A new era in IVF laboratory quality control

“Quality is not an act; it is a habit.”

Dr. Hamid Nazarian, PhD
Reproductive biology
Shahid Beheshti university of medical sciences

Cryopreservation key performance indicators and benchmarks

The Alpha Consensus Meeting 2012

This proceedings report presents the outcomes from an international workshop designed to establish consensus on definitions for key performance indicators (KPIs) for oocyte and embryo cryopreservation, using either slow freezing or vitrification; minimum performance level values for each KPI, representing basic competency; and aspirational benchmark values for each KPI, representing best practice goals. This report includes general presentations about current practice and factors for consideration in the development of KPIs. A total of 14 KPIs were recommended and benchmarks for each are presented. No recommendations were made regarding specific cryopreservation techniques or devices, or whether vitrification is 'better' than slow freezing, or vice versa, for any particular stage or application, as this was considered to be outside the scope of this workshop

- **Comparison of cryopreservation by slow freezing or by vitrification**
- **Media and device: comparing apples with apples**
- **Basic principles of defining and using benchmarks Clinical outcomes related to blastocyst morphology before vitrification and after thawing**
- **A continued role for slow freezing of blastocysts Clinical outcomes related to blastocyst morphology before freezing and after thawing**

- **Defining KPIs for cryopreservation of oocytes and embryos in clinical assisted reproductive technology**
- **Oocyte KPIs**
- **Zygote KPIs**
- **Embryo KPIs**
- **Blastocyst KPIs**
- **……**

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Guidelines on IVF Culture Conditions

Cairo Consensus 2018

- **KEY MESSAGE**
- This report presents outcomes from an international expert meeting to establish consensus guidelines on IVF culture. Topics reviewed were: embryo culture; temperature; humidity; gas control, pH; workstations; incubators; micromanipulation; handling and assessment; stasis, composition, supplementation, type of culture and storage; equipment and monitoring. More than 50 consensus guideline points were established.

- **Embryo culture – basic principles and interactions**
- **Temperature in the IVF laboratory**
- **Humidity in culture**
- **Carbon dioxide control and medium pH**
- **Oxygen tension for embryo culture**
- **Workstations – design and engineering**
- ***Handling and assessing oocytes and embryos***
- ***Processing oocytes and embryos during cryopreservation***
- ***Dish preparation***
- **Incubators – maintaining the culture environment**
- ***Factors influencing stability of the culture environment***
- ***Principles for incubator management***
- ***General rules for incubator QC***
- **Micromanipulation – maintaining a steady physcochemical environment**
- ***Intracytoplasmic sperm injection (ICSI)***
- ***Oocyte handling during micromanipulation***
- ***Mechanical stress during micromanipulation***
- ***Culture system configurations during micromanipulation***
- **Handling practices**
- ***General practices***
- ***Oocyte recovery***
- ***Sperm preparation***
- ***Vitrification/warming***
- **Assessment practices**

IVF laboratory environment and air quality

Cairo consensus 2018

- **KEY MESSAGE**
- An international expert meeting on the technical and operational requirements for assisted reproduction tehnology laboratory air quality established 50 consensus points regarding site suitability, design criteria for new construction,laboratory commissioning and ongoing volatile organic compounds management that provide aspirational benchmarks for existing laboratories and guidelines for constructing new laboratories.

- **Design philosophy for a new ART laboratory suite**
- **Physical isolation criteria**
- **Retrofitting existing laboratory suites**
- **Controlling VOCs: the fabric of the laboratory**
- **Measuring VOCs and aldehydes**
- **Sources of aldehydes in ART laboratory settings**
- **Avoiding VOCs in culture**
- **Avoid introducing VOC into the laboratory**
- **Decrease ambient VOCs in the laboratory**
- **Decrease VOCs in incubators**
- **Decrease VOCs in cultures**
- **Assessing site suitability**
- **Basic design criteria (new construction**
- **Laboratory commissioning and ongoing VOC management**

https://doi.org/10.1016/j.rbmo.2018.02.005

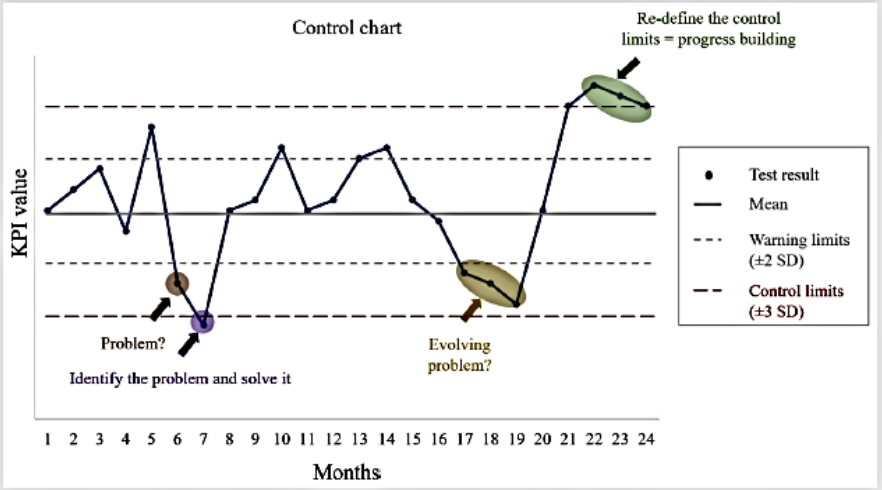
KPI (key performance indicator)

Vienna consensus 2017

Performance indicators (PIs) are objective measures for evaluating critical healthcare domains

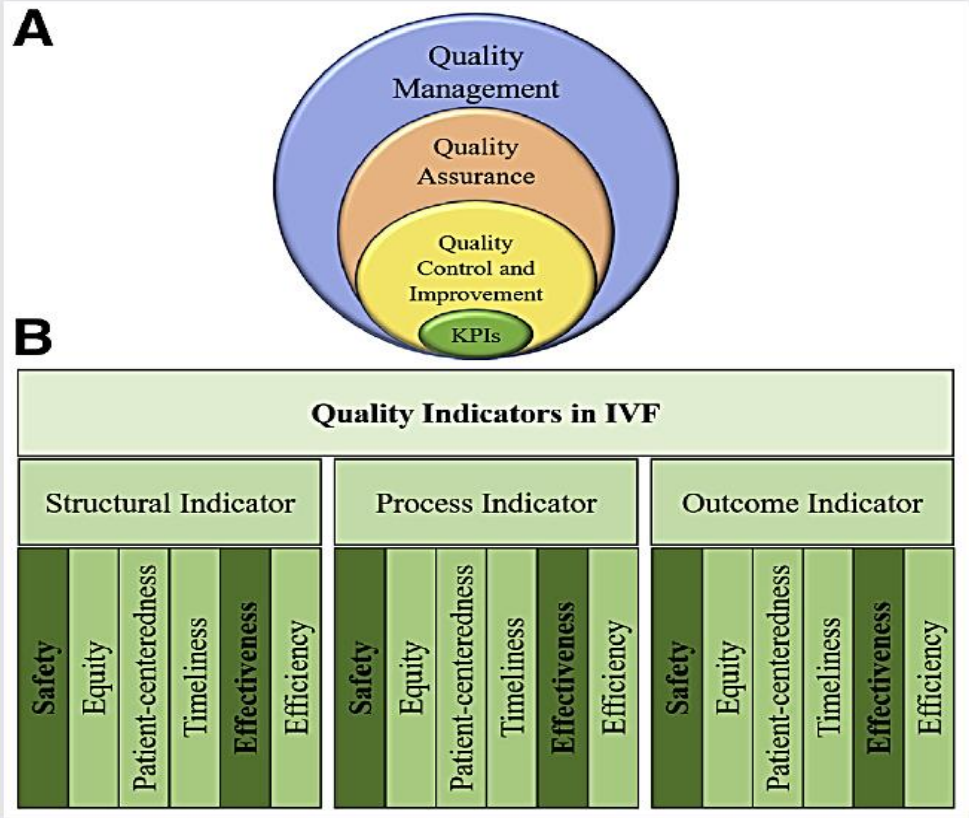
1. **1- structural indicators**
2. **Process indicators**
3. **Outcome indicators**

FIGURE 2



Representative scheme of a control chart and its use. KPI = key performance indicator; SD = standard deviation.

Fabozzi. KPIs in the ART laboratory. Fertil Steril 2020.



(**A**) Definition of a quality management system. KPIs = key performance indicators. (**B**) The six dimensions of health care.

Fabozzi. KPIs in the ART laboratory. Fertil Steril 2020.

https://doi.org/10.1016/j.fertnstert.2020.04.054

Structural measures of KPI

Type of indicators	Area	Key performance indicator (KPI)	Dimension
measures the quality of the IVF laboratory by outlining the characteristics of physical and human resources	**Facility**	Percentage of staff injuries in a given time period relative to the total number of ART procedures conducted	Safety
		Percentage of accidents during handlings relative to the total number of ART procedures conducted in a given time period	Safety, effectiveness
		Average time required to move a dish or sample from a place to another (e.g., from incubator to cabinet or from cabinet to micromanipulator)	Safety, effectiveness
	Equipment	Number of critical instruments (e.g., incubators, safety cabinets, micromanipulators) relative to the total number of ART procedures conducted in a given time period	Safety, effectiveness
		Number of unscheduled maintenance interventions relative to the total number planned per year	Safety, effectiveness
	Staff	Number of operators relative to the total number of ART procedures conducted in a given time period	Safety, effectiveness
		Achievement of competency values established by consensus papers (e.g., Vienna consensus KPIs for fresh IVF and ICSI cycles or Alpha KPIs for oocyte and embryo cryopreservation) per operator per month	Effectiveness, efficiency
		Number of CPD credits per operator per year	Effectiveness, efficiency

https://doi.org/10.1016/j.fertnstert.2020.04.054

Process measures of KPI

Type of indicators	Area	Key performance indicator (KPI)	Dimension
measures how well the IVF laboratory works	Protocols and procedures	Interval between the scheduled and the effective time for a given procedure	Safety
		Time elapsed between drop deposition and oil coverage during dish preparation	Safety, effectiveness
		Average duration of gamete/embryo manipulations in minutes (e.g., denudation, ICSI, embryo biopsy)	Safety, effectiveness
		Proportion of fragments lysed or lost after embryo biopsy	Effectiveness, efficiency
		Number of accidents (e.g., gamete/embryo loss during denudation) per operator relative to the total number of ART procedures conducted in a given time period	Effectiveness, safety
		Interoperator agreement in oocyte/embryo morphological grading	Effectiveness, efficiency
	Protective measures	Percentage of laboratory staff injuries while handling liquid nitrogen per number of ART procedures per year	Safety
		The number of cross-contamination or operator infections per number of ART procedures conducted with infectious material	Safety
	Identification and traceability	Number of identified mistakes (e.g., mislabeled samples) per operator relative to the total number of ART procedures conducted in a given time period	Safety, effectiveness

https://doi.org/10.1016/j.fertnstert.2020.04.054

Outcome measures of KPI

Type of indicators	Area	Key performance indicator (KPI)	Dimension
Measures the effectiveness of the IVF laboratory	**Results**	Achievement of the minimum standards for the KPIs established for monitoring laboratory performance by consensus papers (e.g., Vienna consensus KPIs for fresh IVF and ICSI cycles or Alpha KPIs for oocyte and embryo cryopreservation) per month	Effectiveness, efficiency
		Intermediate: All the KPIs listed in Vienna and Alpha consensus with the exception of implantation and live-birth rates **End result:** Implantation and live-birth rates	

https://doi.org/10.1016/j.fertnstert.2020.04.054

Outcome indicator of KPI

Vienna consensus 2017

Table II RIs for identifying performance of the ART laboratory.

RI	Calculation	Benchmark ialue
Proportion of oocytes recovered (stimulated cycles)	$\frac{\text{no. oocytes retrieved}}{\text{no. follicles on day of trigger}} \times 100$	80–95% of follicles measured
Proportion of MII oocytes at ICSI	$\frac{\text{no. MII oocytes at ICSI}}{\text{no. COCs retrieved}} \times 100$	75–90%

MII, metaphase II; RI, reference indicators; COC, cumulus-oocyte complex.

Outcome indicator of KPI

Vienna consensus 2017

Table III PIs for the ART laboratory.

PI	Calculation	Competency value (%)	Benchmark value (%)
Sperm motility post-preparation (for IVF and IUI)	$\frac{\text{progressively motile sperm}}{\text{all sperm counted}} \times 100$	90	≥95
IVF polyspermy rate	$\frac{\text{no. fertilized oocytes with} > 2\text{PN}}{\text{no. COCs inseminated}} \times 100$	<6	
1 PN rate (IVF)	$\frac{\text{no. 1PN oocytes}}{\text{no. COCs inseminated}} \times 100$	<5	
1 PN rate (ICSI)	$\frac{\text{no. 1PN oocytes}}{\text{no. MII oocytes injected}} \times 100$	<3	
Good blastocyst development rate	$\frac{\text{no. good quality blastocysts on Day 5}}{\text{no. 2PN/2PB oocytes on Day 1}} \times 100$	≥30	≥40

PN, pronucleus; PI, performance indicator; PB, polar body.

Outcome indicator of KPI

Vienna consensus 2017

Table IV KPIs for the ART laboratory.

KPI	Calculation	Competency value (%)	Benchmark value (%)
ICSI damage rate	$\frac{\text{no. damaged or degenerated}}{\text{all oocytes injected}} \times 100$	≤10	≤5
ICSI normal fertilization rate	$\frac{\text{no. oocytes with 2PN and 2PB}}{\text{no. MII oocytes injected}} \times 100$	≥65	≥80
IVF normal fertilization rate	$\frac{\text{no. oocytes with 2PN and 2PB}}{\text{no. COCs inseminated}} \times 100$	≥60	≥75
Failed fertilization rate (IVF)	$\frac{\text{no. cycles with no evidence of fertilization}}{\text{no. of stimulated IVF cycles}} \times 100$	<5	
Cleavage rate	$\frac{\text{no. cleaved embryos Day 2}}{\text{no. 2PN/2PB oocytes on Day 1}} \times 100$	≥95	≥99
Day 2 Embryo development rate	$\frac{\text{no. 4-cell embryos on Day 2}}{\text{no. normally fertilized oocytes}^{a}} \times 100$	≥50	≥80
Day 3 Embryo development rate	$\frac{\text{no. eight cell embryos on Day 3}}{\text{no. normally fertilized oocytes}^{a}} \times 100$	≥45	≥70
Blastocyst development rate	$\frac{\text{no. blastocysts Day 5}}{\text{no. normally fertilized oocytes}^{a}} \times 100$	≥40	≥60
Successful biopsy rate	$\frac{\text{no. biopsies with DNA detected}}{\text{no. biopsies performed}} \times 100$	≥90	≥95
Blastocyst cryosurvival rate	$\frac{\text{no. blastocysts appearing intact}}{\text{no. blastocysts warmed}} \times 100$	≥90	≥99
Implantation rate (cleavage-stage)[b]	$\frac{\text{no. sacs seen on ultrasound}^{c}}{\text{no. embryos transferred}} \times 100$	≥25	≥35
Implantation rate (blastocyst-stage)[b]	$\frac{\text{no. sacs seen on ultrasound}^{c}}{\text{no. blastocysts transferred}} \times 100$	≥35	≥60

Artificial intelligence (AI) can be a tool for KPI monitoring

1. Artificial intelligence (AI)
   - Monitoring individual embryologist performance
   - for quality assurance in an ART laboratory
2. convolution neural network-based deep learning technique

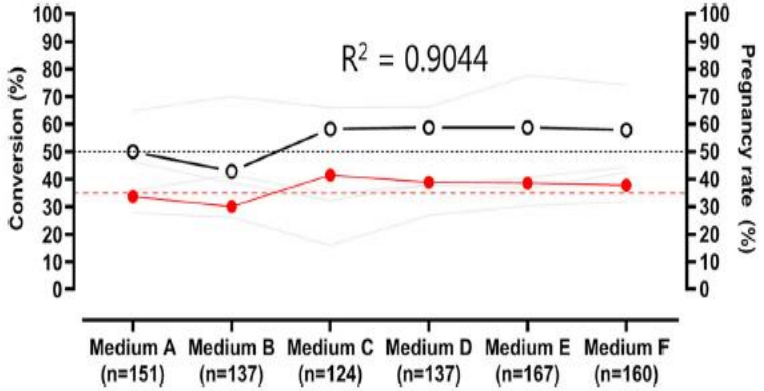


Fig. 2 Early developmental stage markers as predictors for KPI monitoring. A deep neural network (AI) [8] analyzed embryo images acquired at 70 h post-insemination and provided a score (KPI score) taking into account all embryos within a given group. A total of 876 embryos were cultured in 6 different lots of media (Media A-F; CSC-Complete, Irvine Scientific) and under identical conditions at 37°C, 5% O_2, and 6.5% CO_2 with oil overlay (Ovoil, Vitrolife) over a 6-month period

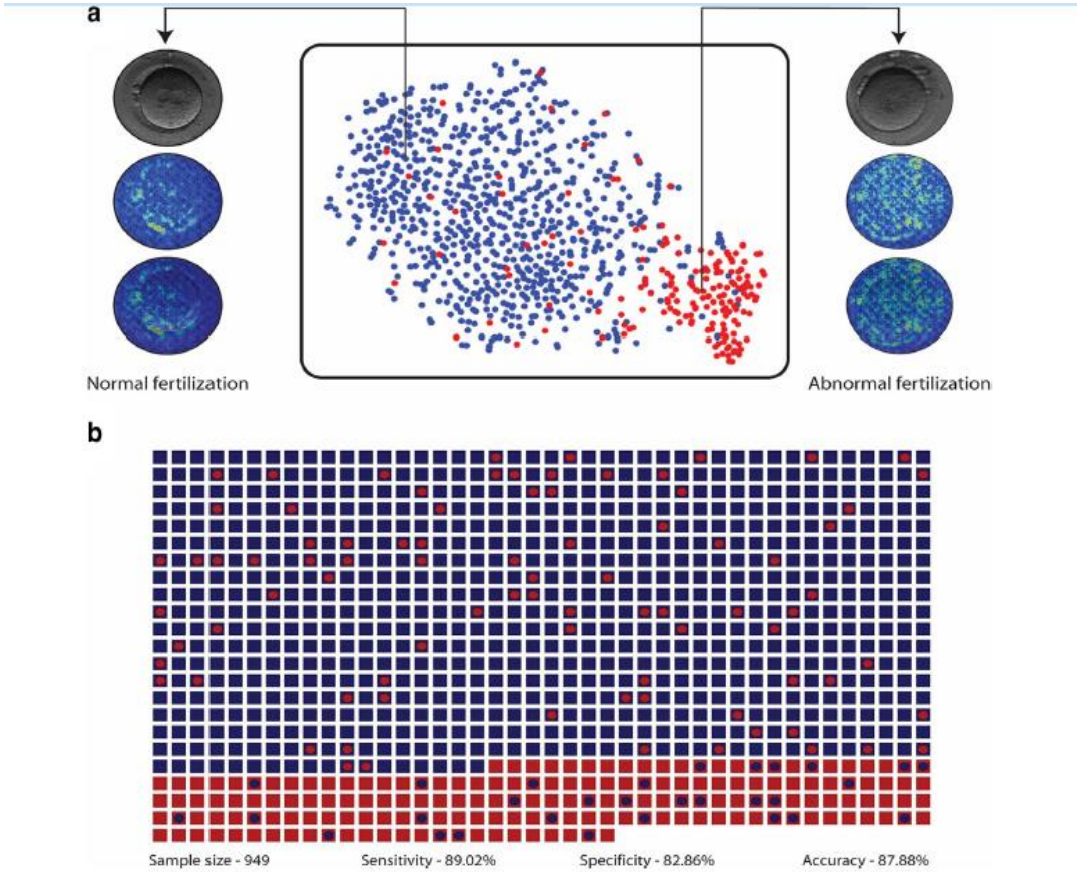


Fig. 1 Fertilization assessment. a The t-SNE plot for the Xception model trained to classify abnormally fertilized embryos (non-fertilized, 3PN, 1PN etc. embryos) and normally fertilized embryos (2PN embryos). The saliency map of the two embryos provides an example of the features that network uses to classify embryos at the pronuclear stage. b The dot matrix plot illustrates the system's performance in evaluating embryos (n=947) from the test set of patients. The squares represent true labels and the circles within them represent the system's classification. Blue squares and circles represent normally fertilized embryos while red squares and circles represent abnormally fertilized embryos

https://doi.org/10.1007/s10815-021-02198-x

A fresh look to The mouse embryo assay (MEA)
can be a tool for KPI monitoring

- **standards of testing for FDA approval of new products**
- **Proficiency testing of culture media**
- **Quality control within the laboratory**
- **Embryology training**

Ways To Increase The MEA's Sensitivity

1. **the 1-cell MEA** is a more sensitive and useful assay to test culture media for toxicity and suboptimal culture characteristics as compared to the 2-cell MEA
2. **extended MEA** where embryos are cultured for 144 h instead of the traditional 96 h is another way to increase the assay sensitivity (up to four times higher)
3. **morphologic assessment**, and embryo **cell count at the completion of the 72, or 96, hours** of culture
4. **mouse embryo genetic assay (MEGA).** This assay tracks important geneticmarkers, such asOCT4 through the embryo's development to monitor its growth
5. **Morphokinetics** is another valuable adjunct for detecting suboptimal culture media
6. **outbred CF1 mouse embryos** are more genetically diverse and more sensitive to toxins than the recommended hybrid embryos
7. **MEA should be performed with a simple media**, **without the addition of albumin**, and **at atmospheric oxygen concentration** to maximize the stress on the embryos

https://doi.org/10.1007/s10815-020-01768-9

FMEA (failure mode and effect analysis)

Failure Modes and Effects Analysis (FMEA) is a systematic, proactive method for evaluating a process to identify where and how it might fail and to assess the relative impact of different failures, in order to identify the parts of the process that are most in need of change. FMEA includes review of the following:

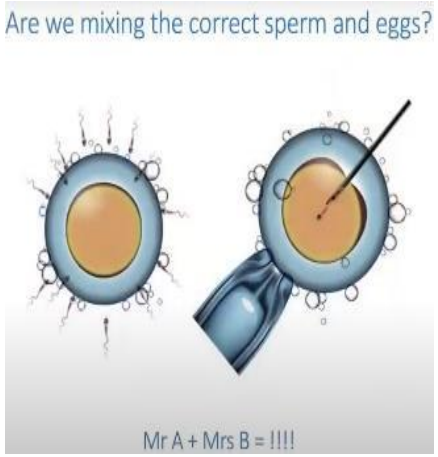
- Steps in the process
- Failure modes (What could go wrong?)
- Failure causes (Why would the failure happen?)
- Failure effects (What would be the consequences of each failure?)

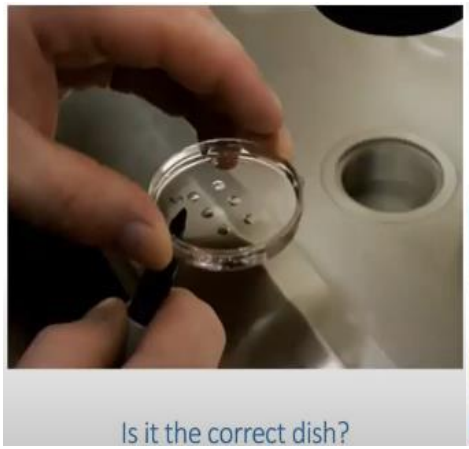
Teams use FMEA to evaluate processes for possible failures and to prevent them by correcting the processes proactively rather than reacting to adverse events after failures have occurred. This emphasis on prevention may reduce risk of harm to both patients and staff. FMEA is particularly useful in evaluating a new process prior to implementation and in assessing the impact of a proposed change to an existing process.

... at egg collection

... at embryo transfer

Labelling / chain of custody

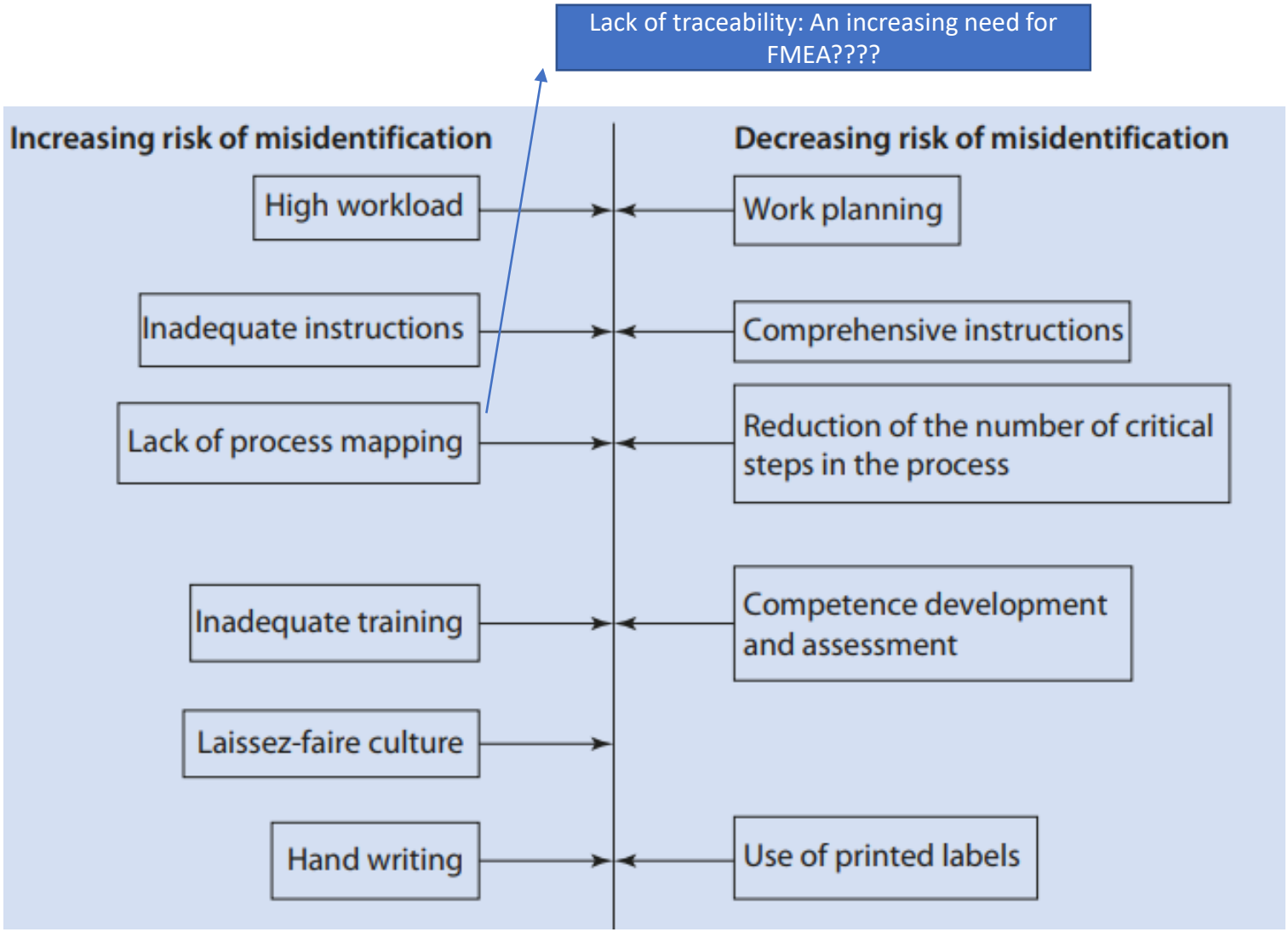




Is it the correct dish?

FMEA (failure mode and effect analysis)

Example: Misidentification



FMEA :Misidentification

1. One of the most dreaded adverse events
2. Reasonably high probability of occurring
3. Dire consequences to the patients, the offspring, the embryologist, the owners, and the profession.
4. Any nonconformity in this area, even if it is discovered before any damage has occurred, must be recorded and treated as a serious incident, analyzed, and acted on.

When?	Where?	What went wrong?
2000	UK	Missing embryos
2001	UK	White parents / black twins
2001	Canada	Donor sperm used by mistake
2002	UK	Wrong embryos transferred
2003	Ireland	White parents / black twins
2004	USA	Wrong embryos transferred
2004	USA	Wrong sperm used
2004	Italy	Wrong sperm used for two patients
2007	Canada	Five women received wrong sperm
2007	UK	Wrong frozen embryo transferred
2009	UK	Three couples wrong sperm at ICSI
2009	USA	Wrong frozen embryo transferred
2009	UK	Frozen embryos lost

When?	Where?	What went wrong?
2010	Singapore	Wrong sperm used
2010	Thailand	No genetic link to parents
2010	UK	Lost frozen embryo
2011	Hong Kong	Wrong embryos transferred
2011	UK	Sperm destroyed by mistake
2012	UK	Wrong sperm donor used
2012	USA	White patient / mixed-race child
2013	Italy	Wrong embryos transferred
2014	USA	Wrong embryos transferred
2014	Poland	Wrong sperm used
2016	Netherlands	Wrong sperm used
2016	Czech Rep	Wrong embryos transferred
2017	Israel	Wrong embryo transferred

FMEA (failure mode and effect analysis)

Example: Misidentification

- We can reduce the risk of misidentification (RPN) by boosting traceability and improving identification either via lowering the occurrence rate or increasing the detection rate (lowering its score). (we can not do anything about severity of an event)

- Human error is more likely in conventional identification (witnessing) systems (labeling, double check with human witness): due to increased workload, distraction, or even inadequate instructions (SOP).

- Is there any solution??? Here it is: Electronic Witnessing:

1. Lowering the occurrence rate
2. Increasing the detection rate

RI Witness™

Confidence, Efficiency and Trust

FMEA (failure mode and effect analysis)

Example: Misidentification

Electronic Witnessing

- Self-adhesive RFID tags are attached to all laboratory plasticware

- RFID Readers are situated wherever samples are handled:
  - Embryology lab - associated with each stereo microscope
  - Andrology - associated with each work area for semen processing
  - Reception or egg pick-up and embryo transfer rooms, where patients will be treated

- Each RI Witness work area has a networked tablet or PC:
  - User can simply and quickly log into the system using personalized key fob without having to enter a passcode
  - Software integrated with your patient database*

- Tags are passive and have no energy source:
  - Readers only identify tagged plasticware placed within the work area

key performance indicators (KPIs) of ART laboratories during the pandemic

- **Time taken for preparing the clinics and staff to the new norms**
- **Operationalization and outcomes of telemedicine services**
- **Key performance indicators after resumption of services**

(1) the preparedness of laboratory and hospital setup may not be time-consuming but the supplies need to be ensured,

(2) (2) there will be a need for an individualized approach for selecting couples to undergo IVF,

(3) (3) the performance of clinicians and embryologists in the face of uncertainties and anxieties due to the pandemic may not be compromised if adequate measures are taken and training provided.

The role of SARS-COV-2 testing in asymptomatic individuals undergoing IVF remains unclear and when access to testing is restricted

it is important to develop clinic-specific triaging norms to resume services

It is possible to provide safe ART services even

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Thank you for your attention