QUARTS

Quality for Assisted Reproductive Technologies in Switzerland

Requirements Specification

for an

Accredited Laboratory for Reproductive Medicine

of the

SGRM – Swiss Society of Reproductive Medicine

and the

AGER – Working Group for Gynaecological Endocrinology and Reproductive Medicine of the SGGG

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Abbreviations

AGER	Arbeitsgemeinschaft für Gynäkologische Endokrinologie und Reproduktionsmedizin der Schweizerischen Gesellschaft für Gynäkologie und Geburtshilfe/Working Group for Gynaecological Endocrinology and Reproductive Medicine of the Swiss Society of Gynaecology and Obstetrics
ESHRE	European Society of Human Reproduction and Embryology
FIVNAT	“Fécondation In Vitro National”. Swiss register of laboratories for assisted reproduction; Committee of the SGRM
ISO 17025	Accreditation standard for testing laboratories
ISO 15189	Accreditation standard for medical laboratories
ICSI	Intracytoplasmic sperm injection
IVF	In vitro fertilisation
QMS	Quality management system (= entirety of relevant documents)
UK-NEQAS	United Kingdom National External Quality Assessment Service
SGGG	Swiss Society of Gynaecology and Obstetrics
SGRM	Swiss Society of Reproductive Medicine

Names and definitions of human germ cells

Gametes	Sperm and unfertilised egg cells
Impregnated egg cell	Fertilised egg cell
Embryo	Fertilised egg cell as from the cell division stage
Blastocysts	Embryo pre-implantation with a cavity (mostly as from the 5th day of development)

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Foreword on the first edition 2017

The specialist societies SGRM (Swiss Society of Reproductive Medicine) and AGER (Working Group for Gynaecological Endocrinology and Reproductive Medicine) of the SGGG (Swiss Society of Gynaecology and Obstetrics) took the Federal Act on Medically Assisted Reproduction (Reproductive Medicine Act, FMedG) and the Reproductive Medicine Ordinance (FMedV) as an opportunity to develop a quality label for reproductive medicine (QUARTS) and hereby presents the Requirements Specification of the module: Accredited laboratory for reproductive medicine.

IVF laboratories differ considerably from other laboratories to the extent that the current accreditation standards do not appear entirely suitable for demonstrating that the necessary quality standards are met. The accreditation standards of the International Standard Organization (ISO) do not cover the particularities of IVF laboratories either. In addition, work within a reproductive medicine laboratory does not take place in an isolated manner, but rather it involves close, multifaceted exchanges with the clinical treatment providers of patients and couples.

The public expects the highest safety standards for fertility treatment. Externally monitored quality is valued highly and both specialist societies aim to meet this expectation by producing this Requirements Specification and the associated accreditation system.

This Requirements Specification is based on two document groups/standards that are relevant to the accreditation of IVF laboratories.

1.) The accreditation standard for testing laboratories ISO 17025 and the accreditation standard for medical laboratories ISO 15189
2.) The “Revised guidelines for good practice in IVF laboratories (2015)” of the European Society of Human Reproduction and Embryology (ESHRE)

The ISO standards set out the general framework conditions for work in laboratories, whereas the ESHRE guidelines go beyond this and include issues specific to IVF. Both sets of standards cover quality management as well as the structures and processes required for the successful and safe operation of a laboratory. For the accreditation of an IVF laboratory, specific result parameters must also be met, which must be evaluated in close conjunction with the clinical treatment providers.

A German translation of the requirements specification is aviable.

1 General details of the laboratory

Requirement 1.1
The laboratory provides the following structural information when applying for accreditation: • Name of the laboratory • Type of company (or part of which company) • Name of the manager of the basic clinical facility (practice, clinic) • Name of the laboratory manager • Name of the staff member responsible for the accreditation (e.g. QM Officer) • Address and contact details of the laboratory (place, street, building number, email, telephone) • If available: Details of the certification of the basic clinical facility (practice, clinic) • If available: Details of the certification/accreditation of the laboratory
Documents to be provided during the audit
Extract from the commercial register
Declaration of independence from the laboratory manager (exclusion of influence from third parties on the procedures and results of the laboratory)
Certification and accreditation documents (if available)

2 Scope of application

The scope of application is defined by the laboratory on applying for the accreditation. As a general rule, the scope of application covers all activities performed by the laboratory as part of assisted reproduction. The scope of application is recorded on the accreditation certificate and published on the website of the specialist societies. The accreditation applies only to the procedures specified in the scope of application. The laboratory can only state that it is accredited (e.g. on its homepage) for those procedures that are recorded in the scope of application section of the accreditation certificate.

Procedures to be selected for the scope of application:

Basic activities of the ART laboratory

- Receipt and preparation of gametes for fertilisation (egg cells, sperm)
- Fertilisation (IVF, ICSI)
- Cultivation of the preimplantation embryos (2PN, cleavage stage embryos, blastocysts) and preparation for embryo transfer

Cryopreservation and thawing of

- Sperm
- Egg cells
- 2PN
- Preimplantation embryos

Specimen collection for PGT (preimplantation genetic testing)

- Polar body retrieval, embryo biopsy, trophectoderm biopsy
- Preparation of specimens for dispatch
- Interface organisation with the molecular genetics laboratory

Handling potentially infectious specimens (e.g. HIV, hepatitis B)

Sperm diagnostics

- Spermiogram analytics
- Further tests as listed by the relevant IVF laboratory.

Requirement 2.1
The laboratory has a document describing how new procedures are introduced. This ensures that new procedures can be introduced and included in the scope of application during the validity of the accreditation. The following applies in this respect: • Procedures that are already established based on corresponding publications, or in the form of commercial kits, can be introduced by the laboratory on the basis of the available data and following internal validation. Attention is paid here that both the procedure itself and the reagents and materials used are evaluated and validated. • Procedures that are not yet established must undergo separate evaluation and validation measures by the laboratory.
Documents to be provided during the audit
Description of how new, already established procedures are introduced and validated in the laboratory. Description of how as yet unestablished procedures are evaluated and validated in the laboratory on their introduction (optional: this usually applies only to large laboratories)

3 Organisation of the laboratory

Requirement 3.1
The laboratory manager requires at least the following qualifications: • Academic qualification in a medical or scientific subject (e.g. Master's, PhD, MSc) • At least 6 years of documented experience as an embryologist (with proof of further training and continuing education) • Transitional arrangement for laboratory managers with many years of experience but without an academic qualification as at 1/9/2017 in accordance with the recommendations of the Swiss Society of Reproductive Medicine • The statutory requirements for laboratory management remain reserved The laboratory staff have the necessary specialist skills: Completion of an apprenticeship with a biomedical or laboratory medicine connection or a subject-related university degree. Internal training and further education in the field of embryology must be documented. The adequacy of the number and qualification of the laboratory staff in relation to the treatment frequencies must be demonstrated based on an appropriate concept.
Documents to be provided during the audit
Proof of qualification of the manager Proof of qualification of the laboratory staff

Requirement 3.2
The responsibility for the following tasks must be defined, as well as the required skills and job description: • Management (including selecting procedures and materials, cooperating with competent authorities, responsibility for SOPs, for safety in the laboratory, for the QM system, for risk and prevention management, for the selection of laboratory staff, for induction, approvals and continuing professional development and further education, for the introduction and monitoring of key figures, for research projects, for the recording of clinical results and adverse events, for the selection of subcontractors and for communication.) • Technical/laboratory work • Administration • Training and education • Quality management (including management of the QMS, access to the senior management) • Communication
Documents to be provided during the audit
Organisational chart of the laboratory (stating the above-mentioned tasks) Job description for the above-mentioned tasks Arrangements for substitutes Documentation of the training and approval of staff

4 Quality management of the laboratory

Requirement 4.1
The laboratory has established a QM system ("Knowledge management / Knowledge database"). The QMS contains all information and documents relevant for the laboratory for all relevant methods and processes, including the documents required by this Specification. If a laboratory has a valid certification according to ISO 9001, ISO 15189 or ISO 17025, the requirement of section 4 is met per se.
Documents to be provided during the audit
Description of the QM system Table of contents of the QM system

Requirement 4.2
An appropriate version management system (title, date, version, scope/number of pages, person approving the document) and a controlled and traceable approval process (responsibility for drawing up, approving, reviewing/amending, archiving) ensure that every document in the QMS is current, correct, available and clearly labelled. The taking out of circulation and archiving of documents that are no longer valid is possible and controlled by the QMS.
Documents to be provided during the audit
Description of the version management and approval process for the documents in the QM system

Requirement 4.3
Records (documents of an evidence nature) are clear and traceable, collected in full, and archived in an accessible manner for a period to be defined. The legally prescribed retention periods remain reserved. For patient-related records, data protection (confidentiality, property rights) and data security (fire, theft, water, data loss) are adhered to. Direct contact with patients is documented. This requirement applies both for paper documents and for electronic documentation.
Documents to be provided during the audit
Description of the data protection (confidentiality within the laboratory and with respect to third parties) Description of the databases used, including the data security Description of the filing method for records

Requirement 4.4
The laboratory management has formulated a strategy. This includes the following aspects as a minimum: • Vision and aims of the laboratory • Commitment to “Good manufacturing Practice” and “Good Clinical Practice” / to providing a good level of quality for the patients. • Commitment that all staff shall meet the requirements of the QM system • Commitment to readiness for continual improvement • Commitment that all statutory and regulatory requirements shall be met
Documents to be provided during the audit
Strategy paper of the laboratory

Requirement 4.5
Error management (particularly non-compliance, organisational problems, emergencies, complaints, adverse events) is described and implemented. Correction management (particularly avoidance/prevention of renewed errors, improvement measures) is described and implemented.
Documents to be provided during the audit
Description of the error management Description of the correction management Overviews (e.g. annual review) of the errors recorded Overviews (e.g. action plan and implementation results) of the defined corrective measures

Requirement 4.6
The risk management (including definition of a laboratory-specific risk catalogue, identification of risks, risk process analysis) is described and implemented.
Documents to be provided during the audit
Description of the risk management Risk analysis of procedures (also possible as an integrated part of the procedural SOP) Overviews (e.g. annual review) of the reporting of serious near misses in the CIRS (Critical Incident Reporting System)

Requirement 4.7
Internal audits are established in the laboratory. Internal audits are carried out at least once a year on the basis of an audit plan. Every method/procedure is audited internally at least once every three years. In case of deviations, corrective measures are taken. An auditor for the performance of internal audits should be independent (not from the same laboratory/the same facility) and competent.
Documents to be provided during the audit
Audit plan for the period up until the next accreditation audit Audit reports since the last accreditation audit List of internal auditors with qualification profile

Requirement 4.8
The laboratory draws up an annual quality report (also: quality management review, management review). This report must include as a minimum: • Description of the met aim(s) • Description of the KPIs • Description of relevant changes (organisation, personnel, procedures) • Measures and improvements The quality report is provided to the accreditation body each time by the middle of the year for the previous year and checked by the accreditation body for plausibility. If any irregularities are noted, the accreditation committee is informed and, if applicable, conditions are imposed for the laboratory. A form for drawing up the quality report is provided by the accreditation body on its website (www.doc-cert.com)
Documents to be provided during the audit
Quality reports since the last accreditation audit

5 Results and key figures of the laboratory

Requirement 5.1
The laboratory has a database that enables an evaluation and statistical analysis of the relevant key figures at least annually. Corrections in the database must be traceable. It must be possible to evaluate the following Key Performance Indicators (KPI) by means of data input as a minimum. *See Appendix* The KPIs are regularly evaluated by the laboratory. Centres with at least 30 cases per year should perform the analysis on a monthly basis. Longitudinal comparisons ensure that no systematic errors occur. For appropriate KPIs, a limit figure is set by the specialist societies in accordance with the literature or national statistics (FIVNAT). If the laboratory does not meet this limit figure in a certain year, actions for improvement shall be initiated. If the laboratory (together with its clinical facility) fails to meet the limit figure in at least two consecutive years, it shall appoint an external expert to carry out a joint quality audit. An evaluation of the individual laboratory staff members should be carried out and analysed. The annual analysis and any measures are communicated to the laboratory staff. *For all KPIs of which the results are subject to influences from multiple factors, the auditor shall take the centre-specific circumstances into account and assess the achieved results accordingly.
Documents to be provided during the audit
Description of the database Evaluation of the last complete annual cohort (max. 2 years in the past) Any applicable action plan in case of deviations

Requirement 5.2
The laboratory takes part in at least one external quality assurance programme. This includes, for example, programmes of the ESHRE, SWICE or UK-NEQAS.
Documents to be provided during the audit
Report / results of the quality assurance programme

6 Safety in the laboratory

Requirement 6.1
The layout of the laboratory follows the requirements relating to the organisation of the work flow and safety. The following activities must be carried out in a separate space from the IVF area. • Changing clothing • Washing hands • Office work • Storage of gas cylinders The following activities must be done in a separate space or at a different time from the treatment cycles: • Cleaning and sterilization of materials
Documents to be provided during the audit
Layout plan of the laboratory with rooms allocated according to activities

Requirement 6.2
Access to the laboratory is only allowed by authorised personnel. Staff and visitors who are not authorised personnel must provide ID and their entry is documented with time details. The records are retained. Visitors are briefed by a laboratory staff member on the necessary conduct inside the laboratory and they sign a form regarding compliance with data protection (protection of patient data, protection of company data).
Documents to be provided during the audit
List of authorised persons Data protection declaration for visitors Documentation regarding access by unauthorised persons

Requirement 6.3
The protection of the laboratory staff, patients and biological material is assured by an emergency plan. This plan may also be part of a superordinate emergency plan (e.g. hospital). The power supply of relevant equipment (incubators, refrigeration systems) is assured in an emergency. A contact list of all laboratory staff and necessary persons in case of an emergency is kept in the laboratory and at a central coordination centre (part of the emergency plan). An alarm system is in place. Cooperation with a comparable laboratory nearby is agreed in writing, so that necessary treatments are not interrupted in case of an outage. A backup solution is in place for the relevant equipment and systems in case of an outage.
Documents to be provided during the audit
Emergency plan Cooperation agreement with a nearby laboratory. List of replacement equipment (also in central list of equipment)

Requirement 6.4
The laboratory meets the national, cantonal, regulatory and medical requirements for occupational health and safety. This concerns the height of the work surfaces (bench), the height of the microscope, the room temperature (heating and air-conditioning systems), the lighting conditions and work area per laboratory staff member. It also concerns hygiene (hand disinfection, surface disinfection, cleaning) and handling of hazardous biological materials (needle-stick injuries, seropositive patients). A current version of a hygiene plan (description of the general hygiene procedures and how to handle infectious material / patients; cleaning, disinfection, clothing, cosmetics, gloves, nutrition) is available for the laboratory. The particularities of a reproductive medicine laboratory (lighting, disinfection) must be taken into account in this. The internal audits also check that these requirements have been met. It is checked that the laboratory staff have been vaccinated against hepatitis B. This vaccination is strictly recommended to the laboratory staff.
Documents to be provided during the audit
Audit report on occupational health and safety Hygiene plan Description of procedure for handling needle-stick injuries Description of procedure for handling seropositive patients

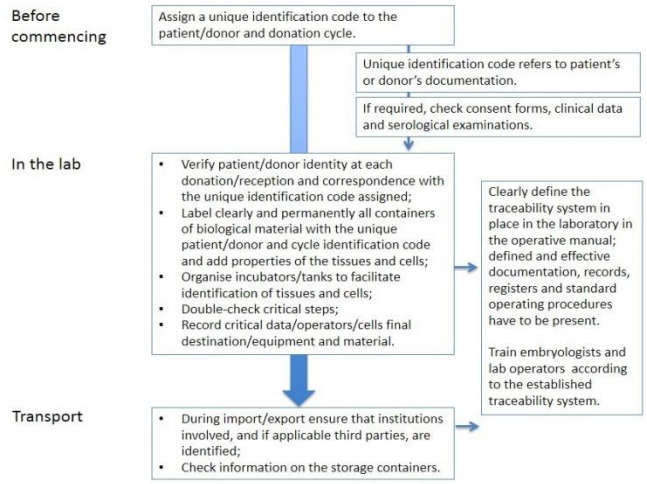
Requirement 6.5
Gametotoxic components are minimised within the IVF laboratory. This applies to floors, surfaces, paints/varnishes, equipment and room air. The laboratory provides concepts to demonstrate that this requirement is met.
Documents to be provided during the audit
Concept on the minimisation of gametotoxic substances in the laboratory and treatment area Concept on local validation of room functions and equipment in case of changes (initial use, renovation, conversions, after maintenance)

Requirement 6.6
The type and quantity of laboratory equipment must be appropriate for the type and frequency of treatment. A concept to this effect must be documented. This concerns the following equipment in particular: Incubators; ICSI microscopes, stereo microscopes, heat sources, cryotanks, refrigerators, centrifuges, laminar-flow benches. Incubators for the embryo cultures are continuously monitored and have an emergency power supply. The gas supply is monitored. There is an emergency plan available. All laboratory equipment must have a CE mark. If a piece of equipment does not have a CE mark, its suitability for use in the IVF laboratory must be demonstrated in another way (validation, literature). An equipment logbook and operating instructions must be available and accessible for every piece of equipment. For each piece of equipment, it must be defined how, when and on the basis of which specifications, maintenance, inspections and calibration are carried out. The decommissioning process is controlled and implemented accordingly. Decommissioned equipment must be labelled specially as such.
Documents to be provided during the audit
List of incubators with the associated validation reports, and equipment logbooks and test reports Documentation regarding continuous monitoring and the emergency power supply (also possible through the building management system). Equipment lists with proof of validation, CE mark and operating instructions. Maintenance logbooks and, if applicable, proof of calibration for all equipment. Proof of calibration of test equipment Description of the equipment decommissioning process.

Requirement 6.7
The air purity is monitored regularly by means of particle measurements. An air purification system is present. The air quality must be measured periodically in accordance with a documented concept. The air quality must be GMP grade A in the workbench area and grade D in the other areas.
Documents to be provided during the audit
Test reports relating to air quality Maintenance reports for the air quality measurements

Requirement 6.8
Storage following cryopreservation takes place outside of the IVF laboratory. The liquid nitrogen (LN) level is continuously monitored. Personnel who handle LN and cryo products require special instruction on use of the equipment, the work steps and the protective equipment. The safety of the personnel is assured in rooms in which liquid nitrogen (LN) is present. A low-oxygen alarm and adequate ventilation are recommended.
Documents to be provided during the audit
Description of the continuous monitoring Proof of monitoring Description and proof of the special instruction Description of the safety precautions in relation to risks from liquid nitrogen (LN)

7 Identification and traceability

Requirement 7.1
The identification of patients and germ cells/embryos and the traceability of all materials and products are controlled and described for all procedures. The traceability includes the details of the staff and the time and place (for storage) of every relevant work step. The records must be retained as a minimum in accordance with the general statutory provisions for medical treatment data. A backup system must be present. If cryopreserved cells or tissues are used, the traceability back to the cryopreservation and the process steps immediately prior to that must be assured. The identity of both partners must be traceable in the case of cryopreserved embryos. The retention period is therefore extended to the period of cryopreservation. Below is an example from the ESHRE Guideline: 
Documents to be provided during the audit
Description of the identification of patients and germ cells / embryos and of the traceability

Requirement 7.2
The laboratory staff are specially trained on the necessary and correct documentation for traceability. The correct documentation is checked during the internal audits.
Documents to be provided during the audit
Proof of training Audit report with inspection report on the documentation

Requirement 7.3
Certain critical work steps require use of witness systems (e.g. the four-eye principle, electronic witness system). Witness systems must be used for at least the following procedures: • Team time out at time of egg retrieval (interface between clinical team and laboratory team) • Team time out at time of embryo transfer (interface between clinical team and laboratory team) • Team time out on handover of native or processed sperm for planned insemination (interface between clinical team and laboratory team) • Team time out on receipt and handover of cryopreserved cells or tissues from or to external parties (interface between external party and laboratory team) • Handover of processed sperm for insemination in the case of planned IVG or ICSI (internal laboratory interface)
Documents to be provided during the audit
Description of the witness systems used in the laboratory

Requirement 7.4
All media, reagents and consumables, including disposable products, used for the procedures have been tested and approved with respect to their suitability. The laboratory describes when which test procedures are used for these materials. The quality of the associated suppliers is checked and evaluated (including for example temperature checks during transport). If the requirements are not met, improvements are initiated and if necessary the supplier is changed. Batch management is implemented (including receipt, consumption, destruction)
Documents to be provided during the audit
Description of the use of the media, reagents and consumables Supplier evaluation Description of the batch management

8 Laboratory procedures

Requirement 8.1
An SOP is available for every procedure for which the laboratory applies for accreditation (see section 2). The provisions of the ESHRE Guideline should be taken into account in the SOPs. Sections that are identical for several SOPs of one laboratory can be drawn up as separate documents. In such a case, the SOP makes reference to these documents. Changes to the SOPs must be traceable.
Documents to be provided during the audit
SOP for every method/procedure to be accredited

Requirement 8.2
The procedural SOPs cover the following issues (only the relevant issues are to be covered by each procedure): • Background to the method • Responsibilities (person responsible, persons involved, qualification requirements) • Framework conditions (areas, technology, subcontractors, environmental conditions (e.g. temperature, pH-level, osmolality, O_2 concentration), environmental risks, information systems, interferences (e.g. LN_2, surface contamination, virus carriers), customer requirements) • Procedural description with subdivision into pre-analytics, analytics and post-analytics (indication, patient information, informed consent, requirements, examination material, transport, incoming goods inspection, identification, reagents/consumables, individual work steps, documentation and records, witness systems, traceability) • Evaluation (measurement ranges and normal values, selection criteria, morphological criteria, result deviations and abnormal results, approval, findings, reports, errors and corrections) • Storage, disposal and cleaning • Quality assurance • Literature and specifications
Documents
SOPs in accordance with the scope (section 2)

Requirement 8.3
The laboratory checks its procedures on a regular basis to ensure they are up-to-date and correct. The laboratory has available a description of who is responsible for the monitoring and update of the procedural SOPs, and when, and how the process of revision, presentation to the team, staff training and renewed approval is governed.
Documents to be provided during the audit
Description of how the procedural SOPs are monitored and amended.

Appendix to Requirement 5.1

The key performance indicators are published in English only.

Inclusion Criteria:

- woman's age ≤ 40y
- ejaculated sperm (excl. TESE/MESA)
- insemination of fresh oocytes

Key performance indicators:

KPI	Key performance indicator	Calculation	Center result	Competency value	Benchmark value
1.	ICSI damage rate	no. damaged or degenerated x 100 all oocytes injected		≤10%	≤5%
2.	ICSI normal fertilization rate	no. oocytes with 2PN and 2PB x 100 no. MII oocytes injected		≥65%	≥80%
3.	IVF normal fertilization rate	no. oocytes with 2PN and 2PB x 100 no. COC inseminated		≥60%	≥75%
4.	Failed fertilization rate (IVF)	no. cycles with no evidence of fert`n x 100 no. ofstimluated IVF cycles		n.d.	<5%
5.	Cleavage rate	no. cleaved embryos on Day 2 x 100 no. 2PN/2PB oocytes on Day 1		≥95%	≥99%
6.	Day 2 embryo development rate	no. 4-cell embryos on Day 2 x 100 no. normally fertilized oocytes[a]		≥50%	≥80%
7.	Day 3 embryo development rate	no. 8-cell embryos on Day 3 x 100 no. normally fertilized oocytes[a]		≥45%	≥70%
8.	Blastocyst development rate	no. blastocysts Day 5 x 100 no. normally fertilized oocytes[a]		≥40%	≥60%
9.	2 PN cryosurival rate	no. cleavedembroys Day 2 x 100 no. warmed 2PNs		n.d.	n.d.

KPI	Key performance indicator	Calculation	Center result	Competency value	Benchmark value
10.	Blastocyst cryosur-vival rate	no. blastocysts appearing intact x 100 no. blastocysts warmed		≥90%	≥99%
11.	Implantation rate (cleavage stage)[b]	no. sacs seen on ultrasound[c] x 100 no. embryos transferred		≥25%	≥35%
12.	Implantation rate (blastocyst stage)[b]	no. sacs seen on ultrasound[c] x 100 no. blastocysts transferred		≥35%	≥60%
13.	Successful biopsy rate	no. biopsies with DNA detected x 100 no. biopsies performed		≥90%	≥95%
14.	live birth rate cleavage stage-fresh	no. of live births x 100 no. offresh ET of Day 2-4 embryos		n.d.	n.d.
15.	live birth rate cleavage stage cryo	no. of live births x 100 no. of FET of Day 2-4 embryos		n.d.	n.d.
16.	live birth rate blastocyst fresh	no. of live births x 100 no. of fresh ET of Day 5-6 Blastocysts		n.d.	n.d.
17.	live birth rate blastocystcryo	no. of live births x 100 no. of FET of Day 5-6 Blastocysts		n.d.	n.d.

ICSI= intracytoplasmic sperm injection; MII = metaphase II; PB = polar body ; PN = pronucleus.

[a] Defined as oocytes with 2PN and 2PB on Day 1.

[b] Based on total number of embryos transferred to all patients in the reference group, not just to those for whom an implantation occurred.

[c] Definition reached after discussion, as some felt that no. fetal heartbeat detected/no. embryos transferred was a more meaningful Indicator.