# ISAR Consensus Guidelines on Safety and Ethical Practices in *In vitro* Fertilization Clinics

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**Abstract**

**Study Question:** What are the Safe and Ethical practices for ART applicable in INDIA? **What is Already Known:** The Indian IVF industry is booming; with mushrooming of assisted reproductive technology (ART) clinics in the country, the need for regulation is immense. The ISAR has taken up this initiative to lead the way forward in establishing practice guidelines for the safe and ethical use of ARTs in our country. These guidelines discuss the points to consider before the starting of an IVF unit, to the designing of the laboratory, the staffing pattern and experience recommendations, laboratory safety guidelines, documentation and patient traceability, gamete traceability, handling biological material, the consumables and media, and different consents and checklists and also propose key performance indicators for the Indian scenario. **Study Design, Size, Duration:** This is the report of a 2-day consensus meeting where two moderators were assigned to a group of experts to collate information on safe and ethical ivf practices in INDIA. This meeting utilised surveys, available scientific evidence and personal laboratory experience into various presentations by experts on pre-decided specific topics. **Participants/Materials, Setting, Methods:** Expert professionals from ISAR representing clinical and embryology fields. **Main Results and the Role of Chance:** The report is divided in various components including the regulations, the various requirements for an ART center, qualifications and trainings, recommendations on good practices and quality management: the report and recommendations of the expert panel reflect the discussion on each of the topics and try to lay down good practice points for labs to follow. **Limitations, Reasons for Caution:** The recommendations are solely based on expert opinion. Future availability of data may warrant an update of the same. **Wider Implications of the Findings:** These guidelines can help labs across the country to standardise their ART services and improve clinical outcomes. **Study Funding/Competing Interest(S):** The consensus meeting and writing of the paper was supported by funds from CooperSurgical India.

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# Introduction

Infertility is a significant health problem across the reproductive age group in India. As a result, the demand for medically assisted modalities to alleviate infertility services is growing. Since the birth of the first baby through *in vitro fertilization* (IVF) in 1978 in the UK, more than 8 million births have taken place worldwide through assisted reproductive technology (ART).[1,2]

The rapid evolution of ART for the treatment of infertile couple was one of the extraordinary restorative accomplishments throughout the world. Infertility has remained a social taboo since ages; with changing times and rapid developments taking place in the field of modern science, our philosophies have evolved eventually, the desire of a child, a family successor continues to be a significant concern. The researchers have continued to make dynamic advances in the journey and led to improvements in the modern medicine giving a ray of hope to the millions of infertile couples, extensive refinement of techniques in the field of ART open opportunities finding solutions to fertility problems for the wider population, but the ready access to these services also allow misuse which needs to be regulated.[3]

## The regulatory perspective of in vitro fertilization in India

In 1982, the Indian Council of Medical Research (ICMR), a pioneering Indian organization in the field of Biomedical Sciences, took the initiative realizing the significance of infertility treatment and introduced a project (led by T. C. Anand Kumar and Indira Hinduja) at Institute for Research in Reproduction (now ICMR-National Institute for Research in Reproductive Health) at Mumbai. As a result, India's first fully scientifically documented test-tube baby, "Harsha," was born on August 6, 1986. Since then, the demand for infertility management in the country led to the mushrooming of the IVF clinics in the country.[3]

ART in India is facing quite a few regulatory concerns, and risks need evaluation at a larger scale chiefly due to the absence of any regulations. The services offered by the ART clinics are questionable. To regulate these clinics, the ICMR developed the National Guidelines for Accreditation, Supervision, and Regulation of ART Clinics in India in 2005 which was transformed into ART (Regulation) Bill, 2017 and Surrogacy (Regulation) Bill, 2016.[3] The bill is still under scrutiny.

## 1. Assisted Reproductive Technology Clinics in India as Per the National Registry

In India, the number of ART centers is rising over the last decade. At the time of formulating this consensus and based on the number of applications received, the list of enrolled ART clinics is 490 under the National Registry of ART Clinics and Banks governed by the ICMR.[4,5]

It is a vast market, and hence, many multinational companies have come up with their setup. Unfortunately, this health sector is still unorganized and unregulated.

It is assumed that we have more than 5000 large and small centers working in India offering ART services. In India, we have active societies such as Indian Society for Assisted Reproduction, Indian Fertility Society, and Association of Clinical Embryologist which have a large number of members. Unfortunately, they do not have hold regulatory powers as far as ART practices in India are concerned.

Table 1: Distribution of *in vitro* fertilization centers according to the number of cycles

| Cycles | Number of centers | | |
|---|---|---|---|
| | | 2011 | 2012 |
| <50 | 78 | 84 | 96 |
| 51–100 | 16 | 15 | 17 |
| 101–200 | 9 | 13 | 16 |
| 201–500 | 9 | 8 | 5 |
| 501–1000 | 2 | 3 | 5 |
| >1000 | 0 | 0 | 0 |
| Total | 114 | 123 | 139 |

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Clinics involved in any one of the following activities should be regulated, registered, and supervised by the State Accreditation Authority/State Appropriate Authorities.

1. Any treatment involving the use of gametes that have been donated or collected or processed *in vitro*, except for artificial insemination (AIH) of husband's semen, and for intrauterine insemination (IUI) by level 1A clinics who will not process the gametes themselves
2. Any infertility treatment that involves the use and creation of embryos outside the body
3. The processing or/and storage of gametes or embryos
4. Research on human embryos.

The term ART clinic used in this document refers to a clinic involved in any one of the first three of the above activities.

### Recommendations on assisted reproductive technology clinics

Once the bill is passed, All ART centers/clinics should be registered with the National Registry of ART Clinics and Banks in India, ICMR.

There should be a provision for licensing of embryologists.

Registration of patients should be done with photograph identity and complete address (address proof is mandatory).

The ART professionals may be guided by the white paper/guidelines issued by the National ART bodies till the appropriate advisories are issued by the Government of India (GOI).

There should be a grievance redressal forum for ART centers in the country.

## Standards for in vitro fertilization clinic in India as per the Indian Council of Medical Research guidelines 2010

The ICMR recently finalized the National Guidelines for the Regulation of ART clinics. According to the ICMR guidelines, infertility clinics have been categorized into three levels based on the availability and complexity of ART service. The guidelines provide minimum requirements regarding staff in infertility clinics as well as physical requirements for an ART clinic.[6]

**Table 2: The categorization of *in vitro* fertilization clinics**

| | |
|---|---|
| Level 1 (primary infertility care units) | In this type of clinics, preliminary investigations are carried out and type and cause of infertility are diagnosed |
| | Primary infertility care unit or clinic could be a doctor's consulting room, such as a gynecologist's or a physician's consulting office, or even a general hospital |
| | Depending on the severity of infertility, the couple could be treated at the Level 1A clinic or referred to a specialty (Level 1B, Level 2 or Level 3) clinic |
| | The gynecologist or the physician in-charge of a Level 1A infertility care unit should have an appropriate postgraduate degree or diploma and be capable of taking care of the above responsibility |
| | A Level 1A infertility care unit will not require an accreditation under these guidelines |
| Level 2 (secondary infertility care units) | In this type of clinics, preliminary investigations are carried out and type and cause of infertility are diagnosed |
| | Primary infertility care unit or clinic could be a doctor's consulting room, such as a gynecologist's or a physician's consulting office, or even a general hospital |
| | Depending on the severity of infertility, the couple could be treated at the Level 1A clinic or referred to a specialty (Level 1B, Level 2, or Level 3) clinic |
| | The gynecologist or the physician in charge of a Level 1A infertility care unit should have an appropriate postgraduate degree or diploma and be capable of taking care of the above responsibility |
| | A Level 1A infertility care unit will not require an accreditation under these guidelines |

*Contd...*

| Table 2: Contd... | |
|---|---|
| Level 3 (tertiary level infertility care units) | In this type of clinics, preliminary investigations are carried out and type and cause of infertility are diagnosed<br>Primary infertility care unit or clinic could be a doctor's consulting room, such as a gynecologist's or a physician's consulting office, or even a general hospital<br>Depending on the severity of infertility, the couple could be treated at the Level 1A clinic or referred to a specialty (Level 1B, Level 2, or Level 3) clinic<br>The gynecologist or the physician in-charge of a Level 1A infertility care unit should have an appropriate postgraduate degree or diploma and be capable of taking care of the above responsibility<br>A Level 1A infertility care unit will not require an accreditation under these guidelines |

## 2. Code of Practice

Code of practice deals with all aspects of the treatment provided and the research done at registered clinics. Those areas that affect the doctors, scientists, and patients and are a part of this code are summarized below. The aim is to provide more comprehensive coverage of key aspects of the IVF laboratory, to give continuous support to laboratory specialists and consequently contribute to improving IVF patient care.

### Infrastructure

Embryology laboratories are an essential part of an ART clinic.
Areas should be minimal but scalable.
Small laboratory, positive pressure with high-efficiency particulate air filters is recommended.

#### Recommendations on laboratory space and design

- The embryology laboratory should have adequate space to ensure safe and comfortable working conditions, and the design should be appropriate for the volume and scope of the procedures performed
- The location of storage areas and equipment should be planned for optimal efficiency in each working area
- Laboratory design should facilitate cleaning as per the required standards
- Floors, walls, and ceilings must have nonporous surfaces that can be cleaned easily
- Separate office space should be available for carrying out administrative/documentation work
- Access to the laboratory should take account of the need for environmental control and security
- Oxygen depletion monitor is only required for a cryostorage facility where liquid nitrogen is handled
- The laboratory and operation theater (OT) access should be independent of each other but should be interconnected by pass box/glass doors, etc.
- An adequate changing rooms based on workload should be located in the vicinity of the scrub area.

#### Recommendations on laboratory equipment

- The laboratory should contain all essential items required for IVF, in a number appropriate to the workload
- The incubator number is critical and should be based on the number of cycles and embryo culture duration
- Gametes and embryos should be conveniently distributed across incubators to minimize door openings
- Equipment must be adequate for optimal laboratory work, easy to disinfect and kept clean to avoid contamination
- We recommend not more than four patients at a given time per incubator standard sized 150 L box incubator, bench-top incubators can accommodate more as the gas and temperature recovery rates are faster.

## Recommendations and consensus on air quality

- Air quality monitoring should be used as a routine measure of quality assurance (for example, through particle counts or the use of settle plates; recording any cultures observed)
- Air handling unit (AHU) with heating ventilation and air conditioning is recommended with 12–15 air changes per hour
- Separate system for filtration of volatile organic compounds (VOCs) and microbial decontamination is recommended
- Filters should be routinely changed depending on the workload of the laboratory
- Positive pressure modules may be used in lieu of AHU.

## Consensus on air quality

| Parameters | Group consensus (as per the ESHRE guidelines, 2015) |
|---|---|
| Particle counts<br>Microbial contamination<br>VOCs filtration | Grade A environment with a background of at least GMP Grade D |

VOC=Volatile organic compounds, GMP=Good manufacturing practices

## Recommendations on infrastructure

- Group recommendation. A Background knowledge in infrastructural and architectural needs for an ART clinic is recommended before setting up an ART Lab.
- The minimum recommended laboratory space is 120 sq feet
- Cryobiology laboratory minimum recommended space is 100 sq feet
- It is preferable to have an IVF OT as per NABH norms
- The interiors, physical characteristics, and air quality values should be adhered as per the specifications mentioned above
- Powerpoints should be enough and at regular distances with UPS backup and generator backup
- Scrub and wash area should be designed near the vicinity of IVF OT and laboratory with well-concealed drainage
- There should be no water source inside the laboratory
- Separate exclusive air conditioning (preferably attached with an AHU) is recommended to maintain the laboratory room temperature between 24°C and 26°C
- The laboratory should be adequately lit with warm-diffused recessed lights.

## Recommendations on laboratory safety

- It is the duty of all laboratory personnel to inform laboratory and/or center management of any circumstances in which the safety of laboratory personnel, and/or the safety and integrity of gametes, and/or the embryos in their care are compromised
- The laboratory design should allow all procedures to be carried out without compromising the safety of staff, patients, or patients' gametes or embryos[7]
- Equipment should be placed such that there is sufficient and safe operating space
- Attention should be given to the ergonomics of the operator, bench height, adjustable chairs, microscope eye height, efficient use of space and surfaces, and sufficient air conditioning with controlled humidity and temperature
- Measures should be taken to minimize exposure of gametes and embryos to VOCs and other potentially toxic substances[7]
- All staff should have appropriate equipment handling trainings[7]
- The storage room should have an oxygen depletion monitor, linked to an external warning system
- All cryostorage vessels should have an alarm system to alert staff

- Only trained scientific, technical, medical, or nursing staff or staff in training who are under supervision should be allowed to enter the laboratory while procedures are taking place
- Visitors should never be left unsupervised in clinical laboratory areas
- Only authorized person should enter the laboratory. Unauthorized person can enter the laboratory only when accompanied by an authorized person. Appropriate dress should be worn before entering the laboratory.

## 3. Staffing

### Minimum standards for the staffing

For the ART laboratory, several professional associations and laboratory organizations have already framed and published the rules and guidelines; however, in India, there are no specific recommendations for staffing versus workload.[8]

### Staff requirement

- The number of staff should be based on the number of cycles performed in a year
- The type of services offered strongly influences the number of people required
- As an approximate guide, clinics that perform up to 150 retrievals and cryopreservation cycles per year should always have a minimum of two qualified clinical embryologists
- Appropriate human resources should provide an adequate climate to perform all laboratory tasks on time to ensure patient safety and quality of care.

**Table 3: Recommendations on staffing**

| Number of laboratory cycles performed annually | Minimum number of embryologists |
|---|---|
| 1–150 | 2 |
| 151–300 | 3 |
| 301–600 | 4 |
| >600 | 4+1 additional embryologist per additional 200 cycles |

### Consensus on staff qualification and minimal staffing

#### *Clinical embryologists*

- Minimum requirement should be MBBS/MSc in biological sciences
- Clinical embryologists represent the first line of participation in daily clinical practice
- Laboratory director should possess a higher academic degree (MD/MSc/PhD) with a minimum of 6 years of documented human embryology experience.

### Indian Council of Medical Research regulations on staffing

#### *Laboratory director*

The laboratory director or another experienced person having the ability level for training can train individuals joining the team. The training progress must be strictly followed and documented properly. The promotion of a new team member to a higher level of ability can work under supervision or can work without supervision and may train other persons [Table 4]. The procedures must be documented and approved by the laboratory director.

The number of cases per procedure that must be performed to transit from one training level to the next is indicated. These numbers need to be adopted by the individual centers.

**Table 4: Proposed training plan for new staff members in the *in vitro* fertilization laboratory**

| Procedure | Observation and experienced staff member (cases) | Performed under supervisions (cases) | Allowances for working independently (cases) | May instruct beginners, after (cases) |
|---|---|---|---|---|
| Semen analysis | 15 | 35 | 50 | 200 |
| Semen preparation | 15 | 35 | 50 | 200 |
| Preparation of culture material | 20 | 30 | 50 | 200 |
| Oocyte retrieval | 30 | 50 | 80 | 200 |
| Preparation of culture material | 15 | 35 | 50 | 200 |
| Embryo development | 15 | 35 | 50 | 200 |
| Embryo transfer | 30 | 50 | 80 | 200 |
| Cryopreservation and thawing of sperm | 15 | 35 | 50 | 200 |
| IVF | 30 | 50 | 80 | 200 |
| ICSI | 30 | 50 | 80 | 200 |
| Cryopreservation of oocytes and embryo | 30 | 50 | 80 | 200 |

IVF=*In vitro* fertilization, ICSI=Intracytoplasmic sperm injections

### *Clinical embryologist responsibilities*[9]

- Execution of standard operating procedures (SOPs)
- Participation in daily practice, communication, and organization
- Contribution to clinical laboratory decisions
- To impart training to the staff members and students.

### *Clinical embryologist qualification*

If the clinic is in existence for at least 1 year before the promulgation of these rules, a person with a BSc or BVSc degree but with at least 3 years of first-hand validated hands-on experience of the techniques [Table 4] and of discharging the responsibilities listed below would be acceptable for functioning as a clinical embryologist.
He/she must be either a medical graduate or have a postgraduate degree or a doctorate in an appropriate area of life sciences.

### Staff management

The laboratory should establish documented procedures for staff management that ensure all staff should have:

- An initial orientation and induction
- Basic training and advanced training as required
- On-going competence assessment with audits
- An annual joint review (with the line managers)
- Continuous education and professional development
- Staff records
- Access to hands-on training.

There should be a system of short-term comparisons between team members on a regular basis (for example, monthly, but independent of the weekday and workload). Short-term quality control can involve one member comparing his or her results with another staff member using the same sample or patient.
Quality control measures are mentioned below:

- Grading of oocyte maturity and fertilization rates
- Classification of embryo quality
- Evaluation of basic sperm parameters of original and prepared semen samples. Semen collection container should be of IVF grade.

## 4. Quality Management

### Definition and concept of quality

The ISO 9000:2000 standards define quality as "the degree to which a set of inherent characteristics fulfills requirements." The requirements in this definition could be specified by the supplier, by the customer, or may also be legal.[10]
Quality-of-care is a multi-dimensional concept, encompassing treatment efficacy and impact on the health and welfare of both patients and offspring. Besides, the concept of quality includes the cost in financial and human terms of achieving the desired outcome.[11]

### General QMS requirement as per the ISO standards

The organization/clinic should:[11]

- Identify the process needed for the quality management system and their application throughout the in-clinic setup
- Determine the sequence and integration of these processes
- Have SOPs for all procedures
- Ensure the availability of resources and information necessary to support the operation of these procedures
- Implement actions necessary to achieve planned results and continual improvement of the system
- Define job roles and responsibilities
- Ensure full traceability
- Use quality-tested products
- Have annual maintenance contracts (AMC) in place for critical equipment
- Protocol verification and corrective actions
- Performance reviews and internal/external audits
- Risk assessment and analysis
- Key performance indicator (KPI) monitoring.

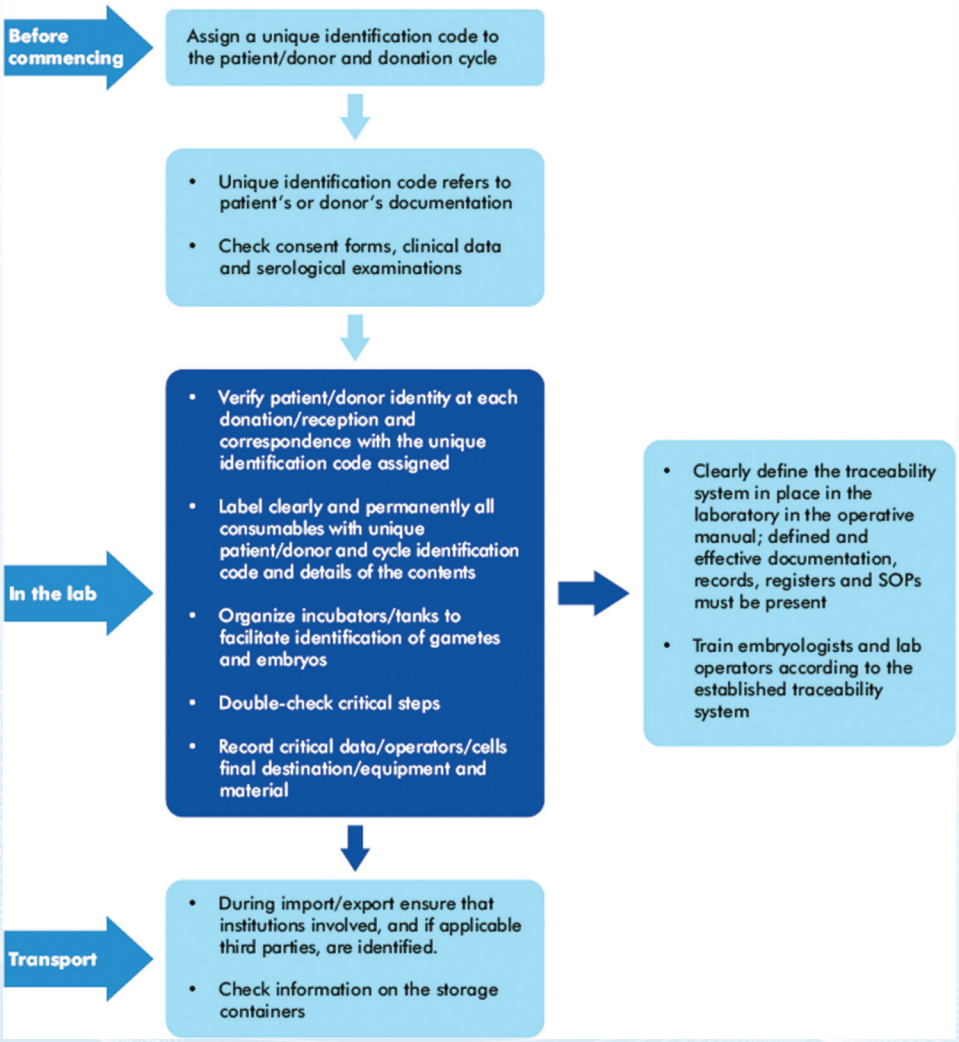
## 5. Identification and Patient Traceability

### Guidelines for identification of gametes

- Before commencing a treatment cycle procedure, the embryologist should check that the patient has signed a valid informed consent form
- Patient's gamete, embryo, tissue, plastic ware, and culture plates' identification system should be followed diligently in all the cases
- Minimum of three identification markers should be used for patient identification out of which one should be unique to the patient
- IVF centers must double-check the identification of samples and the patients or donors to whom they relate at all critical points of the clinical and laboratory process
- Laboratories must have in place robust, effective processes to ensure that no mismatches of gametes or embryos or identification errors occur

- Verification of patients and witnessing protocols should be followed when any of the following clinical or laboratory procedures take place:
  - Ovum pick up and oocyte collection
  - Semen collection and sperm preparation
  - Insemination through IUI/IVF/intracytoplasmic sperm injection (ICSI)
  - Embryo transfer
  - Cryopreservation
  - Disposal of gametes and embryos
  - Transport of gametes and embryos.
- Incubators should be organized to facilitate the identification of sperm, oocytes, zygotes, and embryos
- The identity of the laboratory person handling the samples at each point of the process, from receipt through final disposition, date and time, should be documented. This permits tracking of the example throughout its period in the laboratory, also at later dates
- In cases where donor oocytes/sperm are used, traceability must be assured
- All cells and embryos for genetic investigation must be individually handled, carefully identified and labeled, and tracked during the whole procedure. During these steps, double identity checks are strongly recommended
- Electronic systems such as bar-coding and radio frequency identification (RFID) are appropriate, subject to a risk assessment to ensure that any system introduced will not harm gametes or embryos. The system must be deemed reliable and ensure that any electronic devices employed are safe. Integrated witness systems should be fully validated. Double-witnessing is required for entry, exit points, and the mixing of sperm and oocytes. A hard copy of electronic witnessing should be retained.

ESHRE recommendations for identification of patients and traceability of their reproductive cells[8]



## 6. Witnessing Systems in In vitro Fertilization

### Background

Manual and electronic witnessing is used simultaneously to (i) ensure enough in-house validation, (ii) assess the exact mismatch rate (i.e., operator noncompliance), and (iii) analyze documented procedure timings. The introduction of the electronic witness system (EWS) in the IVF clinical practice is a recent innovation. Although EWS is recommended to improve traceability and reducing IVF mix-ups, only a few centers have implemented the technology to this point all around the world.[12,13]

### Timing of errors in the in vitro fertilization process

Most important errors could be wrong identity of couple or patients, improper specimen labeling, egg collection, sperm reception and preparation, mixing wrong sperm and eggs, or injecting wrong sperm into eggs, improper transfer of gametes or embryos between tubes/dishes, improper transfer of embryos into a woman, insemination of a woman with wrong sperm prepared in the laboratory, placing wrong gametes or embryos into cryopreservation, removal of wrong gametes or embryos from cryopreservation, disposal of wrong gametes or embryos and transporting wrong gametes or embryos, etc.

### Error detection

Error detection during IVF could happen in the laboratory, after embryo transfer, after live birth, after IUI, after embryos frozen, prior or during embryo transfer, before IUI, and before treatment starting, and most of the times, it is detected at a later phase beyond repair time.

#### *In vitro* fertilization zero tolerance for error: Demands high integrity

Though couples may desire to have a child with their gene pool, but no couple would like to have a child without consent, deliberate, or accidental mix up of gene pool.
Integrity in IVF is crucial and has excellent value, and it demands ethical practices. it must be considered as a serious incident and should be followed up with a audit.
Utmost care must be taken by the stakeholders to minimize such errors. Currently, most of the laboratories have introduced the couple's ID check and double witnessing of the procedure to avoid any form of error in the IVF procedure effectively.

#### Manual witnessing system

Manual double witnessing (MDW) can be defined as the "double-checking performed on all clinical and laboratory procedures" with the expectation that if an "operator" makes an error, it will be caught by the other "witness." Although MDW is a safeguard requirement whose apparent value is self-evident, evidence suggests that it may not be as safe and effective as it should be.

#### *Disadvantages of manual double witnessing*

- MWS may introduce errors
- Embryologists could end up in doing IVF process-related mistakes
- Embryologists could face legal challenges and regulatory sanctions, while patients would have to cope with the psychological damage and with the loss of confidence in the IVF process impacting on future cycles
- Numerous problems with double checking have been identified previously relating to independent redundancy, attentional blindness and ambiguous accountability

- Common checking failures include check omission, check incomplete, involuntary automaticity, and noncontemporaneous checking
- Following are the probable errors in the IVF process:
  - Mixing up of wrong samples (deliberate or accidental – with similar names–mix up of samples)
  - Mismatching the wrong eggs with wrong sperm
  - Mismatching the wrong embryos to the wrong patient
  - Contaminating one semen sample with another
  - Patients who deliberately bring a different third-party sperm sample

### Electronic witness system

The introduction of the electronic witness system (EWS) in the IVF clinical practice is a recent innovation. Without an EWS, the primary control measure used to reduce the risk of biological sample mix-up is a human double-checking approach. However, this mechanism of control is vulnerable to human errors, including check omission, check incomplete, involuntary automaticity, and no contemporaneous checking. For these reasons, several alternative options have been developed in order to replace the majority of human manual witnessing steps in IVF: (i) systems based on barcode labels, (ii) systems based on silicon barcodes that are injected directly into eggs or embryos, and (iii) systems based on RFID technology.[12]

#### *Advantages of electronic witness system*

- Prevent potential errors (including identification errors)
- Safe and secure to use
- Cost-saving
- Monitors every instance
- To help establish accountability, less ambiguity, and reduce liability
- Minimize stress and interruptions
- Enhances patient satisfaction and overall well-being
- Protecting and managing every aspect of the daily workload
- RFID prevents embryologists from accidentally working on more than one patient's eggs or sperm at a time and, second, it marks each course step, preventing embryologists from omitting critical tasks in the process
- Using RFID tags, the patient's identity is monitored at every stage of the treatment, and at the same time, the system captures information regarding the cycle progress and operator actions.

## Consensus on the integrity of samples, couple's/sample identity, check-in *in vitro* fertilization

- Need to implement compulsory identity check with the government-issued photographic ID of couples seeking IVF treatment
- Generally, photograph identity in the form of an electronic file is recommended
- Need to check the ID of couples on every visit to the clinic with the uploaded photo ID (electronic version)
- There must not be any deliberate act of mixing gamete/transferring embryo of a third person.

Except for OD/ED/D-sperm where written consent is required before planning the procedure.

## Double witness of couples' identification check

Need to witness couples ID check at different stages of the procedure in the clinic, namely semen collection (with photo ID, wife's full name, date of birth, and address), ovum pick-up (OPU) (husband's full name, date of birth, and address), embryo transfer (husband's full name, date of birth and address, and cross-checking of her husband's name on the sample tube), and artificial insemination (AID) by donor (final cross-checking of her and her husband's full name, date of birth, address, and ID of sample by the treatment recipient woman).

### Double witne]ssing of samples – procedures

Standard IVF procedure at the time of insemination is crucial for better clinical outcomes. There is a need to counter check various checkpoints, namely couple's names with the semen sample (dish with oocyte and embryology sheet), loading sperm and egg onto ICSI dish (name on tube with sperm, dish with egg and embryology sheet), freezing/thawing the embryos (agree or approval by the person performing the procedure and another laboratory staff for the correct identity of gametes/embryos), and check for same identification on the straw, canister, and cane.

## 7. Consensus on the Handling of Biological Material

### Recommendations on protective measures

- Protective measures should be in place to ensure aseptic conditions for gamete and embryos
- Everybody fluid sample (semen, blood, follicular fluid) should be handled using universal precautions (i.e., as if it were contaminated)
- Laboratory clothing should be autoclaved and worn only in sterile areas and removed upon leaving the laboratory, avoiding transmission of contaminants
- Safety glasses or goggles are suggested where appropriate
- Disposable nontoxic (nonpowdered) gloves and masks should be worn by all clinical and lab personnel during procedures
- All procedures and manipulation of body fluids should be performed to minimize the creation of droplets and aerosols
- Gloves should be removed and discarded when leaving the laboratory. Gloves should never be reused
- Eye and face protection, cryogenic gloves, and apron should be worn by laboratory staff when cryogenic materials are handled
- Mechanical pipetting devices should be used for the manipulation of liquids in the laboratory. Mouth pipetting is not recommended
- Eating, drinking, smoking, application of makeup, or manipulation of contact lenses are not permitted in the laboratory
- Disinfection and sterilization of potentially infected equipment should be done when samples of seropositive or infected patients are handled
- Incubators should be frequently cleaned and sterilized
- Nitrogen tanks should be maintained as per the manufacturer's guidelines.

### Recommendations on biomedical waste

- Published biomedical waste rules by the GOI should be followed
- Every IVF center must have the license for biomedical waste management from the state pollution control board and pollution control committee.

### Recommendations on spill management

- All spillages must be dealt as soon as possible
- An embryo-safe disinfectant at the correct concentration must be used for handling spillage during the procedure
- Suitable disposable wipes must be used for disinfecting and cleaning the spillage.

### Recommendations on transportation of biological materials

- Adhere to the rules and regulations as issued by ICMR
- The export or import of human gametes from another country is permitted as per the permission of the National Registry of the Assisted Reproductive Technology Clinics and Banks in India of the ICMR
- However, gametes can be transported within the country with the proper documentation.

## 8. Consumables and Media

### General guidelines for suppliers

- Procurement of disposables, media, and oil must be done from reliable sources
- Suppliers manufacturing facility should have relevant ISO certification and should provide evidence of using good manufacturing practices (GMP)
- Media, disposables, and oil should be of embryo culture grade quality

### Guidelines: User (embryologist)

- Embryologist must verify all the QC documents before accepting the consignment
- All the disposable consumables should be sterile, single-use and consumed within the expiry date
- Embryologist should record batch number, expiry date, entry date, and number of times media/oil bottles are opened along with dates
- Pharmaceutical medical-grade refrigeration facilities should be available for storage of media and reagents
- All the media should be kept at the temperature recommended by the supplier/manufacturer.

### Recommendations for oocyte retrieval

Oocyte retrieval is the fundamental step during IVF as it requires constant stability for temperature and pH. It is a time-bound procedure, i.e., done at 34–36 h post trigger.
Before the procedure, an identity-check of the patient is mandatory.
Culture media should be equilibrated at least for 4-6 hrs and (HEPES/MOPS) media need to be prewarmed before the procedure.
Necessary equipment such as test tube warmers and dishes needs to be maintained at 37°C on the day of procedure.
Ovum aspiration pump with a pressure setting between 100 and 120 mmHg should be strictly maintained.
The aspirated follicular fluid is screened under a stereomicroscope for the presence of oocytes. Prolonged oocyte exposure to follicular fluid is not recommended.
Prolonged oocyte exposure to follicular fluid is not recommended.
The oocytes retrieved are immediately transferred post washing in the flushing medium to culture media, and it should be achieved in minimal time.
Exposure to light should be minimized.
Documentation involving the duration of cumulus-oocyte complexes retrieval, number of collected oocytes, and the team involved in the entire procedure should be maintained.

### Recommendations for sperm preparation

- Sperm count, motility, and morphology play a pivotal role in human fertilization and hence have to be carefully assessed before and on the day of procedure
- Clear instructions should be given to the patient before the collection of the same. The collection room should be in the nonsterile area of the clinic setting. Home collection should ideally be not allowed, however; in some circumstances, it can be allowed. Consent regarding the identity of the sample should be documented
- Properly labeled IVF tested plastic-ware that is nontoxic and mouse embryo assay, limulus amebocyte lysate, and human sperm survival assays tested should be used for noninterference with the semen
- Identity before the collection should be checked. Masturbation is the preferred method
- Postcollection, sample should be sent to laboratory as soon as possible avoiding extreme temperatures (<20°C and >37°C)
- Sperm analysis and preparation should start within 1 h of collection. Prolonged sperm exposure to seminal plasma is not recommended

- Medical history such as the use of medication, fever during the previous months, and completeness of the ejaculate collection should be documented
- Semen preparation is done to maximize the chances of fertilization with significance for extracting motile spermatozoa eliminating non-motile and dead spermatozoa additionally removing de-capacitation factors from the seminal plasma and to capacitate the spermatozoa
- There should never be preset parameters for preparation, rather should be designed according to the characteristics and origin of individual samples
- Swim-up and discontinuous density gradients are the two most preferred and widely accepted
- A backup of the sample for patients with difficulty in producing sample is important. Proper counseling for the cryopreservation for oocytes should also be done as an alternative way
- Patients should be tested for serious transmissible infections such as hepatitis A, HIV, hepatitis B surface antigen, and venereal disease research laboratory test. Standard precautions for handling biological material must be practiced in the laboratory. Extensive semen preparation by density-gradient centrifugation followed by swim-up is recommended.

## Recommendations for insemination of oocytes

- Insemination can be achieved by either IVF/ICSI. The most crucial factor in IVF is the number of progressively motile sperm used for insemination. They must be enough to optimize the chance of regular fertilization. A motile sperm concentration ranging between 0.1 and 0.5 $\times$ $10^6$/mL is used. Motility and quality of sperm also play a pivotal role
- Double-density is the preferred method employed for semen preparation in case of IVF. The final sperm suspension should be in a medium compatible with oocyte culture
- A double-check of the identity of gametes at the time of insemination procedure is mandatory
- Records of "the time of insemination" should be kept
- Co-incubation of cumulus–oocyte complexes and sperm is usually performed overnight. Short protocol can also be performed where if, signs of fertilization not seen, early rescue ICSI comes into play
- Oocytes are injected 38–41 h posttrigger
- This procedure entails the deposition of a single spermatozoon directly into the cytoplasm of the oocyte, bypassing the ZP and the oolema
- Optimal and sterile conditions should be maintained during the micromanipulation to avoid the detrimental effect of variation, media, and altered air quality on the gamete under manipulation
- Prior to micromanipulation, oocytes are exposed to 80 IU/mL of hyaluronidase for the removal of cumulus cells. For final removal of corona cells, the oocytes are repeatedly aspirated in and out with decreasing inner diameters of 300, 170, and 140 $\mu$flexipets, respectively
- ICSI dishes are prepared according to the embryologist performing the procedure with polyvinylpyrrolidone, flushing media, and oil being the main key players
- Both the micropipettes are aligned and are bent to an angle of approximately 35°
- Before the injection of gametes, a double-check is mandatory.
- Exposure during sperm identification and immobilization followed by injection should be minimized. Normal and motile sperms are selected. In the case of only immotile sperm cells, a non-invasive vitality test can be used to select viable sperm for injection. In the case of TESA samples, motility enhancers such as theophylline could be used.
- Tail immobilization is done by striking below the mid-piece
- Main points during ICSI are: Only mature oocytes should be injected and each oocyte morphology should be recorded. Morphologically abnormal oocytes like giant or having a large polar body should not be injected. The polar body should be at 3 or 6 O' clock position. Oolemma rupture should be assessed
- Minimum exposure of oocytes should be done and procedure timings should be recorded
- Post-ICSI, inseminated oocytes should be immediately washed and shifted to culture dishes with double-

witnessing. Dishes to be well-labeled and should not be exposed before a fertilization check
- If M1 or abnormal oocytes are injected, they should be ideally kept in a separate dish or marked if kept in the same dish.

## Recommendations for scoring for fertilization

- All inseminated or injected oocytes should be examined for the presence of pronuclei (PN) and polar bodies at 16–18 h postinsemination
- In case of IVF, loosened residual cumulus cells must be removed by aspirating them in and out with denupets of varying diameters to access the fertilized oocytes
- The zygotes are transferred to pre-equilibrated culture media dishes
- For better understanding regarding the pronuclear morphology, assessment should be done under an objective lens of ×200
- Embryos as a result of abnormal fertilization such as 1 PN or 3PN should not be transferred or cryopreserved unless deemed euploid by PGT-A.

## Recommendations for scoring for fertilization

- For optimal embryo growth, culture conditions should be consistent
- There are two different approaches that can be used to optimize embryo development-sequential or single-step media. In case of sequential culture, dishes are changed according to the stage of embryo whereas, for a single step, embryo grows in one type of media dish during its entire *in vivo* journey
- Dishes can be made in accordance with the laboratory SOP's. An optimal drop of culture media should be made, while dish preparation remains under sterile conditions. Oil overlay over the culture dishes minimizes the changes to temperature, pH, and osmolality
- For incubation of embryo, there are various kinds of incubators available that are used according to the need and workload of the laboratory. Regular maintaining and cleaning of the same should be maintained
- Scoring of the embryo should be performed at high magnification (at least ×200) using an inverted microscope
- Evaluation of cleavage-stage embryos should include cell number, size and symmetry, and percentage of fragmentation. Blastocyst scoring should include expansion of the blastocoel cavity, the morphology of the inner cell mass, and trophectoderm
- Assessment should be performed at crucial developmental stages postinsemination. Embryo development can also be assessed using time-lapse imaging, allowing an uninterrupted evaluation involving the morphokinetics during growth
- Embryo selection for transfer is primarily based on the synchrony between embryo and endometrium. Other selection parameters, such as time-lapse kinetics, may be considered
- Single embryo transfer is recommended to avoid multiple gestations transfer strategies should be customized according to the patient profile
- Embryo quality and stage of development, female age, ovarian response, and treatment plan should be taken into consideration before transfer
- It is advisable not to transfer more than two embryos in good prognosis patients
- Cryopreservation should be performed for supernumerary embryos, according to their quality, patient wishes, and national legislation along with consents and records for same
- A checklist for the embryo transfer procedure should be maintained that includes identification number, name of the patient and partner, time of embryo transfer, catheter lot number, signature of the doctor and embryologist along with witnesses, and any adverse events during the procedure
- A double identity-check of the patient, the patient file and necessary consents, and the culture dish is mandatory immediately before the transfer.

### Recommendations for cryopreservation

Cryopreservation refers to the cooling of cells and tissues to sub-zero temperatures to stop all biologic activity and preserve them for future use. It can be performed for gametes and embryos.

- Along with facilities, trained embryologists should be available in the laboratory to perform the necessary procedures
- Different approaches including slow freezing and vitrification can be used according to the type of biological material that needs to be cryopreserved
- For sperm, rapid cooling is a possible and convenient method for cryopreservation
- For oocytes, vitrification has been reported to be highly successful and is recommended
- For cleavage-stage embryos and blastocysts, high success rates have been reported when using vitrification
- It is important to understand that while dealing with infectious biological material, cross-contamination via liquid nitrogen needs to be reduced. Separate cryocans for such samples and embryo should be maintained
- Disposables and dishes need to be discarded in accordance with biosafety regulations
- At cryopreservation, documentation on biological material should include: Identification number, patient and partner name, device labeling, cryopreservation method, media used, date and time of cryopreservation, embryologist's name, embryo quality and stage of development, number of oocytes or embryos per device, number of devices stored per patient, and location of stored samples
- Cryodevices must be clearly and permanently labeled with reference to patient details, treatment number, and/or unique identification code
- At thawing for the same biological material, documentation should include: double witnessing for the name of patient and partner, thawing method, thawing media, date and time of thawing, embryologist name, and postthawing sample/oocyte/embryo quality
- A double-check of patient identity is recommended at every step of cryopreservation and thawing
- Accidental thawing should be avoided.

## 9. Consents and Checklists

- The ART clinic should obtain written permission from the couple before conducting any ART procedure.
- A standard consent form (should be bilingual) recommended by the ICMR should be used by all ART clinics.
- Specific consent must be obtained from couples who have their gametes or embryos frozen, regarding what should be done with them if he/she dies/divorce or becomes incapable of varying or revoking his or her consent and if they are unable to bear the maintenance.
- Appropriate consent to be obtained for fertility preservation cases.

### Recommended consent forms as per Indian Council of Medical Research guideline

- Form D: Consent form to be signed by the couple for IVF and ICSI
- Form G: Consent for freezing of embryos
- Form H: Consent for surgical extraction of sperm
- Form I: Consent for oocyte retrieval/embryo transfer
- Form J: Agreement for surrogacy (but status is controversial)
- Form K: Consent form for the donor of eggs
- Form L: Consent form for the donor of sperm
- Consent for release of cryopreserved oocytes/embryos
- Consent for embryo biopsy for PGT
- Consent for disposal of oocyte/embryos

## 10. Risk Analysis and Mitigation in an In vitro Fertilization Laboratory

### Background

IVF laboratory procedures involve handling male and female gametes. An error at any of the intermittent steps may have direct consequences including a possible change of genetic filiation of a family. Unlike other laboratories where-in case of mishandling or mistake, reports can be cancelled, and tests can be repeated, this option is not available for an IVF laboratory. Once the baby is born or even once the pregnancy is established, the issue becomes much complicated-emotionally, ethically, and legally.

### Clinical recommendations on risk mitigation

#### Strict adherence to the consensus guidelines to ensure patient's identity and safety

- A copy of the patient's consent should be kept in laboratory records
- From the statistical analysis and legal point of view, correct data entry is crucial to assess the center's performance and to safeguard allegations from patient-related to misuse of genetic material
- To avoid repetition of the same incidents in the future, a separate audit logbook must be maintained citing all problems encountered and measures taken to solve those issues.

Assisted conception is unlikely to be any less prone to adverse incidents; indeed, there have been several high-profile cases which have drawn attention to this problem. Because of the nature of the work undertaken in assisted conception, there is the potential to affect not only future generations but also many patients simultaneously because of the storage of biological material. It is, therefore, essential to implement strategies to reduce the likelihood of patient safety incidents. Risk prediction and mitigation strategies should be referred to in Table 5.

**Table 5: Predicted risks and mitigation strategies**

| Risk | Mitigation strategy |
|---|---|
| Loss of power | Generator/UPS |
| $CO_2$/special gas mix failure | Automatic gas changeover manifold; regulators |
| Liquid nitrogen storage tank emptying | Liquid nitrogen level alarms |
| | Regular measuring/top-up of tanks. Replacement at end of life span. Safety training is a must |
| Staff member injured | Low oxygen level and high $CO_2$ alarms PPE |
| | Fire alarms/extinguishers |
| Break into laboratory | Security monitoring; security response; locks on liquid nitrogen tanks |
| Equipment failure | Alarm system; spare equipment; service/maintenance contracts; arrangements with competitors |
| IT virus/hacking – loss of data | Regular backups (stored offsite); antivirus software |

PPE=Personal protective equipment, UPS=Uninterruptible power supply

## 11. Incident Reporting

It is an occurrence that is inconsistent with the routine care of the patient or the regular running of the organization.

### Categorization of incidents[14]

#### Adverse events

It can be further classified as:

- Near miss (A "near miss" is considered an unplanned event that did not result in injury, illness, or damage – but had the potential to do so)

- Serious
- Adverse event affecting gametes
- Adverse reaction affecting individuals.
  - A patient being implanted with an embryo that is intended for someone else

The death of a patient or an incident which affects a few patients (e.g., when a storage unit malfunctions which may irretrievably damage the embryos, eggs, or sperm of several patients).
Transmission of communicable diseases/illnesses/conditions is leading to prolonged hospitalization and treatment or even death.

### Moderate incidents[14]

- The loss of embryos for one patient
- Breaches of confidentially where sensitive personal data or data relating to more than one patient is sent to the wrong recipient or when a piece of equipment malfunctions affecting the quality of a patient's embryos
- Eggs rendered unusable during processing (for example, the moving of an egg between dishes).

## Classification of incidents based on origin[14]

| Clinical | Administrative | Laboratory |
|---|---|---|
| OHSS<br>Patients are starting a treatment cycle<br>before all their screening results were returned and reviewed<br>Screening results not being checked or being misinterpreted<br>Donors being accepted and matched with a recipient without the screening results being available or checked, or screening results being misinterpreted.<br>Misplacement of an embryo during embryo transfer, ovarian abscesses following egg collection, vaginal bleeding and urinary tract infections as well as allergic reactions to medications.<br>Infections found in embryo cultures that originated from the patient or their partner. | Most incidents relating to a breach of patient confidentiality involved information being posted to an incorrect address<br>Examples<br>Clinical consultation reviews<br>Letters to referring physicians<br>Consent forms<br>Invoices for treatment and or storage fees blood results<br>Scan findings and complete sets of medical records | Equipment-related<br>Power failures<br>Equipment being moved or disconnected during the general laboratory cleaning<br>Pipes/tubes supplying essential gases to incubators to maintain the quality of embryos becoming distorted, leading to the quality of embryos being comprised<br>Faulty transport incubators<br>Process related<br>Failure to carry out specific witnessing steps. Where cryopreserved material is moved from one location to another without the movement being witnessed, or without the logs documenting the storage location being updated.<br>Failure to follow protocols for freezing.<br>Operator related<br>Dishes containing eggs or embryos that were knocked or dropped.<br>Pipettes that were accidently knocked whilst moving eggs or embryos (causing damage or loss of samples).<br>Failure to operate equipment properly.<br>Turning off a piece of equipment mid-cycle. |

OHSS=Ovarian hyperstimulation syndrome

| Risk grading matrix[15] | | |
|---|---|---|
| Level | Descriptor | |
| 5 | Almost certain | Likely to occur on many occasions |
| 4 | Likely | Probable but not persistent |
| 3 | Possible | May occur occasionally |
| 2 | Unlikely | Not expected to happen but possible |
| 1 | Rare | Difficult to believe it could happen again |

### Clinical recommendations on reporting an incident

- Centers must have an internal event reporting policy
- All adverse incidents should be reported to the relevant authority
- This notification must include the:
- Contact details of the person responsible
- Date of the initial information or report
- Name of any individual affected
- Date and time of the serious adverse event or reaction
- Details of gametes or embryos involved in the incident
- Type of incident, including any transmission of infectious agents.

## 12. Laboratory Procedures, Documentation, and Data Management

Based on existing literature,[9,11] the group decided on certain consensus points that are mentioned below.

- All processes should be mapped, using appropriate flow chart methodology
- The process map then forms the basis of standardized operating procedures (SOPs)
- The SOPs should be structured in a standardized format and their distribution must be controlled
- SOPs should be written based on the documented scientific evidence and authorized, signed and updated SOPs for all processes to optimize outcomes
- The KPIs should be clearly defined, monitored and documented in a computer database[9]
- Procedures should maximize the chance of success and minimize risk
- Before the implementation of any new method, it needs to be validated and monitored in the current setting
- Importantly, the clinical and laboratory staff members need to undergo training and prove competence for each procedure performed
- The data on the performance of the clinic, but also of the individuals should be collected and analyzed regularly
- Data should be audited, assessed and structured to discern the input quality, the process quality and the output quality as appropriate
- The list of data required for collecting and auditing is presented in Table 3. In addition, data on the functioning of equipment and technical systems, e.g., air quality and level of microbial contamination, must be collected and regularly audited.

| Table 6: Recommendation on a collection of data | | |
|---|---|---|
| Input quality | Process quality | Output quality |
| Indication, age, protocol start and total follicle-stimulating hormone dose | Oocyte damage rate after ICSI | Rates of positive β-hCG test |
| Numbers of follicles, eggs | Fertilization rate and failed fertilization rate | Implantation and delivery rate |
| Percent immature, percent degenerated and the cycle cancellation rate | Embryo cleavage rate | Freeze-all rate |
| | Embryo utilization and embryo cryo survival rate | Serious adverse event rate |
| | Average cell numbers on day 2 or day 3 | |

ICSI=Intracytoplasmic sperm injections, β-hCG=β-human chorionic gonadotropin

## 13. Key Performance Indicators and Benchmarking for India

KPIs are Indicators deemed essential for evaluating the introduction of a technique or process; establishing minimum standards for proficiency; monitoring ongoing performance within a QMS (for internal quality control, external quality assurance); and benchmarking and quality improvement. In general, the results of a series of KPIs will provide an adequate overview of the most critical steps in the IVF laboratory process.[15]

**Table 7: Reference indicators for identifying the performance of the assisted reproductive technology laboratory**

| RI | Calculation | Benchmark value |
|---|---|---|
| The proportion of oocytes recovered (stimulated cycles) | Number of oocytes retrieved/number of follicles on day of trigger ×100 | 80%–95% of follicles measured |
| The proportion of MII oocytes at ICSI | Number of MII oocytes at ICSI/number of COCs retrieved ×100 | 75%–90% |

MII=Metaphase II, RI=Reference indicators, COC=Cumulus oocyte complex, ICSI=Intracytoplasmic sperm injections

**Table 8: Proposed key performance indicators values**

| KPI | Expected value (%) | Target value (%) |
|---|---|---|
| Day 3 embryo development rate | 70 | >90 |
| Blastocyst development rate | >40 | >60 |
| Successful biopsy rate | >90 | >99 |
| Implantation rate (cleavage-stage) | >25 | >35 |
| Implantation rate (blastocyst-stage) | >35 | >60 |
| Blastocyst cryo survival rate | >90 | >99 |
| ICSI damage rate | <10 | <5 |
| ICSI normal fertility rate | >65 | >80 |
| Failed fertility rate (IVF) | <5 | <5 |
| Cleavage rate | >95 | >99 |
| Day 2 embryo development rate | >70 | >80 |
| Sperm motility postpreparation for IVF | 90 | 95 |

KPI=Key performance indicators, ICSI=Intracytoplasmic sperm injections, IVF=*In vitro* fertilization

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