial Device Description:**	**Usage of Dev ce:**	**Software Version:**
In-house IVD - cell free PGT-A	In-house IVD - cell free PGT-A		
Model #:	**Serial #:**	**Batch #:**	**Lot #:**
Purchase Date:	**Expiry Date:**	**Date of Implant:**	**Date of Explant:**
Date of In tal Procedure:	**Place of Implantat on:**	**Reported Dev ce Locat on:**	**Access Contact Title:**
Access Contact First Name:	**Access Contact Surname:**	**Access Contact Phone:**	**Access Contact Fax:**
Access Contact Email:	**Licence Status:**	**Status Effective Date:**	**Addit onal Devices Added:**
			0

Manufacturer Information Sect on

Manufacturer Name:		Manufacturer Client Id:	Address 1:
Monash IVF Group			
Address 2:	**Town/Suburb:**	**State/Province:**	**Country:**
Postcode:	**Phone:**	**Fax:**	**Email:**
Manufacturer Informed:	**Date Aware of Adverse Event:**	**Contact Title:**	**Contact First Name:**
Yes	25/09/2020	[redacted]	[redacted]
Contact Surname:			
[redacted]			

Supplier Information Sect on

Supplier Name:		Address 1:	Address 2:
Town/Suburb:	**State:**	**Country:**	**Postcode:**
Phone:	**Fax:**	**Email:**	**Website:**
Supplier Informed:	**Date of Supplier Contact:**	**Contact Title:**	**Contact First Name:**
Contact Surname:	**Contact Phone:**	**Contact Fax:**	**Contact Email:**

Report Status

For webs te publication:	Ready for Publ cat on:	Investigated:	Investigat on Reason:	Team Assignment:	Team Pr ority:
	No	Yes	More information is required	Team C (IIa, I and IVD 1-4)	Routine

Team Review

Reviewed by Team:	Reason Sent To Meeting:	Outcome from team meeting:
27/10/2020	Advice from IVD section given on requirement of more information	Investigat on (within DIR) is recommended

Notes for Team meeting:

Exempt in-house IVD - still required to comply w th post-market reporting. Request investigat on report - possibly request updates (depending on expected time-frame of final report). As sponsor had not thoiught t necessary to notify TGA of the incident, they may be unaware of their requirement to subm t a final report. Contact sponsor and advise them they are required to submit a final report within 100 days.

Outcomes from Team Meeting:

Investigat on to enquire: Rate information, Investigation report. What standards is this IVD done under? Prov de ev dence that testing was conducted according to these standards. To clarify w th SW the role and scope of DPMM in regulating this IVD.

DPRC Review

Reviewed by DPRC:	DPRC Reason Sent To Meeting:	Outcome from DPRC Meeting:

Meeting Notes:

Initial Risk Analysis

Background Information	Risk Assessment - Section A	Risk Assessment - Section B	Risk Assessment - Section C	Risk Assessment - Section D	
Date:	Sever ty:	Incidents in the last 12 months:	Manufacturer analysis:	Assessor:	Manufacturer documentat on:
16/10/2020	1 - No harm has been reported to occur		Yes	[redacted]	Yes - manufacturer HAS documented issues or compl cat ons of this type
Inc dents in last 24 months:	Manufacturer act on:	ESTIMATED LEVEL OF INVESTIGATION:	FINAL LEVEL OF INVESTIGATION:	Injured Party:	Dev ce Recalls:
	Yes	Level 3 Investigat on (for multiple DIRs/a DII)		Patient	0. No recalls for similar inc dents in Australia
Inc dents in last 36 months:	IVD status:	EXCEPTION TO INVESTIGATION LEVEL:		Found Prior To Use:	Is AE covered by current recall:
	A point of care IVD			No	No
Inc dents Worldwide:	Number of potential contributing factors:			Reusable:	Similar events (past 6 months):
	Yes - some potential factors (up to 3)			Yes	0 inc dents
Products supplied the last 12 months:	Specif c factors identified:	ESTIMATED LEVEL OF PRIORITY:	FINAL LEVEL OF PRIORITY:		3 or more events - batch/model:
	Compatibil ty of device - patient characterist cs, Use of device - fit for purpose	Routine			
Products supplied last 24 months:	Number of potential sens tivities:	EXCEPTION TO PRIORITY LEVEL:			3 or more events - health district:
	Yes - multiple potential sens tivities (more than 3)				
Products supplied last 36 months:	Specif c sensitiv ties identified:				3 or more events - organisation:
	Dev ce uses new technology, New evidence about dev ce eff cacy, Public interest/requests for informat on, Media interest/requests for informat on, Industry interest/requests for informat on, Investigations/requests by government, Enquiries/investigat ons/actions by the TGA, Potential for current inc dent to become sensitive				
Products supplied Worldwide:	Consultations during risk assessment:	Final Risk Assessment:			
	I discussed issues with one of my peers	No			

Additional Risk Analysis

Click 'N' to start a new risk analysis

Analysis Details	Statistics Checklist Section				
Update Dev ce Details?:	Background Information	Risk Assessment - Section A	Risk Assessment - Section B	Risk Assessment - Section C	Risk Assessment - Section D
	Date:	Sever ty:	Incidents in the last 12 months:	Manufacturer analysis:	

Copy Data From:						
	Assessor:	Manufacturer documentation:	Incidents in last 24 months:	Manufacturer action:	ESTIMATED LEVEL OF INVESTIGATION:	FINAL LEVEL OF INVESTIGATION:
	Injured Party:	Device Recalls:	Incidents in last 36 months:	IVD status:	EXCEPTION TO INVESTIGATION LEVEL:	
	Found Pr or To Use:	Is AE covered by current recall:	Incidents Worldw de:	Number of potential contributing factors:		
	Reusable:	Similar events (past 6 months):	Products supplied the last 12 months:	Specif c factors identified:	ESTIMATED LEVEL OF PRIORITY:	FINAL LEVEL OF PRIORITY:
		3 or more events - batch/model:	Products supplied last 24 months:	Number of potential sens tivities:	EXCEPTION TO PRIORITY LEVEL:	
		3 or more events - health district:	Products supplied last 36 months:	Specif c sens tivities dentified:		
		3 or more events - organisat on:	Products supplied Worldwide:	Consultations during risk assessment:	Final Risk Assessment:	

Sponsor/Manufacturer Informat on Sect on

Search Sponsors:	Name:		Client #:
65620	Monash IVF Group		65620
Attention To:	Address 1:	Address 2:	Town/Suburb:
[redacted]	Pelaco Building 1 Level 1 / 21-31 Goodwood Street		Richmond
State:	Postcode:	Phone:	Fax:
VIC	3121	[redacted]	
Email:			
[redacted]			

Investigation Informat on Section - Subm tted by Sponsor/Manufacturer

Dev ce Analysis Results:	Corrective/Preventative Actions:
	Ongoing
Details of Similar Events:	Add tional Details (use for tables):
CAPA# Reference:	

Risk Assessment

Frequency:	Sever ty:		
Rating:		Type Cause and Outcome:	Number of Similar Events:
Expected Rate:	Actual Rate:		

Countries Similar Events Also Occurred:

Completed Act ons:	Planned Actions and Proposed Timelines:

Suspension of the test and working through communications with affected patients	Proposed re-val dat on of test under extended comm ttee Appointment of external reviewer to completed RCA relating to validat on

Additional Comments:

Reason for Level 1 Investigation

Details of Reasons	
Reason for Level 1 Investigation	
Sensitiv ties - requests for informat on	

Focus of Level 2 Investigation

Details of Focus	
Essential Principles	If 'Other' Selected

Sources of Evidence for Level 2

Details of Source			
Sources of Evidence	If 'Others' please specify here	Expected Sourcing Date	Date of Evidence Received

Evidence

Investigation Questions (Level 1 and Level 2):

Request for information made under Schedule 3 Part 6A.3 & 6A.4 of the Regulat ons - refer to TRIM D20-3634097

Potential Risks

Delays in response by product manufacturers:	Delays in response by inc dent reporters:	Delays in analysis w thin the TGA:	Delays in reporting by other sources (e.g. clin cal registries):
☑	☐	☑	☐

Other Risks (which need to be specified):

Next Steps for Level 1 & Level 2 Investigations

Next Steps for Level 1 Investigation:	Next Steps for Level 2 Investigat on:

Click **[N]** to begin a new Correspondence entry. Note that the Email address specified here will receive a notificat on if the Date Received is not filled in by the Date Expected.

Correspondence and Chronology Details

Include?	Heading	Type L1	Type L2	Email	Sent	Expected	Received	Response	Notes
☐		Sponsor Routine Correspondence	Sponsor Request for Informat on Letter - s41JA		30/10/2020	26/11/2020	27/11/2020		

List of Problem Observed Codes - Click **[N]** to begin entering information.

Problem Observed Details

Problem Observed (Level 1)	Problem Observed (Level 2)	Problem Observed (Level 3)	If 'Other' Selected

Output Problem	Incorrect, Inadequate or Imprecise Result or Readings	False Positive Result		

Clinical signs symptoms and conditions

Details			
Level 1	Level 2	Level 3	
Others	Insufficient Informat on		

Health Impact

Details			
Level 1	Level 2	Level 3	
Delay to Treatment/ Therapy			

Investigation Findings

Finding Details				
Investigat on Findings (Level 1)	Investigat on Findings (Level 2)	Investigat on Findings (Level 3)	If 'Other' Selected	

Investigation Conclusion

Conclusion Details			
Investigat on Conclusion (L1)	Investigation Conclusion (L2)	If Addit onal Conclusion Detail Requested	

Investigation Outcomes

Outcome Details			
Outcome of Investigation (L1)	Outcome of Investigat on (L2)	If Addit onal Conclusion Detail Requested	

Investigation Summary

Latest Investigation (DII) where this DIR is the Primary DIR:	Latest Investigation (DII) where this DIR is a Related DIR:	Investigator:	Peer Review:	Peer Review Complet on Date:
			Yes	

Investigator's Notes:

NOTE - For Peer Review pr or to closing
After reviewing requested informat on - change to "Awaiting Final", send to OPR - Make a note to triage final report to [redacted]

30 October 2020 - Request for information sent (Not ce requiring informat on/documents to be prov ded under Schedule 3, Part 6A, Clause 6.3 and 6.4 of the Therapeutic Goods (Medical Dev ces) Regulations 2002) (D20-3641206)
27 November 2020 - Monash IVF responded (D20-3822434)

Review of documents provided:
1. TGA Response to NI Questions v1.0 27Nov20
(Q1) - Prov ded a general description of the "cell-free" as compared "biopsy" pre-implantation genetic test (PGT) and the indication of results - (a) suitable for transfer (Euplo d or "no abnormal ty detected); (b) chromosomally abnormal & unsuitable for transfer (Aneuplo d); (c) Inconclusive (unable to yield a result) - embryo treated in same way as an untested embryo.
MIVF state cell-free PGT-A is a screening test only design to detect abnormal chromosome number (aneuplo dy) for whole chromosome number wh ch may lead to miscarriage or serious condit on effecting pregnancy and live birth.
WARNING to Patients:

Summary Findings:

Recall Number:

Patients are advised: "This test is only a screening test and therefore cannot prov de an absolute guarantee of the chromosome status of the embryo. In some embryos, the b opsied cell/s or culture media may not be representative of the whole embryo.
While every effort is made to ensure that the PGT-A test offered has the highest possible accuracy using the currently available technology, results are not 100% accurate. There ore, prenatal diagnosis is highly recommended in an ensuing pregnancy."

(Q2) - Prov ded an updated procedure for reporting adverse event (their reporting procedure, at the time of the adverse event, was not prov ded) - Reviewed in section 2. Monash IVF Group Adverse Event Feedback Policy v5.0 9Nov20
- Their rationale for the 4 month delay in reporting their concerns regarding the signif cant increase in aneuplo dy rates when they first became aware of the issue, in June 2020 as part of their routine surveillance program, and only notified TGA in October 2020 was:
(a) initial concern were raised in June 2020 which triggered a review of the validation data. This review revealed irregular ties which led to the decis on to suspend the test as of 25 September.
(b) The precaut onary suspension of the test did not appear, to Monash IVF, to meet the Adverse Event Criteria listed on the TGA webs te.
(c) Confirmat on that Monash IVF Group Adverse Events and Feedback Pol cy to the version provided (see (2) below) following discussion with [redacted] (TGA) to include refertence and link to the NPAAC document: Requirements For the Development And Use Of In-House In Vitro Diagnostic Medical Dev ces (IVDs).

(Q3) Although Monash IVF dentified increased rates of aneuploidy results in June 2020 between the surveillance populat on (n=805) compared to the val dation populat on, they only suspended the test after their investigation dentified irregular ties in the val dation data in September 2020 (when number of tests conducted was in the order of n=1300). Therefore between when they noticed concern and when they suspended use of the test, around an additional 500 tests had been conducted. Monash IVF claimed that the increased rates observed in June 2020 were NOT the grounds for suspending the test. The grounds for suspending the test was related to the IRREGULARITIES IN THE VALIDATION DATA wh ch were identified in September 2020.

(Q4) Monash was asked to prov de informat on on their documented procedures for reviewing experience gained in the post-product on phase and how corrective act ons are applied to the design or product on of such dev ces.
Monash prov ded informat on for their genet cs laboratory at Repromed advising they participate in ALL external QC programs available for their preimplantat on genetic testing program but that no such external QC programs are available for the cell-free PGT.
An internal QC program was developed for the cell-free PGT.
Monash IVF claim that "results from our internal QC program have all been concordant since it was established", but d d not provide any details or data.
Repromed also monitor false negative rates for all screening tests and that the false negative rate appeared to be in-line with the biopsy PGT test (false negative - calling an embryo healthy when t was not). The issue with the cell-free PGT-A test was false positive (calling an embryo unhealthy/aneuploid when it was healthy/euplo d)

Monash IVF didn't actually answer the quest on asked. No details of the system for reviewing experienced gained in the post-product on phase was provided. It was expected that copies of their QMS documents would be prov ded that demonstrated how they monitored and reviewed post-production data.
No information was provided on how corrective act ons will be applied to the design or production of a dev ce(IVD test), only that "learnings from our experience w th this process will be incorporated into future design of any tests implemented across Monash IVF Group".

Could request addit onal information - please prov de a copy of your documented procedures for reviewing experience gained in the post-product on phase and the process for how any necessary corrective actions will be applied to the design or production of a dev ce.
Could request a copy of their internal QC program for the test.

(Q5) Referred to (3) below: IVD Val dation Document - Next Generat on Sequencing v1.0 for details of the design specif cat on of the device, including relevant standards, risk analysis or other solut ons adopted to ensure the dev ce complies w th the EPs.

(Q6) Referred to (4) below: Monash IVF Group validat on of NGS summary for clin cal ev dence as required by the clin cal evaluation procedures (Schedule 3, Part 8 of the Regs)
(Q7) Referred to (3 & 4) below: request for val dation report.

2. Monash IVF Group Adverse Event Feedback Policy v5.0 9Nov20
Provides definitions of
Events - something that requires reporting in Riskman - incidents, near misses, feedback, suggestions for improvement, supplier issues, equipment failure, audit findings and hazards

3. IVD Validat on Document - Next Generation Sequencing v1.0
Review for (Q5 above): details of the design specification of the device, including relevant standards, risk analysis or other solutions adopted to ensure the device complies with the EPs.

4. Monash IVF Group validation of NGS summary
Review for (Q6 above): clinical evidence as required by the clin cal evaluat on procedures (Schedule 3, Part 8 of the Regs)

Note: Letter generation buttons disabled if report not ready for website publication or risk analysis not completed.

Device Lookup

This section is used to match information provided via UDIR forms to ARTG information on. You can select a Brand/Name from information provided in the 'Other Devices Involved' table below or enter information on manually.

Other Device (Entered):	Brand Name:	Manufacturer Name:	Device ARTG #:

Other Devices

Device ARTG No:	Manufacturer Name:	Sponsor/Supplier:	GMDN / UMDN Text:	Trade/Brand Name:	Serial #:

Model Number:	Batch #:	Lot #:	Expiry Date:

Related DIR Information on - Click **New** to begin entering information.

Rec No	
1	

Samples Record - Click **[N]** to begin entering information on. **Note:** Sample # Generated on Save.

Rec No	Details	Sample Details			Additional Details				
	Date Entered:	LIMS #:	Sample Requested:	Sample Received:	Manufacturer:	GMDN:	Device Description:	Brand Name:	Serial Number:
	Reason for Testing:	# Samples from Reporter:	# Samples from Sponsor:	Outcome of TGA's Testing:	Lot Number:	Batch Number:	Model Number:	Version Number:	
					Who sent the device to the TGA?:			Why does the TGA have the sample?:	
1									

Additional Patients

Click **[N]** to begin entering information on.

Patient Details

Sex:	Weight:	Age:	

Patient Focused Corrective Action Taken:	Patient History:

Injured - Extent of Injury:	Was device directly linked to death?:	Was device directly linked to permanent disabiltiy?:	Consequence:

Other Consequence:	Describe any test (Lab, xray, etc.):	Additional Event Description:	Medical Problem Device Used For:

Additional Device Information

Where did you get this device from?:

How reliant is the affected person on correct/safe operation of this device?:

Any other relevant information on to aid assessing/investigating the incident?:

Similar Events

Similar events - how many times?:	Date of Recent Report:	Event Reported To:	Reporter Reference Number:

Device Access - Alternate Device Contact Information Prov ded

T tle:	First Name:	Last Name:	Phone:

Fax:	Email:

Inc dent Location Details

Occurred in Australia:	Organisat on:	Address Line 1:	Address Line 2:

Town/Suburb:	State:	Postcode:

Flow Details DIR-REQ - Device Incident Request 283548

Request Details

ID	Type	Location	Status	Assigned By	Assigned To	Assigned On	Pr or ty	Attach
283548	DIR-REQ		Awa ting Final Report	[redacted]	[redacted]	23/09/2021	Normal	0

Signature Details

Role	IRIS Investigator	
User		
Signed At		
Comment		