Fabiola Bento · Sandro Esteves
Ashok Agarwal *Editors*

Quality Management in ART Clinics

A Practical Guide

Springer

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Foreword

This is no ordinary book. It is a detailed description, such as has never before compiled, of the current status of quality management in centers specialized in assisted reproductive technology (ART). It describes in detail the various items of equipment and supplies necessary to set up the laboratory procedures used in the treatment of male and female infertility. This work aims at providing invaluable information on how to set up, organize, manage, and improve an already existing assisted reproduction laboratory. The work approaches several aspects of the procedures involved in running reproductive medicine centers: from the management of systems to appropriately training personnel, to orchestrating top quality control, and finally to deliver outstanding quality assurance. It is gratifying to see that this work is grounded in the belief that the key to running a service is understanding customer satisfaction, the regulations, selecting the appropriate and preparing the appropriate individuals, and picking the ideal management procedures.

Since the first success of IVF in 1978, the field has been transformed by a steady stream of discovery and technological progress. This has led to the expansion of the indications such as diagnosis and treatment of severe male infertility treated by ICSI and the identification and eradication of genetic disorders by PGD, not to mention the improvement of ART successes by the introduction of sophisticated and comprehensive chromosomal screening. These discoveries and techniques are grouped under the term *assisted reproduction techniques*. For the first time, this book describes in a clear and concise manner the "how, why, and therefore" of such procedures. It has been written to be readable and usable by research fellows, embryologists, and technicians who need some insight into the management implementation, and who wish to know the A–Z of how to run and manage a reproductive laboratory as seen and performed by the three distinguished authors.

It is always exciting to browse through a new book, particularly a manual, but as we go along, we often notice that the information is too polished, presented from an ideal standpoint and often dealing with theoretical situations. Such material makes a good book but from a practical point of view often may not prove to be very useful. The authors could have been trapped by the irresistible drive to be too comprehensive and make a thick book that would have lost practical usefulness and contact

with the reality of our times in terms of proficiency testing requirements and regulations.

Instead, Drs. Agarwal, Bento, and Esteves provide breadth and depth on topics related to research, management, and clinical fields. Collectively, they have produced a work that stays on track and provides essential advice to serve researchers, clinicians, and laboratory staff. The authors deliver a quick, practical, troubleshooting manual for the laboratory with an international scope and pedigree. This work will help scientists, embryologists, and technicians feel secure in setting up their systems and dealing with the daily difficulties of a routine. The manual integrates current successful aspects of reproductive clinical practice and introduces innovative facets to these kinds of endeavors. This includes the most relevant experience in this field as it unfolds in the current performance of reproductive laboratories in the United States, Europe, and other reputable representative countries.

In short, the work is dynamic. Those who read it will ultimately be able to better understand and better serve their patients' needs. There is an authoritative exposition of the different steps of ART, ranging from the routine of well-established procedures to the generation of future conduct of practice. This manual represents a milestone in the literature of reproductive medicine and will benefit all who read it.

New York, NY, USA Gianpiero D. Palermo, M.D., Ph.D.

Foreword

Today's world cannot be imagined without assisted reproductive technology (ART), which have been as revolutionary to civilization as modern contraception in the 1960s. After three decades of pioneering discoveries and ongoing developments, assisted reproduction has finally come of age. Quality management has been introduced, many clinics have become certified, and accreditation requirements and national and international regulation have formalized our quality control systems. However, quality management has not only to do with operating procedures, documentation, traceability, and risk minimization but also needs to address safety in the long term. Within the European Society for Human Reproduction and Embryology (ESHRE), a special interest group on "quality and safety in ART" tries to deal with risks and complications in both the short and the long terms. The topics addressed range from ovarian hyperstimulation syndrome and multiple pregnancies to genetic and epigenetic risks in ART offspring. Studying long-term risks is not possible without registration, and registration is impossible without documentation and quality control systems being in place. Quality management therefore is of the utmost importance, not just to please regulatory bodies and authorities in order to get licensed, but because of the safety issues touching the men and women we treat and their children yet to come.

The book you are about to read is in my opinion mandatory lecture for anybody involved in modern assisted reproduction. It should be on the desks in the clinic as well as on the shelves in the lab. It makes it easy to understand the steps to follow in establishing a comprehensive management system and allows the reader to learn from experiences worldwide. Operating in ART is unique because of the necessary integration of clinical, paramedical, laboratory, and administrative activities, making communication between all four groups very important. In this book, you will learn how to deal with setting up quality control systems at all levels and integrating them into one successful unit, where increased patient satisfaction will ultimately

lead to greater success of the clinic and better quality of care for the couples and children we treat. Whether you are about to start a clinic, have just decided to introduce a formal quality management system, or are a veteran in the field of quality control, you will like this book. It has fulfilled the ambition to be relevant at a truly global level and is a "must read" in our field for years to come.

Ghent, Belgium Petra De Sutter, M.D., Ph.D.

Preface

The objective of this book is to help ART centers comply with the demand to establish a Quality Management System, providing a step-by-step logical sequence to facilitate system implementation. The book covers basic concepts that are part of any model of quality management system chosen and also presents the experience many centers around the world have had in developing and using a quality management system, so as to identify common difficulties, challenges, and successes.

Chapter 1 offers an introduction to quality management in ART clinics. Chapter 2 presents some quality management tools, giving practical examples and explaining how these tools can be used and can help make a quality system work. It will neither focus on a particular tool nor go into extensive details about any of them. The idea is to present readers with what is available and enable them to follow whatever trend they may find suitable for their practices.

Chapter 3 starts with basic concepts to start the process of establishing a quality management system, such as how to define one's mission and quality management policies, how to register and control nonconformities as well as define corrective and preventive actions, and how to use satisfaction questionnaires to set goals and monitor performance.

Chapter 4 focuses on the daily activities of an ART Center, showing ways to have an overview of all activities involved, through flowcharts and interactions, and also showing the importance of standardization to achieve uniformity and guarantee quality. SOP's descriptions, reviews, and controls are also addressed.

Chapter 5 talks about training. The intention is not to present a training program but to suggest training subjects that can be covered for a quality system to be successful. It will also address issues such as internal satisfaction and how to evaluate staff's performance.

Chapter 6 focuses on communication. No quality management system can survive without a proper communication system. It will cover auditing processes, discussion and improvement groups, and the presentation of regular reports and indicators.

Chapters 7–10 provide an overview of how reproductive laboratories (RL), i.e., andrology and embryology clinical laboratories, can be integrated in a quality management system. These chapters define and explain the three pillars of quality for RLs attempting to operate in a quality management philosophy, i.e., (1) Defining what you do; (2) explaining how you do; and (3) making sure that what you do is being done in the proper manner, and provide tools and practical examples that will aid in the development of a quality management plan for reproductive labs. In Chap. 7 we provide an introduction to the role of reproductive laboratories in ART clinics. In Chap. 8, we present an overview of the scope of activities and services performed by typical clinical reproductive laboratories. Chapter 9 discusses what is needed for RLs to perform the procedures under their scope of activity. The role of laboratory manuals, personnel, structure and resources, and laboratory safety is fully covered. Chapter 10 describes and explains the critical quality activities for clinical reproductive laboratories operating in the context of quality management. Quality control (QC), quality assurance (QA), and quality improvement (QI) as key quality management elements should be fully integrated to not only identifying problems but also finding their solutions as well as ensuring and optimizing the quality of laboratory services.

Chapters 11 through 21 present the experience of ART Centers around the world in the establishment of their own quality management systems. The collaborating efforts of contributors in this section geographically span Europe, Latin America, Australia, Africa, Asia, as well as the USA. The idea is not to say what is right or wrong, but to show what worked and what did not work in different countries. Despite their regional and cultural differences, they do have a lot in common, and what they reported may enlighten those who are struggling to succeed. ART Centers will answer the following questions besides addressing issues that were particularly important in their practices:

- In your country, should ART Center legally comply with official regulations? Is having a Quality Management System mandatory?
- What are the key elements of your countries regulations, if any, regarding quality management?
- Which Quality Management System is in place at your center? Why did you decide to use this system?
- Which were the main challenges your ART Center faced to implement the Quality Management System and how were they overcome?
- What are the key elements of your Center's Quality Management System?
- What was gained by implementing a Quality Management System?

The ART Centers participating in these chapters are distributed around the world so as to show how this issue is dealt with in different countries and cultures (Fig. 1).

Each country follows its own regulation and directives, regardless of their being mandatory or simply a matter of choice (Table 1). It is interesting to note that some countries have to follow more than one guideline while others have no mandatory guidelines at all.

Fig. 1 Authors who contributed with chapters on international experience and their locations

Table 1 International guidelines and directives for ART

Country	Official guidelines and directives—mandatory	Other guidelines—non-mandatory
Australia	Code of Practice for Assisted Reproductive Technology Units, RTAC—Reproductive Technology Accreditation Committee	
Belgium	EU Directive 2004/23/EG EU Directive 2006/17/EG EU Directive 2006/86/EG Belgium Law (BS 30/12/2008)	ISO 9001:2008
Brasil	RDC 33, 17/02/06, ANVISA—Agência Nacional de Vigilância Sanitária	ISO 9001:2008
	CFM 1957/10, 15/12/10, CFM—Federal Medicine Council	Guidelines and Regulations REDLARA—Latin America Network of Assisted Reproduction
Chile		Guidelines and Regulations REDLARA—Latin America Network of Assisted Reproduction

(continued)

Table 1 (continued)

Country	Official guidelines and directives—mandatory	Other guidelines—non-mandatory
Gulf Countries		American Society of Reproduction Medicine Standards
		European Society of Human Reproduction and Embryology (ESHRE) Standards
		U.S. Department of Health and Human Services Standards
		Australian Council of Healthcare Standards
		International Organization for Standardization—ISO
India		ICMR—Indian Council of Medical Research
		National Guidelines for Accreditation, Supervision and Regulation of ART Clinics in India—2007
Nigeria		HFEA Code of Practice. 6th edition
		ISO 9001:2008
Singapore		ISO 9001:2008
		Joint Commission Accreditation of Health Care Organization (JJCAHCO)—Joint Commission International (JCI)
South Africa	National Health Act (No. 61 of 2003, Chapters 1–3)	American Society of Reproduction Medicine Guidelines and Protocols
	Human Tissue Act (No. 65 of 1983)	HFEA Code of Practice. 6th edition
	Children's Act (No. 38 of 2005)	Standard Guidelines—SASREG (South African Society of Reproductive Medicine and Gynecological Endoscopy
The Netherlands	GMP: Good Manufacturing Practice, Dutch Government	CCKL Code of Practice
	EU Directive 2004/23/EC, Ministry of Health, Welfare and Sports	ISO 15189:2003
	Artificial Insemination donor information Act	
	Embryo Act	
	Safety and Quality of Body Materials Act	
	Requirements for Body Materials Decree	
The USA	CLIA for Andrology Laboratories	CAP Accreditation
	FDA for Cryobiology	

Based on this information, we have tried to gather a heterogeneous group to show how a Quality Management System has been applied in different settings. Despite all differences, similar experiences and difficulties are noticed, and much can be learned from this group. Their experience can help both those who already have a system in place, and sometimes struggle to keep it working, and those who are implementing a brand new Quality Management System.

Campinas, SP, Brazil — Fabiola Bento, B.B.A., M.B.E.
Campinas, SP, Brazil — Sandro Esteves, M.D., Ph.D.
Cleveland, OH, USA — Ashok Agarwal, Ph.D., H.C.L.D. (A.B.B.)

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Part I
Establishing a Quality Management System

Chapter 1
Introduction to Quality Management in ART Clinics

Fabiola Bento, Sandro Esteves, and Ashok Agarwal

Nowadays, the demand for ART treatments has increased dramatically. With the technological advances and widespread flow of information, more and more people are aware of the treatment options they may have to solve their infertility problems. While in the past many couples would simply conform to the fact that they would remain childless throughout their lives, today couples simply do not give up hope and try to fulfill their dream of parenthood using all available resources.

As a result, the number of ART centers around the world has also increased (Fig. 1.1), even though it is believed that more centers are needed to fully respond to this growing demand. The number of ART cycles is increasing; however, available numbers are believed to be underestimated, as keeping track of the cycles performed around the globe is impossible due to unregistered clinics and unreported cycles. Figure 1.2 shows the total number of ART cycles reported to ICMART—International Committee Monitoring Assisted Reproductive Technologies (http://www.icmartivf.org) in 2000 [1], 2002 [2], and 2003 [3] per region. This total includes aspiration cycles, frozen embryo transfers, PGD cycles, and oocyte donation transfer cycles. It is important to note that submission of results by individual clinics to ICMART is completely voluntary. Therefore, its report does not represent every patient who underwent ART treatments, nor every clinic providing ART, and not even every country in which ART is performed. ICMART reported that 65–67% of all registered clinics have sent their ART information and therefore estimates a much higher number of cycles (Fig. 1.3).

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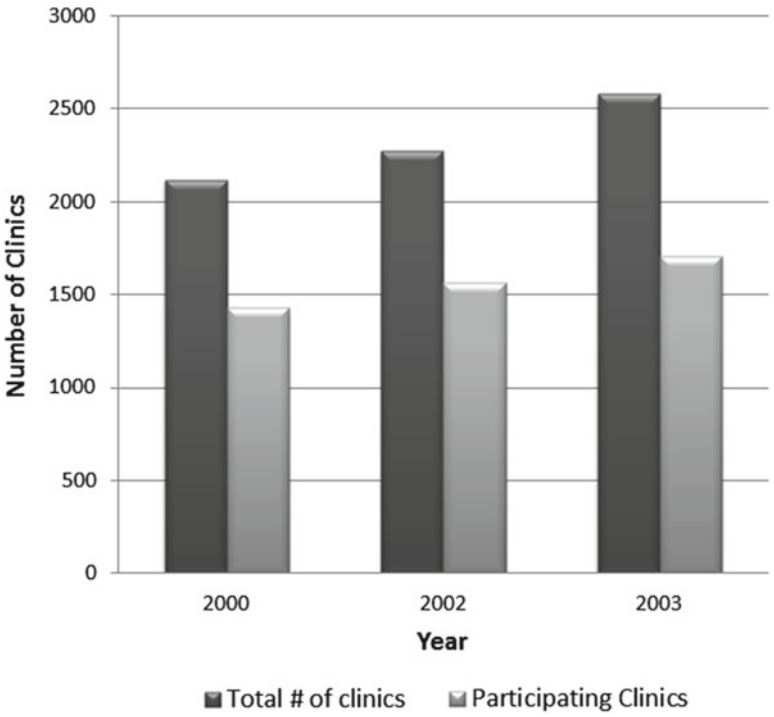

Fig. 1.1 Total number of registered ART centers and total number of ART centers participating in ICMART—International Committee Monitoring Assisted Reproductive Technologies (http://www.icmartivf.org) world reports in 2000 [1], 2002 [2], and 2003 [3]

As previously said, reporting data to ICMART and other monitoring committees is not mandatory and therefore not all centers are registered. However, ART centers around the world follow specific regulations in order to operate. To obtain their licenses, they must fulfill many demands from their countries' regulatory agencies and must follow the rules established by these same agencies. One of the common demands, besides technical standards and equipment, is the establishment of a quality management system.

Even though this is not a new concept, the establishment of a formal system is definitely a new demand. Most ART centers already had their own quality systems in operation; however, they lacked structure and formalization. The focus used to be more on quality control than on quality management. As David Hoyle said, "all organizations have a way of operating which is intrinsically a management system, whether formalized or not" [4]. Formalizing this system was the challenge presented to ART centers, and this book will address this issue directly.

Although this book will talk about regulations, some countries do not have any, and ART centers operate based on the standards they have chosen for themselves. Their focus is on quality and not on compliance. Establishing a quality management system should therefore not be seen as an obligation to comply with regulations and

Fig. 1.2 Total number of ART cycles reported to ICMART—International Committee Monitoring Assisted Reproductive Technologies (http://www.icmartivf.org) in 2000 [1], 2002 [2], and 2003 [3] per region. This total includes aspiration cycles, frozen embryo transfers, PGD cycles, and oocyte donation transfer cycles

should not be adopted just to obtain a certification. It should be seen as the way to achieve goals, satisfy patients, and ultimately being successful.

Besides, quality is variable as it depends on customers' requirements and expectations. What works in one country may not work in another. A quality management system must ensure that these requirements and expectations are known and are being met. However, as they may change over time, organizations must develop ways of listening to their customers and must improve their systems so as to meet these "new" requirements and/or expectations.

Peter Drucker, management guru, suggested in an article in the *Wall Street Journal* that the focus of the new management model is not on how much we are making but on how well we are meeting our customers' requirements. He continued saying that companies have learned from experience that customer satisfaction determines financial success. The goal of the new model is not profits; it is customer satisfaction, with the understanding that profits will improve as quality improves.

With competition, companies had to rethink the way they operate, and as medical services are more and more being seen the same way, as a business rather than a "doctor's office," they also have to adapt in order to meet their customers' expectations and survive.

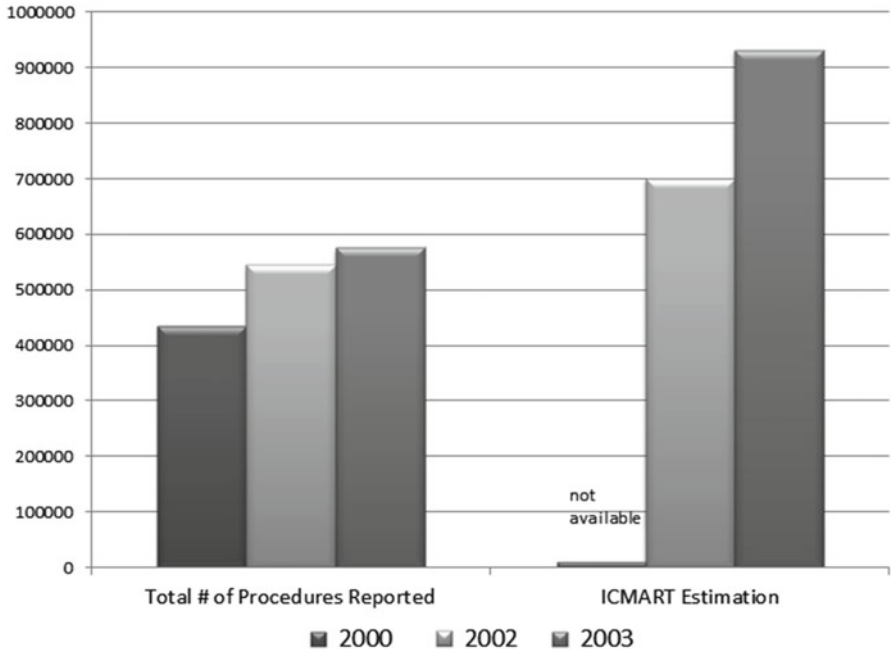

Fig. 1.3 Number of cycles estimated by ICMART—International Committee Monitoring Assisted Reproductive Technologies (http://www.icmartivf.org) in 2000 [1], 2002 [2], and 2003 [3]

It is of the utmost importance to:

- Know who your patients are and what they want from you.
- Define the processes to meet their expectations.
- Define your goals and objectives so that your procedures and processes help you achieve them.
- Measure your performance and your clients' satisfaction periodically to detect possible changes and new demands.
- Involve all personnel in continuous improvement.
- Make changes, adjustments, and improvements based on facts and not on assumptions.
- And, last but not least, satisfy your customers.

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Chapter 2
Quality Management Systems

Silveraldo Mendes

What Is Management?

Management can be defined as "administration" and can be summarized as the group of people that interact in a physical or virtual environment and have the same goal: the success of the "company's business." Companies perform sets of activities in order to produce and offer goods and/or services, with the objective of meeting some human needs. They can be public or private, with or without profits.

All consumers are interested in fulfilling their needs; however, there is something in common that pervades this entire universe of desire, which is the feeling of satisfaction and pleasure. Once decided to spend on a product or service, consumers want to obtain a certain feeling of accomplishment or, in other words, be able to say that what they have spent was worth it.

In case the consumer is fully satisfied, he will be able to say that it was really worth it. Therefore, we can say that the service provider, company, self-employed professional, or other organizations are on the right way to achieve customer fidelization, but before proceeding in this universe of emotions, let's reflect about it. This feeling is wonderful but how can consumers be able to feel it? Obviously, nobody has the exact answer to this question; otherwise, he would be selling it by a great amount of money! But there is one aspect that everybody must pay attention to, regardless of tips and magic formulas, called "quality."

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What Is Quality?

Quality is a subjective concept that is directly related to the perceptions of each individual. Several factors such as culture, mental models, type of product or service, needs, and expectations directly influence this definition. Many people evaluate the quality of a product by its appearance; others by its price or perhaps by the material it is made of. But the only objective and measurable aspect of quality is the "process." Based on the process, we can employ international methodologies and requirements, some of them disseminated by means of certifiable standards, such as the ISO 9001, ISO 14001, ISO 26000, and OHSAS 18001, respectively, directed to quality management, environmental management, social responsibility, and occupational health and safety. But before talking about standards, requirements, and certifications, it is important to understand what is a process and why it is so important in quality.

What Is Process?

Any activity or set of activities that uses resources to transform raw materials, supplies, or simply labor (inputs) into products or services (outputs) can be considered a process. For an organization to function effectively, it must determine and manage various interconnected activities and processes. Often, the output of one process is the input of another one. A process can also be a set of interrelated subprocesses. This concept can be applied to all segments, such as administrative, medical, and manufacturing.

See below for an example of the organizational structure for a process:

My wife and I moved to a new town, and after consulting various schools to enroll our children, we received information about an institution that valued quality in all aspects. The concern was the quality of teachers, curriculum, evaluation of students' performance, meals, security, etc., besides the logistics at the entrance and exit of students and parents.

We noticed some differences right from the beginning, when scheduling the interview with the director. Accessing the website, we were able to set the date, time, and even place, because if we wanted, we could receive a school representative at our own house. Another fact that caught our attention was a video presentation of the facilities and staff.

We chose to personally go to the school to meet the director. When we arrived, the receptionist drew our profile and informed us of personalized services, such as extracurricular activities, access to library, cafeteria menu, meeting with parents, parties, socialization, transportation, uniforms, laundry,

sports, school's supplies, individual lockers for students, intranet, and even a "manager" for our children's account. After that, the receptionist took us to a comfortable room, with music and amenities, and we started our conversation with a representative of the direction. We could then visit the facilities and also receive information about tuition and payment plans.

After enrolling our children in the school, we were given access cards to all facilities and a login and password that allowed us to monitor the services offered by the school's intranet. Our children received a welcome kit, which included from the uniform to the school's supplies, besides a small tablet with GPS system to facilitate mobility in the school's buildings. It also included details about the infrastructure, schedules, and activities.

Accessing the Internet, we could get every detail of our children's "account" and also detailed information about their academic development through a quarterly assessment that was compared to a pool of national and international institutions. This allowed us to evaluate whether the school was aligned with the educational standards and also evaluate if the tuition paid was worth the services received.

On the first day of class, the manager of our children's "account" was at the school gate waiting for our children in order to facilitate integration with the other students and teachers. Through a microchip installed in their uniform, they could be located inside the school, and one could know exactly when they arrived and left the facilities. When our children opened their lockers, all the school supplies were there, and classes started promptly at 07:30AM, with a snack break at 10:00AM and lunch at 12:30PM. Students were encouraged to practice sports at free choice, but always with experts' monitoring.

Due to the tracking system installed, the account manager and teachers were able to follow the footsteps of our children. When entering the classroom or other facility, students already received instructions on how to proceed.

There is a team that regularly gets in touch with parents to assess whether all is well and present a brief report about their children's development, both academic and about their behavior.

This is a fabricated story, or else a desire of a father. This institution does not exist; however, for this to happen, the institution would have to be organized by process. Parents would have to be assisted by a team and this would make all the difference. The operational process begins before parents and students go to the school and never end.

This view of a process goes back to medieval times, when an artisan, in order to produce a masterpiece, worked from purchasing the raw materials to delivering the finished work. When we have mapped and identified each of the subprocesses and interactions (inputs and outputs) of a process, we can fully understand and control it as a whole.

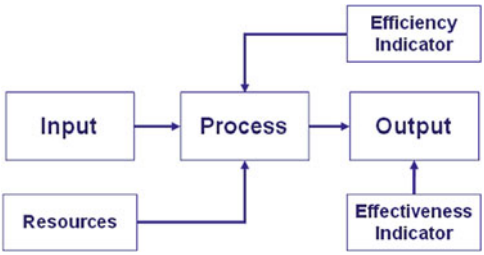


Fig. 2.1 Process mapping

Why Is a Process So Important in Quality?

Once we define what quality means to our business, we are able to assess whether the set of processes and subprocesses are structured and aimed to achieving this concept of quality. It is important to remember that quality is a subjective concept, as discussed earlier. That's why there is such concern with about its continuous improvement.

As quality improvement should be continuous, it must not be stagnated; therefore, nothing is better than knowing the various steps (processes and subprocesses) that shape our business, making it possible to implement necessary changes and updates quickly and safely. But how to know if the changes made are correct? There are performance indicators that classify processes into efficient and effective, for example. They help us monitor quality and also give measurable data to help in decision making and corrections, besides helping in the identification of the resources needed for this task. Figure 2.1 shows a process mapping model.

The conceptual difference between the indicators of efficiency and effectiveness is well explained through an example: "Mark is the production manager of company ALFA that produces its share of products. John is the production manager of company BETA that also produces its share of products, consuming 10% less energy. In this case, if the goal was simply the production, both were effective, but John was more efficient." The indicators will enable us to refine and improve our process continuously, reinforcing the concept of "process management."

Once the concepts of management, quality, and process are understood, there is a solid structure to advance and learn about some requirements, methodologies, and tools to help a business be successful. The word "some" was used because continuous improvement is endless and quality is subjective. Common sense and intuition are still the essence of a management with excellence. To better understand, see the example below, which shows the general resources and indicators to "prepare a barbecue party" (Fig. 2.2).

Requirements, Methods, and Tools

The most popular and widespread international requirements for quality management are described in the ISO 9001, which is generic and applicable to all organizations in any economic sector, regardless of the type of product or service

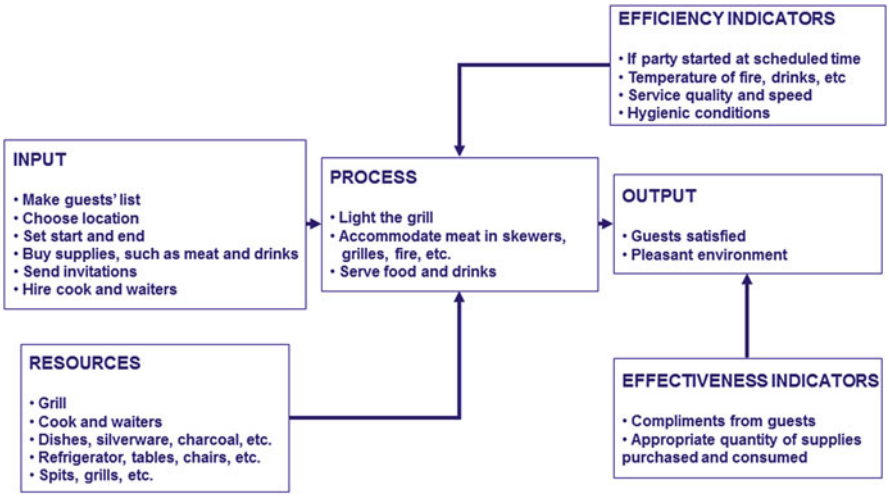


Fig. 2.2 Practical example of process mapping

offered. Some steps should be followed to develop and implement a quality management system:

1. Determine needs and expectations of customers and others (e.g., legislation, industry regulation).
2. Establish a quality policy and quality objectives for the organization.
3. Determine processes and responsibilities to achieve the quality objectives.
4. Identify and provide necessary resources to achieve the quality objectives.
5. Establish methods to measure the effectiveness and efficiency of each process.
6. Apply these measurements to determine the effectiveness and efficiency of each process.
7. Determine means to prevent nonconformities and eliminate their causes.
8. Establish and implement a process for continuous improvement of the quality management system.

An organization that adopts the previous approaches creates confidence in its processes and quality of its products and provides the basis for continuous improvement and consequent increase in customer satisfaction.

The current version of the ISO 9001 approved in the end of 2008 improved its compatibility with the ISO 14001 (environmental management). However, an important change in this version was the concept of exclusion. It allows standard requirements that are not applicable due to characteristics of the organization or its products to be excluded, since properly justified, ensuring its multi-sector or generic use.

A copy of the ISO 9001 is not allowed and is only available with the representative bodies of each country. It is described in items as below:

- Pages 1–2: Preface/Introduction
- Page 3: Purpose/Scope/Normative Reference/Terms and Definitions
- Pages 4–12: Requirements

  - Section 4: Quality Management System
  - Section 5: Management Responsibility
  - Section 6: Resource Management
  - Section 7: Product Realization
  - Section 8: Measurement, Analysis, and Improvement

- Pages 13–20: Tables of Correspondence Between ISO 9001 and Other Standards
- Page 21: Bibliography

The six documents required of the standard are:

- Document Control (4.2.3)
- Control of Records (4.2.4)
- Internal Audits (8.2.2)
- Control of Product/Service does not conform (8.3)
- Corrective Action (8.5.2)
- Preventive Action (8.5.3)

In addition to the requirements of the ISO 9001, it is necessary to define and implement a "quality policy" and a "quality manual." However, that does not mean they are the only documents needed. Once all procedures and operational routines are properly described, each organization must evaluate its entire process, enabling the retention of all information and intellectual capital, one of the "main assets" of any organization.

To implement the ISO 9001, the organization must first say what it does and then do what it says it does. One should write the way activities are performed and then verify if they are all being done as described, to validate what was written. This way, a pattern to control and operate all processes is intrinsically consolidated, establishing the habit of registering the activities as they are performed. These records provide important data for traceability and decision making. A well-implemented system can result in cost reduction since it helps reduce errors and waste.

The standards, by means of their respective requirements, contribute to sustainability, a current topic of great importance, since they support actions that are economically viable and environmentally correct.

There are consulting companies that assist in the implementation of the ISO 9001, sharing best practices for writing documents and manage information. However, having an internal group of employees study and help implement the standard is highly recommended to facilitate the dissemination of the internal culture. Managers should assess their needs and adopt the best practice for their company using external or internal resources.

Regardless of the strategy adopted, when the organization has properly implemented and disseminated the relevant ISO 9001 requirements, it should select an accredited agency to audit and certify the quality management system implemented. A certification is generally valid for 3 years with periodic audits to maintain certification. The objective of these audits is to verify if the system is active and updated.

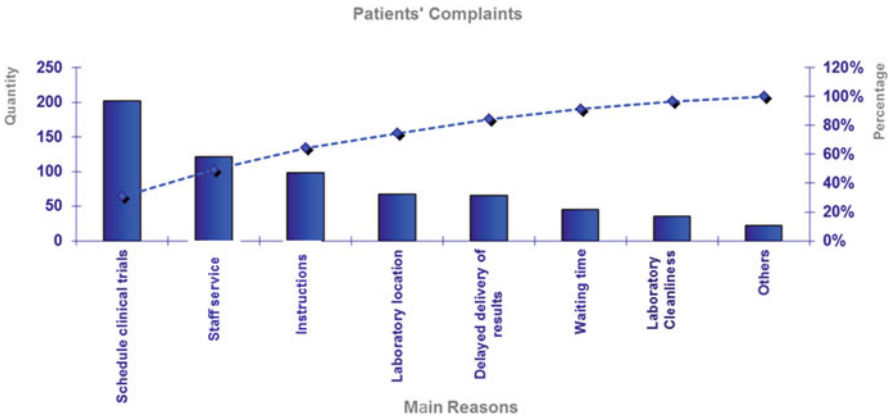


Fig. 2.3 Pareto diagram: main reasons for patients' complaints about clinical tests

Quality Tools and Methods

Quality management is more easily understood and implemented when we resort to some methods and tools, great allies of managers, as information, knowledge, and intuition are the main pillars for success. In an orchestra, for example, each instrument has its particular sound; when played harmonically by skilled musicians and under the command of the conductor, they produce a wonderful music. Making an analogy, the musical instruments are the methods and tools, the musicians are the employees, and the conductor is the manager. The musical instruments are used according to the melody chosen, as the methods and quality tools are chosen by the manager to achieve a predetermined goal. The combination of instruments (methods and tools) must be harmonious in order to extract as much knowledge of the processes as possible. Some quality methods and tools are presented below, without details, with the only objective of showing readers what is available. For more specific information about them, refer to the references at the end of this chapter [1–7].

Quality Tools

Pareto Diagram

Objective: to prioritize problems to be solved (Fig. 2.3):

- Select the problems to be compared
- Set the standard for comparing data
- Select the time period for analysis

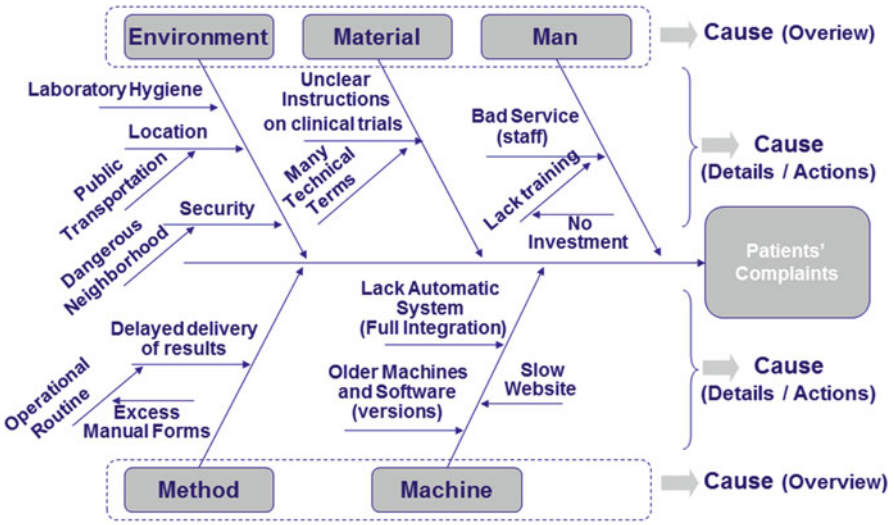


Fig. 2.4 Diagram of cause and effect: analysis of possible causes of patients' complaints

- Collect data from each category
- Compare the frequency of each category
- Record the totals in descending order
- Calculate percentages to the various selected categories

Diagram of Cause and Effect

Objective: to prioritize the factors that may cause an undesired effect (Fig. 2.4):

- Describe the problem clearly
- Brainstorm and record data on those involved
- Draw the diagram with the given problem on the right side
- Indicate the categories of causes
- Group the brainstorm results by category
- Elect the most important causes with the group

Remember: always ask "why it happens" to obtain the causes in the contributors' answers.

Control Chart

Objective: to monitor the stability or instability of a process (Fig. 2.5):

- Define mean values produced by the process
- Define the maximum variation the process reaches
- Obtain the maximum values allowed by the specification
- Prepare the chart and record the values obtained in uniform periods of time

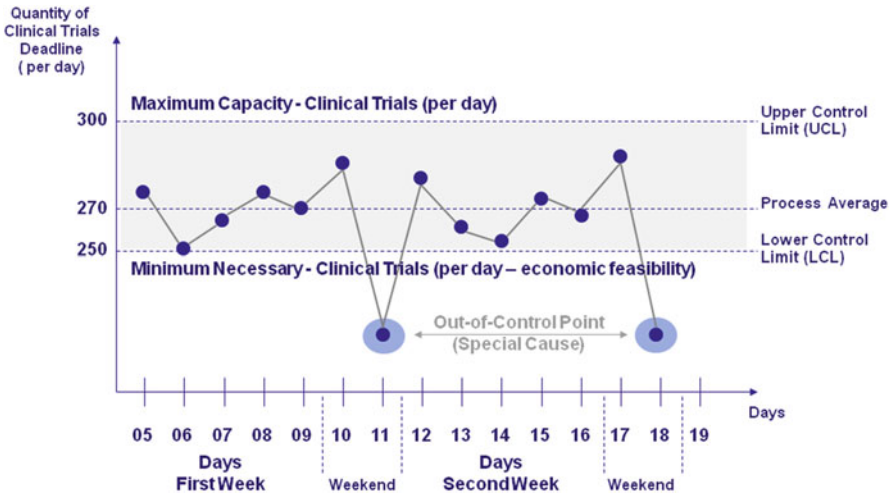


Fig. 2.5 Control chart: number of clinical trials per day and economic feasibility

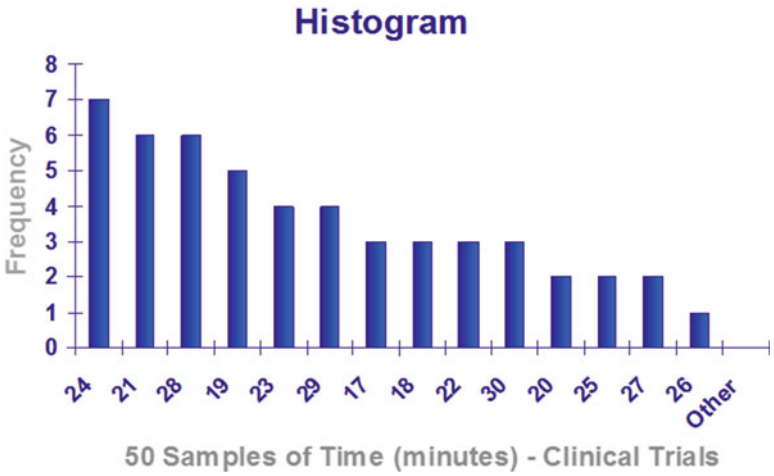


Fig. 2.6 Histogram: time spent on clinical trials during a period of time

Histogram

Objective: to show how to distribute a set of data indicating how a given process varies (Fig. 2.6):

- Register the values found in the process
- Accumulate the data on steps near the specified central value
- Register how often the data repeats itself

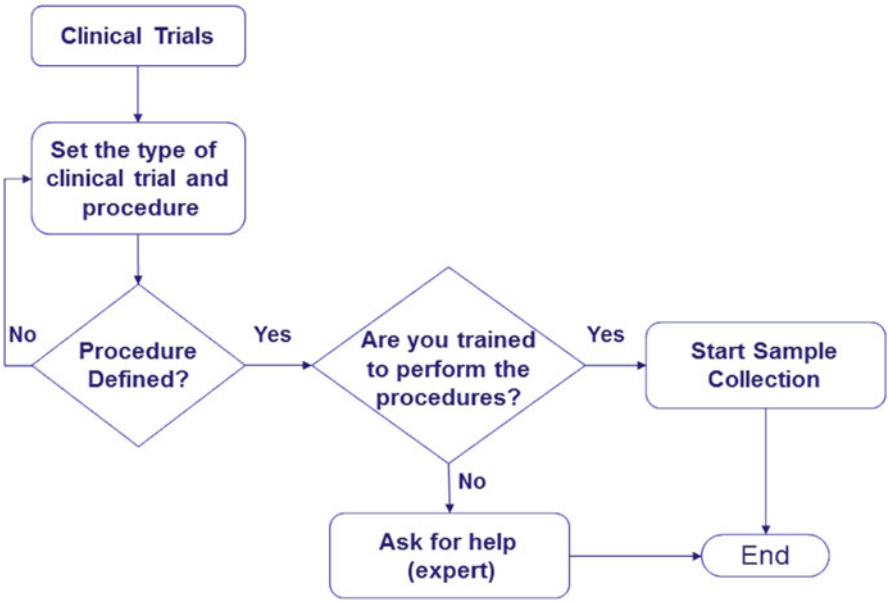


Fig. 2.7 Flowchart example

Flowchart

Objective: to visualize a process and identify improvement opportunities (Fig. 2.7):

- Assemble all information about the process to be studied
- Draw the current flowchart
- Study the critical points and draw the flowchart with the steps that the process must follow if all goes well
- Compare and analyze the differences between flowcharts

Quality Methods

PDCA

Objective: to monitor, correct, and improve a process through a consistent and effective method (Fig. 2.8):

- Set the goals to be achieved and actions to achieve them
- Train all those involved in the outlined guidelines planned and implement the process
- After implementation, collect data to compare with what was planned
- After achieving the goals, formalize the process, making it a standard

Fig. 2.8 PDCA methodology

To better understand the PDCA method, let's go back to the practical example about the barbecue party:

- *Plan* = make the guests' list, set the location, define what will be served, buy food and drinks, etc.
- *Do* = have the party, following all the items previously planned, receiving guests, and serving food.
- *Check* = check if the food and drinks are being served appropriately, if the quantity of items purchased is meeting the demand of guests, etc.
- *Act* = if waiters are slow, request a faster service; if drinks are not at the proper temperature, provide more or less ice, etc.

You can integrate the PDCA methodology, with two others called 6 Sigma and BSC (Balanced Score Card), providing a breakthrough in organizational management model (Fig. 2.9):

BSC = supports the prioritization and management of institutional indicators (Fig. 2.10).

For better understanding, since it is a method to identify and monitor processes and organizational strategies, read the following example, where the color green means that the outcome indicators or groups of indicators are perfect, yellow corresponds to a state of alert because the indicators are within a tolerance but require further monitoring, and red means that the indicators are totally outside the expected or desired goals and need to be investigated, working on the cause and correcting

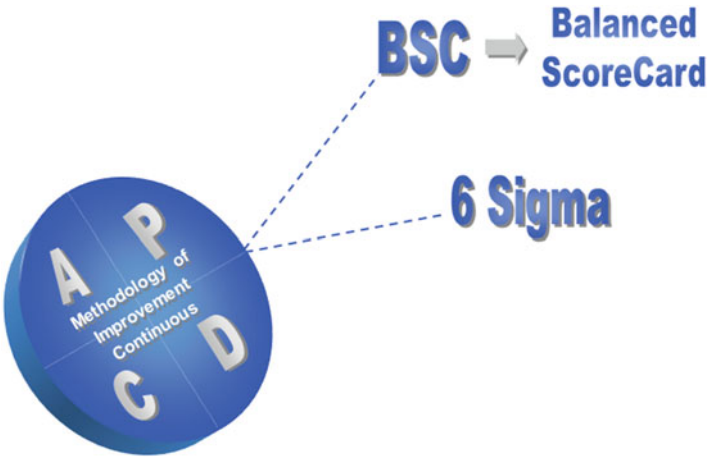
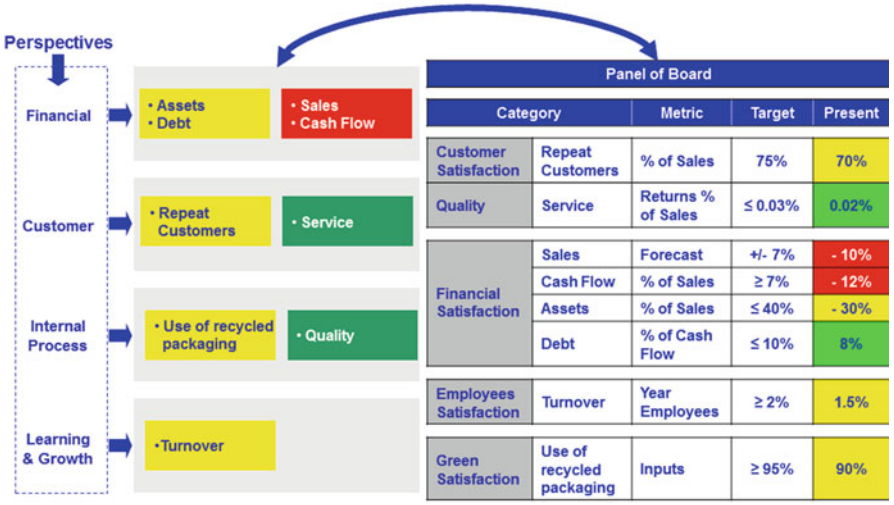


Fig. 2.9 BSC—Balanced Score Card and 6 Sigma

Fig. 2.10 BSC—Balanced Score Card

problems. It is a panel board in which the colors contribute in making decisions and monitoring results of previous plans (Fig. 2.11):

6 Sigma = it is a general map that helps integrate the tools to improve quality and reduce process variability (Fig. 2.12). Table 2.1 shows an example of process more stable and less likely to fail.



Panel of Board

Category		Metric	Target	Present
Customer Satisfaction	Repeat Customers	% of Sales	75%	70%
Quality	Service	Returns % of Sales	≤ 0.03%	0.02%
Financial Satisfaction	Sales	Forecast	+/- 7%	- 10%
	Cash Flow	% of Sales	≥ 7%	- 12%
	Assets	% of Sales	≤ 40%	- 30%
	Debt	% of Cash Flow	≤ 10%	8%
Employees Satisfaction	Turnover	Year Employees	≥ 2%	1.5%
Green Satisfaction	Use of recycled packaging	Inputs	≥ 95%	90%

Fig. 2.11 BSC—Goals and targets

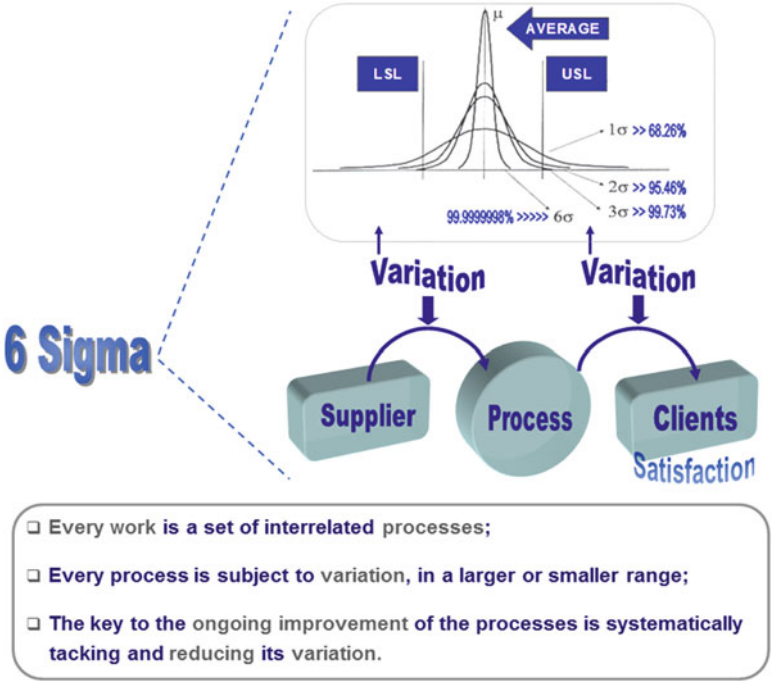


Fig. 2.12 6 Sigma

Table 2.1 An example of a more stable process

One organization has 254,000 contacts per year with clients (through: call center and events)	
99%—variation (success)	6 Sigma—99.9999998% (variation/success)
2,250 unsatisfied contacts per year	1 unsatisfied every 19 years

The 6 Sigma and the BSC methods are used in the PDCA during the following stages:

- *6 Sigma* = during action (act), because the results obtained start a new cycle, improvements are made and expectations are reestablished.
- *BSC* = during control (check), since it is a panel of indicators which provide data for decision making and consequently direct improvement actions.

Conclusion

The company's first step toward quality is to identify its critical processes, focusing on its strategy and vision. After this first stage, the process management starts using tools and methods to ensure quality, as discussed in this chapter, and thus implementing the concept of continuous improvement. Improvement opportunities will be viable only if the process mapping includes the subprocesses.

Another relevant aspect is to define indicators and goals for the processes and subprocesses, which must be periodically monitored. We cannot improve anything if we do not know the results achieved and if we do not compare them to previously defined goals.

The ISO 9001 certification (quality management), through its requirements, is an excellent resource because it defines a clear systematic management for continuous improvement. The written procedures and routines provide updated details about the organization operational system and also provide total traceability while maintaining the intellectual capital.

Learning the concepts of quality management, processes, standards, tools, and methods for quality may seem overwhelming at first, but it is great to see how much is gained and how a company can improve when all is put into practice. Establishing a quality management system may demand hours of work, especially in companies less structured, but it will certainly offer rewarding results.

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Chapter 3
Where to Start

Fabiola Bento

Mission Statement: Why do we exist?

A good way to start a quality management system is defining the mission statement. Missions are very popular nowadays. Even small businesses without a quality management system or even without any quality control at all have a mission statement. However, even though it may seem very simple, it is one of the most important steps toward a good quality system, for everything else that will be defined will have to refer directly to it.

A mission statement must state very clearly:

- What you do
- How you do it
- Who your customers are

The first step is to reflect about the reason why you exist as a business. "What am I here for?" is the basic question. Once you answer this question, you can move on to deeper reflections. If you do not know exactly what you do, or want to do, how can you know how you want to do it or even how you can guarantee its quality? Begin by thinking about the service that is offered at your center. Is it only ART treatments or are any other services offered? For instance, most ART Centers offer diagnosis too, for not all patients will need an ART technique to achieve pregnancy. Define what you do or want to do very clearly.

After that, define how you do it. Describe what technology is used, what the objectives of your center are, your philosophy, and in other words how you run your business.

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And finally define who your patients and/or who the patients you want to have are. Some countries accept only treatments in heterosexual couples, others in single mothers, and so on. No matter what regulation you follow, you must define to whom you want to offer your service.

Once you answer these questions, summarize them and write your mission statement. That may not be easy and take longer than expected. There is no hurry. Your mission can be revised from time to time, as objectives may change, but make sure this first mission is truthful to your objectives, because it will define the aims of your quality management system.

See below the authors' (FB & SE) ART Center mission statement as an example:

> Our mission is to help couples with conception difficulties become parents, especially when the difficulty is totally or partially related to men, through counseling, diagnosis and treatment, offering personalized professional service of excellence, and using all available technologic resources.

From this mission, we can see the answer to the previous questions:

- What we do: help couples become parents
- Who our customers are: couples with conception difficulties, especially those whose difficulty is totally or partially related to men
- How we do it: through counseling, diagnosis, and treatment and using all available technologic resource
- What kind of service we offer: personalized professional service of excellence

This is just an example to illustrate a mission statement. Reading other institutions' mission is a good way of learning how to write your own, even if reading missions from other fields. A mission statement is supposed to sum up your business aim, for both your patients and your staff must have access to it.

See below some other examples of mission statements:

> The mission of the National Gallery of Art is to serve the United States of America in a national role by preserving, collecting, exhibiting, and fostering the understanding of works of art, at the highest possible museum and scholarly standards.
>
> National Gallery of Art, Washington, USA.
> http://www.nga.gov

> The mission of Cleveland Clinic is to provide compassionate healthcare of the highest quality in a setting of education and research.
>
> Cleveland Clinic Foundation, USA.
> http://my.clevelandclinic.org

Once your mission is well-defined, present it to your staff and make sure they understand it, so that they can see their responsibility and involvement in making it "come to life." A mission statement prepares the staff for the quality management system that is being established and is critical, for if the staff is not ready, it will never work. Read Chap. 5 for suggestions of training programs.

Quality Policy and Quality Objectives

Based on the mission statement, a quality policy can be defined. A quality policy is usually brief and can be translated in objectives that are measurable and that can be monitored, in a way that the mission is fulfilled.

See below the authors' (FB & SE) ART Center quality policy as an example:

1. *Guarantee that our clients are satisfied.*
2. *Guarantee the professional development of our staff.*
3. *Continuously improve the quality of our services.*

The secret is to write simple statements that can be translated in many objectives. Make it as simple and direct as possible, and make sure everything can be measurable. In other words, write a policy that can be quantified or checked in some way and that you can determine a goal and check if you have achieved it later.

See below some examples of how to work with the previous quality policy:

1. Guarantee that our clients are satisfied.
   Objective: satisfy clients.
   Indicators: Satisfaction Questionnaires or data collected from a call center.
   Goals: 70% of satisfaction in all areas, or recovery of 50% of patients whose ART treatment was not successful (determine a desirable "dropout rate").
   Frequency: indicators must be checked frequently; for example, every 2 months, the results of the Satisfaction Questionnaires are analyzed. This frequency must be determined.
   Responsibility: the quality manager may be responsible for gathering the information from the Satisfaction Questionnaires.
   Actions can be taken and changes can be made based on the kind of information gathered. It is important to establish goals that can actually be achieved and raise them as improvements are made.
2. Guarantee the professional development of our staff.
   Objective: offer staff regular training.
   Indicators: training programs or investment plans on training.
   Goals: offer a determined number of trainings or hours of training to each individual per semester or per year.
   Frequency: every semester or every year.
   Responsibility: the quality manager along with the directors can develop an annual training program.
   A training program is usually based on the staff's needs and may include meetings, congresses, courses, workshops, lectures, and everything that adds knowledge. The manager may be responsible for gathering information and detecting needs of all sectors and of evaluating the possibility of having this training program according to the costs involved. Training costs money, so never plan courses and participations in meetings that you cannot afford and therefore will not be able to send anyone to attend.

3. Continuously improve the quality of our services.

   Objective: improve laboratory performance, invest in infrastructure and equipment, improve the quality management system, improve general performance, etc.

   Indicators: quality programs for IVF and Andrology Laboratories (see Part II for more details); investment plans determining new equipment to be purchased, training programs to be offered, participating in meetings, etc.; internal and/or external auditing reports and nonconformities and preventive actions recorded in a certain period; check data such as number of ART cycles and results on a daily basis, so as to detect deviations immediately.

   Goals: analyze specific parameters of laboratory performances; spend a certain amount of money yearly in infrastructure improvements and/or new equipment; increase preventive actions and decrease nonconformities; and have an established percentage of pregnancies per month instead of analyzing longer periods to be able to detect deviations faster.

   Frequency: laboratory data can be analyzed every 2 months; investment plans can be checked every 6 months; perform auditing processes every 6 months; check data daily.

   Responsibility: technicians and embryologists can be responsible for reporting the parameters of a specific period of time, and all data may be analyzed by them along with laboratory directors and quality manager; investment plans can be verified by the quality manager; the quality manager can monitor performance daily.

   Actions may be taken to correct deviations, new equipment may be bought if necessity is detected, extra training may be planned when necessary, etc.

The quality policy is as important as the mission statement (Fig. 3.1). It determines the focus of the quality program, shows objectives, sets goals, and lately helps organize a monitoring system. Sometimes an objective may be defined, but you realize it has no indicator. For example, if your quality policy is to satisfy customers and your goal is to achieve 60% satisfaction, but you do not use Satisfaction Questionnaires, how can you know you are accomplishing that? You may then create a questionnaire or any other tool to check it.

Nonconformities

A good way of gathering information for a quality management system is to register nonconformities. Nonconformities can be defined as everything that deviates from what is established; for example, a client's complaint, the use of equipment whose calibration date is expired, having continuous delays in the agendas, and delays in test results, among others. They may be caused by deficiencies in communication, documentation, training, equipment, and materials, among others.

It is also a good way to start, because it makes the staff not only solve problems but also reflect about their causes and therefore solve the source of the problems and avoid recurrence. Besides, it is a good way of involving all staff, for anyone can open nonconformities and many flaws can be detected through this practice.

QUALITY POLICY AND QUALITY OBJECTIVES

POLICY	OBJECTIVE	Indicator	Periodicity	Responsibility	Goal
Guarantee clients' Satisfaction	Satisfy clients	Satisfaction questionnaire	Every three months	Manager Assistant	80% of satisfaction
	Satisfy clients	Satisfaction surveys	Every two months	Nurse	Recover 50% of patients
Improve service quality continuously	Improve laboratory performance	Laboratory report	Every two months	IVF Embryologists	See IVF quality program
	Invest in structure and equipment	Investments' plan	Annually	General Manager	See annual report
	Improve QMS	Internal audit report	Annually	Quality Manager	Decrease number of non-conformities
	Improve QMS	Non-Conformities and Preventive Actions	Annually	Quality Manager	Decrease non-conformities and increase preventive actions
	Improve general performance	Management report	Every month	Quality Manager	Improve results
Guarantee staff professional development	Offer periodic training	Training Program and Investment Plan	Annually	Quality Manager	See plans

Fig. 3.1 Quality policy and quality objectives

For example, processes that are not well-defined may lead to inconsistencies, and consequently complaints, and ultimately nonconformities. It helps detect weaknesses and improvement opportunities, for a client's complaint can be the result of lack of information and consequently lead to wrong expectations. Even though there may be nothing wrong in terms of what was established internally and therefore not characterizing nonconformity, it may show a weak spot in the way we are communicating with our clients. For example, if you determine that nurses will call patients to tell them their pregnancy test results, it is fine until a patient is expecting the doctor himself to do it. Therefore, this type of information must be clearly stated to patients so as not to lead to dissatisfaction and complaints.

However, it is very important to train the staff appropriately, for dealing with "mistakes" is not easy. Nonconformities cannot be seen as criticism but as improvement opportunities. This is not the way it is seen by many, so training programs must be established. For some people, working in teams and seeking continuous

improvement is a natural thing; for others, it is a burden that takes time and preparation to accept.

There are many models of nonconformity registration forms, but all of them cover a few basic items:

Registering the nonconformity:

1. Date.
2. Who is reporting the nonconformity.
3. Area in which it occurred or process affected.
4. Origin of the nonconformity, whether it was an internal detection or a patient's complaint, for example.
5. A description of the problem detected.
6. Immediate action taken, if any.

Corrective action:

1. Analysis of the cause.
2. Corrective actions suggested.
3. Corrective actions approved and therefore taken, with responsibilities and implementation deadlines.

Effectiveness of corrective action:

1. If a corrective action was effective or not.
2. If not, check if a new nonconformity has occurred.
3. Date.
4. Name person responsible for the analyses.

The model used to register nonconformities is not important. It can be a handwritten form or a form in a computer system (Fig. 3.2). Whatever form chosen, nonconformities must be easily registered, understood by all staff, and easily communicated. What is important is not the way nonconformities are registered but how well they are solved. Once a nonconformity is registered, it must be sent directly to the area responsible for proper root analyses and suggestion of corrective actions. This analysis is better performed by the group rather than by individuals, and when it comes to deciding what corrective action to take, the laboratory director and/or quality manager should always be involved, as they are the ones who will later check the effectiveness of the actions taken.

There are many problem-solving tools that can be used to find the root cause of problems, as described on Chap. 2. There is also the 8D Approach to Problem Solving [1]. It was created years ago and is still used because it can be adapted to any situation and field. It basically involves:

1. Using a team approach (group of people from the area and that has the knowledge to solve the problem and implement corrective actions).
2. Describing the problem.

NON-CONFORMITY AND CORRECTIVE ACTION REGISTRATION FORM

NON-CONFORMITY

Date:
Area[1]:
Origin[2]:
Description:
Proponent's Initials:

IMMEDIATE ACTION

Description:
Conducted by:

CAUSE ANALYSIS

Description:
Initials:

CORRECTIVE ACTION PROPOSED

Description:
Proponent's Initials:

CORRETIVE ACTION TAKEN

Description:
Date of Implementation:
People Involved:

QUALITY MANAGER	**CLINICAL DIRECTOR**
Date: Signature:	Date: Signature:

FOLLOW-UP

( ) The corrective action was effective.
( ) The corrective action was not effective. New Non-Conformity # _____
Date:
Initials:

[1]IVF lab, andrology lab, administration, etc.
[2]satisfaction questionnaire, detection in the area, patient's complaint, etc.

Fig. 3.2 Nonconformity and corrective-action registration form

3. Implementing a short-term corrective action (immediate action).
4. Defining or verifying root cause.
5. Choosing or verifying permanent corrective action (confirm short-term corrective action and define other actions, if necessary).
6. Implementing or validating permanent corrective action (define permanent corrective actions needed).
7. Preventing recurrence (through training, review of processes or workflows, etc.).
8. Recognizing the team (reinforce the achievement of the team communicating it internally, sharing knowledge, and publicizing).

See Fig. 3.3a, b for some examples of practical nonconformities that were registered at the authors' (FB & SE) ART Center.

a

Practical Example 1

NONCONFORMITY

Date: September 18, 2007
Department: Andrology Laboratory
Origin: Patient's complaint
Description: Patient reported during appointment with Dr. Z that the result of his semen analysis (#.../97) shows that he is 33 instead of 35 years old. Patient questioned if the results may have been mistyped and doubted the result of the test due to this mistake.
Proponent's Initials: Dr Z.

IMMEDIATE ACTION

Description: Technician was informed immediately and asked to check what happened.
Conducted by: Dr Z.

CAUSE ANALYSIS

Description: Patients fill in a form with their personal information before collecting semen samples. The form filled in by this specific patient reads 33 years old. Therefore the laboratory didn't make any mistake.
Initials: Andrology Laboratory Technician and Quality Manager.

THE NONCONFORMITY DOES NOT PROCEED.

QUALITY MANAGER	CLINICAL DIRECTOR
Date: September 19, 2007 Signature:	Date: September 18, 2007 Signature:

Fig. 3.3 (**a**) and (**b**) Nonconformity and corrective-action registration form—practical examples 1 and 2

b

Practical Example 2

NONCONFORMITY

Date: May 4, 2010
Department: IVF Laboratory
Origin: Detection by the department
Description: The culture medium purchased from Company X was delivered with the temperature above the level recommended by the manufacturer (2 to 8 degrees Celsius), confirmed by the equipment Data Logger EL-USB-02, that registered the temperature during transportation between 10 and 14 degrees.
Proponent's Initials: Embryologist S

IMMEDIATE ACTION

Description: The Clinical Director was immediately informed. Company X was informed about the problem and was asked to replace the culture medium received by new ones kept under correct conditions and temperature.
Conducted by: Embryologist S

CAUSE ANALYSIS

Description: Apparently there was an excess of polystyrene inside the package, isolating the culture medium from the ice blocks, what caused the warming of the culture medium.
Initials: Embryologist S

CORRECTIVE ACTION PROPOSED

Description: During meeting with Company X representative, …, in May 6, 2010, it was decided to simulate a delivery using plastic instead of polystyrene inside the package. The carrier will also be replaced by a faster one.
Proponent's Initials: Embryologist S and Quality Manager

CORRETIVE ACTION TAKEN

Description: The culture medium was replaced in May 06, 2010, a simulation with the new packaging was performed in May 13, 2010 with satisfactory results, and the carrier was replaced by a faster one.
Date of Implementation: May, 2010
People Involved: Embryologist S and Quality Manager

QUALITY MANAGER	CLINICAL DIRECTOR
Date: May 4, 2010. Signature:	Date: May 4, 2010. Signature:

FOLLOW-UP

(X) The corrective action was effective.
( ) The corrective action was not effective. New Non-Conformity # _____
Date: August 30, 2010
Initials: Quality Manager

Fig. 3.3 (continued)

Preventive Actions

After making your staff register and solve nonconformities successfully, they are ready to think ahead and start suggesting preventive actions. This requires knowledge of how everything works, to then be able to detect what can go wrong before it happens. People involved, as time passes, should be able to detect certain conditions, situations, or circumstances that may cause nonconformities. Preventive actions are therefore the actions taken to eliminate these potential nonconformities.

It is important to observe that no one wants to fail, regardless of their commitment with the quality system. Therefore, after some time and some experience, making suggestions to improve performance and prevent nonconformities is not difficult at all. The most difficult part is to enable your staff to have this critical eye and be able to foresee what can go wrong in what they do.

Examples of potential nonconformities are listed below:

1. Suppose the number of cycles performed by your center has increased, and even though the number of embryologists in your center is appropriate, it is at the limit. What will you do if one of the embryologists gets sick and is unable to work, if you know the others will not be able to cope with the amount of work?
2. Your center keeps supplies in stock for future use, so as to prevent lack of supplies in case you have problems with delivery. However, lately, it is taking you a month to receive new supplies, while before it usually took a week. Is your minimum stock sufficient for this 1-month delay? Should you reanalyze your numbers and determine new limits?
3. One of your secretaries is going to retire soon. You hire a new secretary to be trained, but she is not adapting to your routines. You try another one and another one, and you are simply not satisfied with the candidates you find. What are the potential problems you may have if you do not find a candidate in the appropriate time? Can you do anything internally, such as a new distribution of tasks, to prevent problems when this experienced secretary leaves?

The detection of potential nonconformities can lead to the analyses of routines, procedures, or even behaviors. Working with preventive actions has everything to do with quality management and is of extreme importance, because while corrective actions focus on solving quality problems that have already occurred, preventive actions focus on improving quality, therefore being in compliance with the basic principle of any quality system which is “continuous improvement.”

Preventive actions can be registered very similarly to nonconformities (Fig. 3.4). It basically involves:

Registering the potential nonconformity:

1. Date.
2. Name of the person who has detected this potential nonconformity.
3. Area in which it can occur.
4. A description of the potential problem.
5. A description of the cause of this potential problem.
6. Suggested preventive action.

PREVENTIVE ACTION REGISTRATION FORM

POTENTIAL NONCONFORMITY

Date:
Area 1:
Description:
Proponent's Initials:

CAUSE ANALYSIS

Description:
Initials:

PREVENTIVE ACTION PROPOSED

Description:
Proponent's Initials:

CORRETIVE ACTION TAKEN

Description:
Date of Implementation:
People Involved:

QUALITY MANAGER	CLINICAL DIRECTOR
Date: Signature:	Date: Signature:

FOLLOW-UP

( ) The corrective action was effective.
( ) The corrective action was not effective. New Non-Conformity # _____
Date:
Initials:

1 IVF lab, andrology lab, administration, etc.

Fig. 3.4 Preventive-action registration form

Preventive action:

1. Suggested action approved.
2. Implementation date.

Effectiveness of the preventive action:

5. If a preventive action was effective or not.
6. If not, register a new preventive action.
7. Date.
8. Name person responsible for the analysis.

Preventive actions should not be underestimated and should be encouraged at all times. Sometimes potential nonconformities may not seem very serious or really not cause a

significant problem. However, be careful not to discourage your staff. One of the main responsibilities of a manager is to listen to his staff, regardless. Something that may not seem very important to you may be affecting the work of some, and not showing respect to people's opinions may demotivate them and put your quality system at risk.

Satisfaction Questionnaires

Satisfaction Questionnaires represent one of the best forms of communicating with your patients. In many cultures, complaining is "not polite," even when a real problem occurred, and actually formalizing a complaint is not acceptable. In some places, complaining is simply not part of the people's repertoire, and they do not do it. Therefore, people tend to look for another clinic if they are unsatisfied, without even reporting their dissatisfaction.

In order to improve quality, we must have information regarding the general satisfaction of our patients with the service we provide. Many times we may believe everything is fine, even because nobody plans to be unsuccessful or have a "bad" ART Center, when for our patients a few things may be lacking.

A recent study published in Human Reproduction [2] showed that physicians put more value on pregnancy rates than patients. Patients, on the other hand, seek patient centeredness, and this was the most cited reason for changing to another fertility center. This study raises the flag that maybe our definition of high quality may be different from our patients'. We, as ART Centers, tend to focus a lot on results; however, even though results are important, we cannot ignore our patients' needs.

Patient centeredness has been lately discussed in most meetings around the world. So understanding our patients is of utmost importance to be able to satisfy them. There are no rules here, for what a patient wants in Brazil can be completely different from what a patient wants in Africa. Even in the same country, differences can occur. Patients who are in public services may have different expectations from those in a private center and so on.

Following the same idea, Satisfaction Questionnaires may also vary, from place to place and also from time to time. ART Centers must, in their Satisfaction Questionnaires, include questions about aspects they want to know about and believe can be changed or improved. For example, knowing if your patients are satisfied with your administrative staff is important, for you can give them appropriate training on how to deal with your patients' requests or you can even sometimes dismiss an employee for not following the rules and routines previously established.

On the other hand, there is no need to know if your patients are satisfied with your pregnancy rates if you are within international standards. The goal of all ART Centers is to help every couple achieve pregnancy, even though we are aware of our technical limitations. Most patients will obviously be unsatisfied, as unfortunately not all of them will get pregnant.

See below and Fig. 3.5 for some examples of what can be included in a Satisfaction Questionnaire:

1. Satisfaction with doctor: waiting time, dedication, and involvement.
2. Satisfaction with infrastructure: cleanliness, reception area, and clothing.

SATISFACTION QUESTIONNAIRE - IVF TREATMENTS

Q1. Your doctor's name:

→

Q2. Satisfaction with cleanliness and appearance:

	Very Satisfied	Satisfied	Unsatisfied	Very Unsatisfied
Reception area	○	○	○	○
Examination rooms	○	○	○	○
Clothes	○	○	○	○

Q3. Satisfaction with administrative staff:

	Very Satisfied	Satisfied	Unsatisfied	Very Unsatisfied
Explanation and costs	○	○	○	○
Cordiality	○	○	○	○

Q4. Satisfaction with nurses:

	Very Satisfied	Satisfied	Unsatisfied	Very Unsatisfied
Cordiality and help	○	○	○	○
Help before/after procedures	○	○	○	○

Q5. Satisfaction with anesthesiologists:

	Very Satisfied	Satisfied	Unsatisfied	Very Unsatisfied
Cordiality and help	○	○	○	○
Info before/after procedures	○	○	○	○

Q6. Satisfaction with IVF staff:

	Very Satisfied	Satisfied	Unsatisfied	Very Unsatisfied
Information about embryos during cleavage	○	○	○	○

Q7. How many IVF cycles have you been through?

0 cycle	1 cycle	2-3 cycles	more than 3 cycles
○	○	○	○

Q8. In case you have been to another IVF Center, how do you evaluate the services provided by our clinic in comparison to the other clinic?

Better	Just the same	Worse
○	○	○

Q9. In case you have used our Complementary Health Program, say how helpful the service was for your treatment:

	Very useful	Of some help	Didn´t make difference	Didn't use
Acupuncture	○	○	○	○
Psychological Support	○	○	○	○
Nutritional Orientation	○	○	○	○

Fig. 3.5 Satisfaction questionnaire—IVF treatments

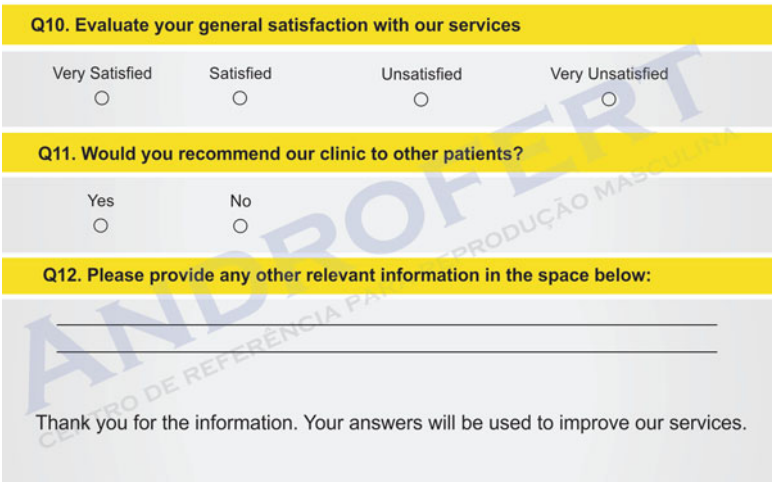

Fig. 3.5 (continued)

3. Satisfaction with reception staff: cordiality, professionalism, and telephone assistant.
4. Satisfaction with nursing service: cordiality and explanation of medication.
5. Satisfaction with administrative staff: cordiality and explanation about costs.
6. Satisfaction with laboratory staff, if in contact with patients.
7. Satisfaction with anesthesiology staff.
8. And any other aspect related to the service you provide.

Satisfaction Questionnaires should be filled in by all patients; otherwise, results can show a false tendency toward unsatisfied patients or very satisfied ones. Find a system to make all patients fill in your questionnaire so that you can have truthful information.

Another suggestion is not to put names on questionnaires. This way, patients will feel comfortable with making complaints if they want to without having to say their names. The idea is to get as much information as possible, to better comprehend and later satisfy your patients.

From the questionnaires' information, potential nonconformities or actual nonconformities can be detected, and many improvement suggestions can be made. Satisfaction Questionnaires have to be used for our own good. Questions must be clear, simple, and straightforward. They cannot be lengthy; otherwise, patients will not fill them in. Therefore, revise your questionnaire periodically, adding new questions or taking out a few ones after you have gathered the information you need.

Figure 3.6 shows an example of a simple Satisfaction Questionnaire regarding the service provided by the Andrology Laboratory of the authors' (FB & SE) ART Center.

SATISFACTION QUESTIONNAIRE – ANDROLOGY LABORATORY

Q1. Name of doctor who asked for the semen analysis:

→

Q2. How long have you waited for the sample collection?

○ 0-15 minutes ○ 16-30 minutes ○ 31+ minutes

Q3. Satisfaction with our staff (before the collection):

	Very Satisfied	Satisfied	Unsatisfied	Very Unsatisfied
Facility to schedule analysis	○	○	○	○
Info about types of tests	○	○	○	○
Instructions received	○	○	○	○
Explanation about costs	○	○	○	○
Cordiality and help	○	○	○	○

Q4. Satisfaction with our staff (on the day of the collection):

	Very Satisfied	Satisfied	Unsatisfied	Very Unsatisfied
Instructions received	○	○	○	○
Info about analysis	○	○	○	○
Cordiality and help	○	○	○	○

Q5. Satisfaction with collecting room:

Very Satisfied	Satisfied	Unsatisfied	Very Unsatisfied
○	○	○	○

Q6. Please provide any other relevant information in the space bellow:

Thank you for the information. Your answers will be used to improve our services.

Fig. 3.6 Satisfaction questionnaire—andrology laboratory

The results of these questionnaires should be tabulated monthly, or if you have few numbers of patients, do it every 3 months. Results should be analyzed and mainly communicated to your staff, to make them aware of their performance, regardless of the results of their laboratory. Communication is ultimately one of the most important aspects of your quality management system (see details in Chap. 6).

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Chapter 4
Defining Processes and Procedures

Fabiola Bento

Processes Versus Procedures

Procedures can be defined as the sequence of steps that must be followed to execute a task, such as how to perform a test to determine a certain semen characteristic or how to schedule an appointment with a doctor. It documents the activities to be carried out, usually determining the order that must be followed and therefore standardizing the way tasks are executed and avoiding differences among technicians and employees in general.

Processes, on the other hand, are much more complex. They focus on a result that must be achieved and select the procedures to be followed to achieve it. Processes can describe resources and behaviors and, differently from procedures, usually include decisions. For example, the process of diagnosing a patient to be able to prescribe some type of treatment may include the performance of different procedures, such as a semen analysis or a blood test.

How to Describe Procedures

Procedures can be described in many forms. They can be written, they can be expressed by flowcharts, or they can even be expressed through drawings. When deciding the form you are going to use, first think about who has to follow the steps (your audience) and how to make it easier for this person, or persons, to understand and follow the procedure without deviations. The way you describe a laboratory procedure can be completely different from the way you describe a procedure for

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your cleaning personnel, because of the different details that should be included and the different demands of the procedure itself.

When describing a procedure, it is important to include some basic information which may vary according to the procedure described:

1. Introduction or objective, describing the importance of this procedure
2. Sample used to perform the procedure
3. Materials, equipment, and reagents used
4. Quality control, saying what is done to guarantee the quality of materials and reagents, for example
5. Description of the procedure itself, or the steps followed
6. Results interpretation, if the case
7. References
8. And any other observation or annexes which are important in the procedure

Describing procedures is very important but should not turn employees into robots. We can introduce machines when and where necessary. Employees should have some flexibility and that is why defining processes is so important. They show where decisions can happen and when they are appropriate. Following the steps defined in a procedure description should not make people unable to adapt and make changes when necessary. See Fig. 4.1 for an example of a procedure.

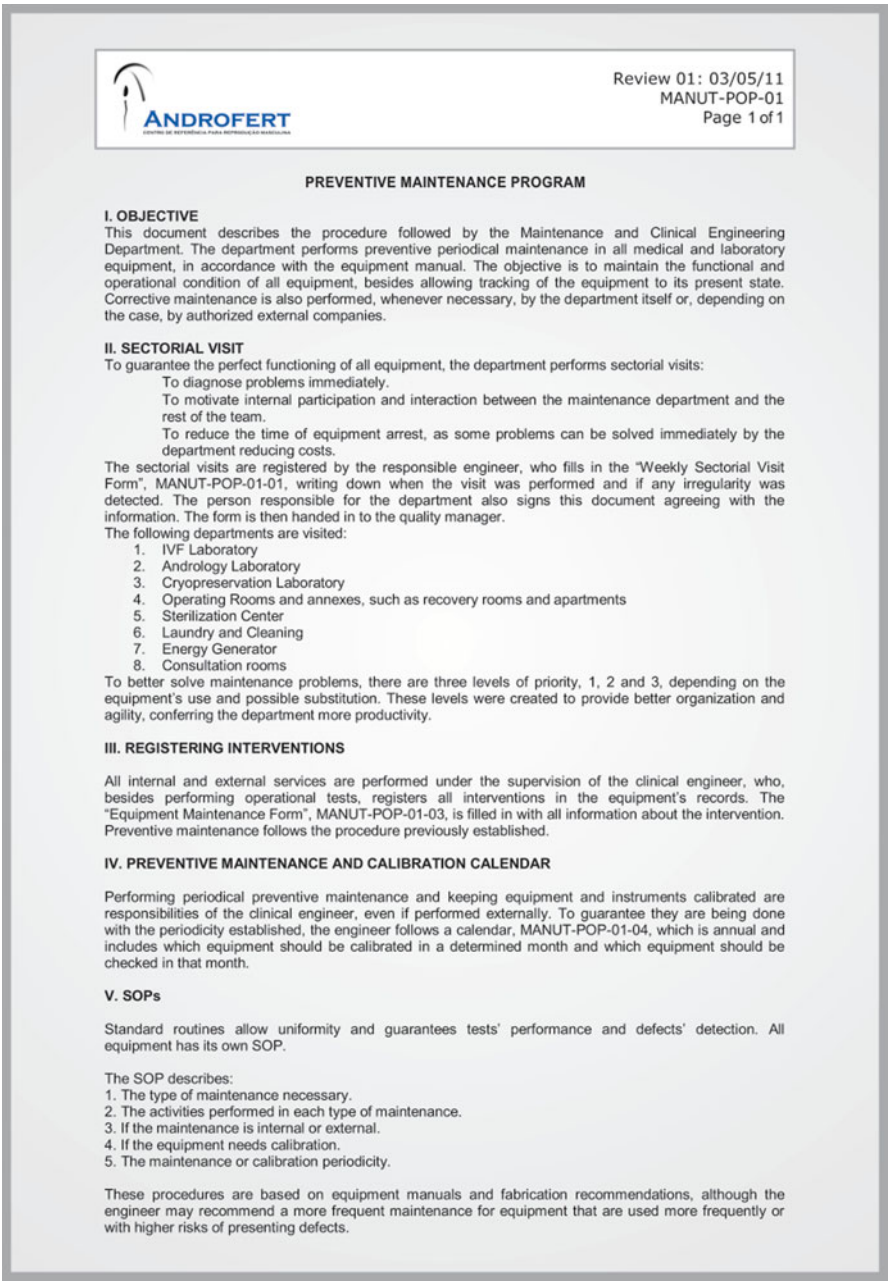
How to Describe Processes

Describing a process is very important to:

1. Visualize the process
2. Identify steps, including unnecessary ones that can be excluded
3. Check the procedures involved in this process that need to be standardized and therefore described
4. Check where you need control
5. Check vulnerabilities that must be treated opportunely

A process can be easily described through flowcharts. Flowcharts use "basic forms" that represent procedures and also decision making. Figure 4.2 shows some of the basic forms used in flowcharts.

Whether you use a flowchart or a written description, describing processes is very important to have a global understanding of how things work within your clinic and also to see the interactions among processes. They help solve nonconformities, for example, as through them one can see if the problem detected is in the department where it was registered or if the problem happened because of a flaw that happened before, during another procedure. For example, the laboratory can



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Review 01: 03/05/11
MANUT-POP-01
Page 1 of 1

PREVENTIVE MAINTENANCE PROGRAM

I. OBJECTIVE

This document describes the procedure followed by the Maintenance and Clinical Engineering Department. The department performs preventive periodical maintenance in all medical and laboratory equipment, in accordance with the equipment manual. The objective is to maintain the functional and operational condition of all equipment, besides allowing tracking of the equipment to its present state. Corrective maintenance is also performed, whenever necessary, by the department itself or, depending on the case, by authorized external companies.

II. SECTORIAL VISIT

To guarantee the perfect functioning of all equipment, the department performs sectorial visits:

To diagnose problems immediately.

To motivate internal participation and interaction between the maintenance department and the rest of the team.

To reduce the time of equipment arrest, as some problems can be solved immediately by the department reducing costs.

The sectorial visits are registered by the responsible engineer, who fills in the "Weekly Sectorial Visit Form", MANUT-POP-01-01, writing down when the visit was performed and if any irregularity was detected. The person responsible for the department also signs this document agreeing with the information. The form is then handed in to the quality manager.

The following departments are visited:

1. IVF Laboratory
2. Andrology Laboratory
3. Cryopreservation Laboratory
4. Operating Rooms and annexes, such as recovery rooms and apartments
5. Sterilization Center
6. Laundry and Cleaning
7. Energy Generator
8. Consultation rooms

To better solve maintenance problems, there are three levels of priority, 1, 2 and 3, depending on the equipment's use and possible substitution. These levels were created to provide better organization and agility, conferring the department more productivity.

III. REGISTERING INTERVENTIONS

All internal and external services are performed under the supervision of the clinical engineer, who, besides performing operational tests, registers all interventions in the equipment's records. The "Equipment Maintenance Form", MANUT-POP-01-03, is filled in with all information about the intervention. Preventive maintenance follows the procedure previously established.

IV. PREVENTIVE MAINTENANCE AND CALIBRATION CALENDAR

Performing periodical preventive maintenance and keeping equipment and instruments calibrated are responsibilities of the clinical engineer, even if performed externally. To guarantee they are being done with the periodicity established, the engineer follows a calendar, MANUT-POP-01-04, which is annual and includes which equipment should be calibrated in a determined month and which equipment should be checked in that month.

V. SOPs

Standard routines allow uniformity and guarantees tests' performance and defects' detection. All equipment has its own SOP.

The SOP describes:

1. The type of maintenance necessary.
2. The activities performed in each type of maintenance.
3. If the maintenance is internal or external.
4. If the equipment needs calibration.
5. The maintenance or calibration periodicity.

These procedures are based on equipment manuals and fabrication recommendations, although the engineer may recommend a more frequent maintenance for equipment that are used more frequently or with higher risks of presenting defects.

Fig. 4.1 Preventive maintenance program from Androfert

Fig. 4.2 Flowchart symbols

label a sample with the wrong last name of a patient or a test result can present the same mistake. Is it really the laboratory's fault or was it a mistake made by the secretaries when filling in the patient's data in the computer system? If you have this global "view," you can pinpoint vulnerabilities and add security procedures to avoid mistakes (Figs. 4.3, 4.4, and 4.5).

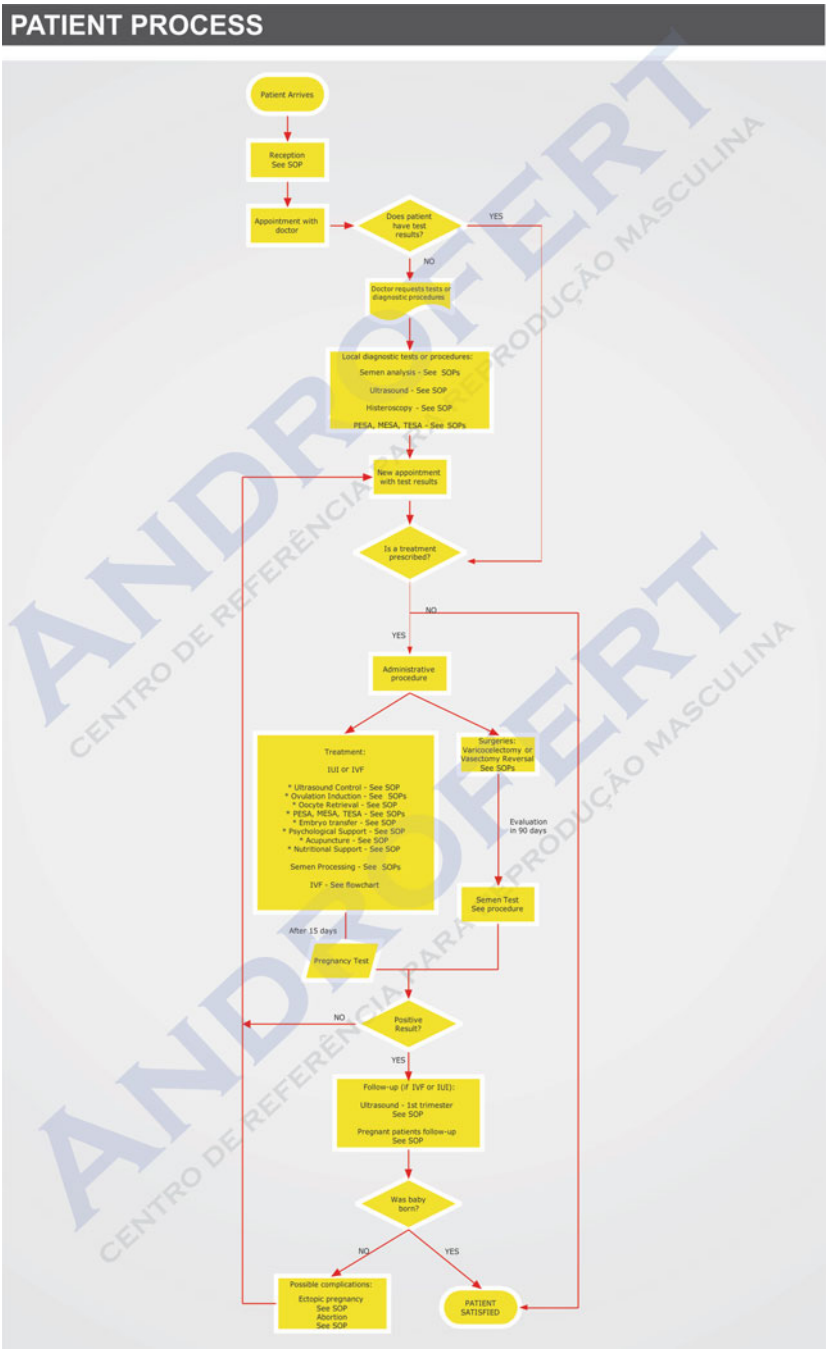

Fig. 4.3 Flowchart—patient process

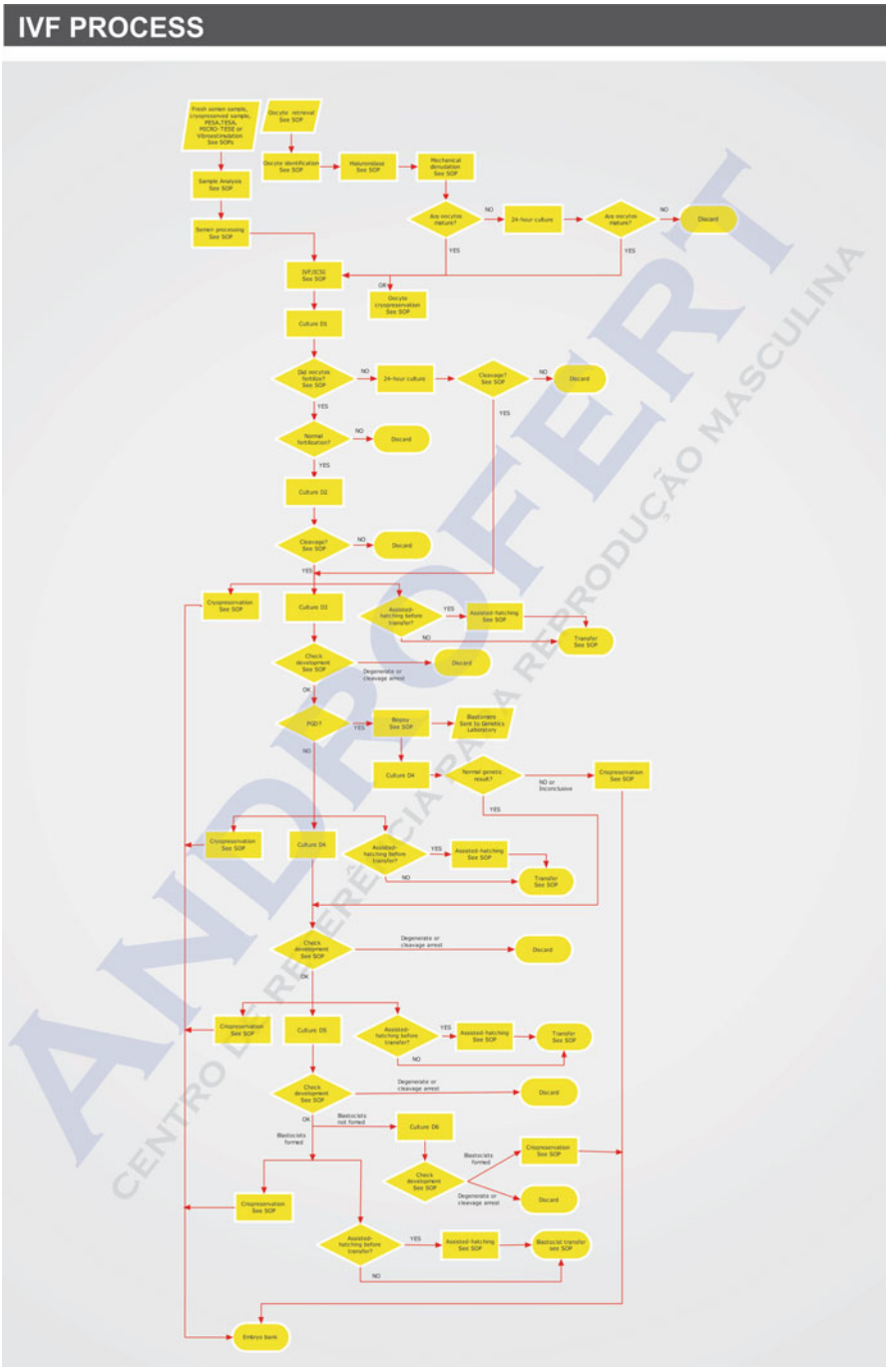

Fig. 4.4 Flowchart—IVF process

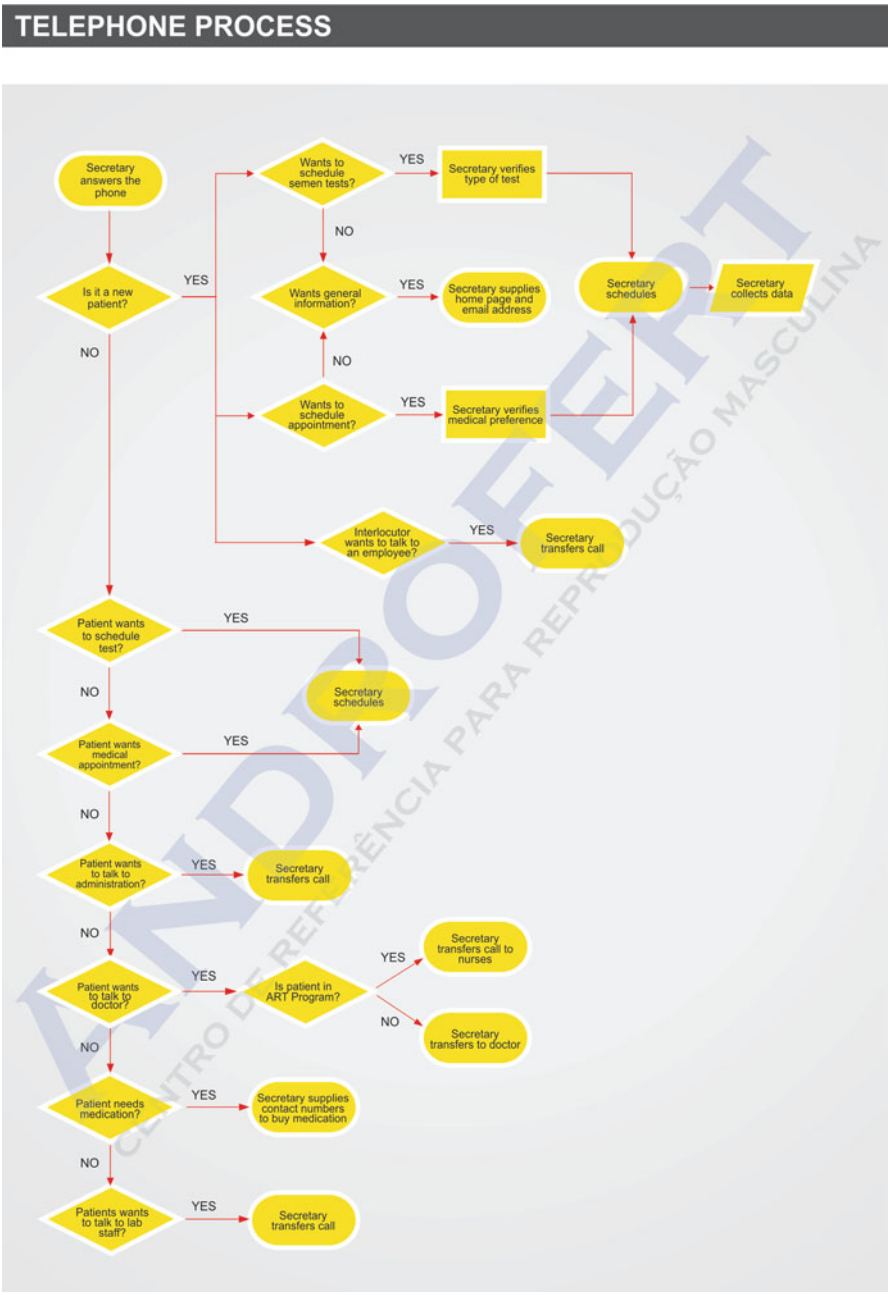

Fig. 4.5 Flowchart—telephone process

Reviewing Processes and Procedures

According to most guidelines, processes and procedures must be reviewed periodically so as to include updates and changes that may have occurred. Regardless of any regulatory demand, processes and procedures do change over time, due to new techniques that may be included, new values of reference that may be established, new routines or resources included, new infrastructure, new equipment, and so on. If changes like the ones exemplified above happen, the process or procedure must be reviewed immediately. If not, it is common practice to review these documents annually.

Reviewing a process is different from reviewing a procedure. A procedure has fixed steps to be followed, so reviewing a procedure requires observation of its completion. At least two people should work on the revision of a procedure: one person executes the steps, while the other observes and checks the description to see if there is any deviation. By the end of the procedure, all deviations detected should be discussed between these two people and later discussed with the manager or director for approval, if changes are necessary. Again, nonconformities may be registered if deviations are inappropriate and should not be occurring.

A process, on the other hand, is more complex. It usually involves many procedures, different departments, and people. Therefore, they should be reviewed by the manager who, along with the director, may identify procedures and decisions involved. Processes can also be discussed with the people involved in the achievement of its objective, for they can have different views of the process and can give valuable suggestions.

Every review must be appropriately registered and approved. The quality manager must keep a control sheet for all documents in use, registering the number of the review, the date it happened, who was responsible for it, who has approved it, and also the changes made. When a procedure suffers dramatic changes, then it is advisable to save the old version of the document for future reference. It is also necessary to have these control sheets signed by the people involved in the review, so as to prove they did happen and to share responsibility.

As previously said, documents must be reviewed every time something changes. However, a document must be reviewed periodically despite significant changes. A very simple idea is to keep a list with all documents with the number of the last review and date. Every month, the quality manager or person appointed can check the list and say which procedures or processes need to be reviewed. Another idea is to have a calendar of reviews, determining which documents will be reviewed in each month. The system used is not important and may be very simple or very sophisticated. It does not really matter, as long as it works. What is important is to keep documents reviewed and updated.

Identifying and Controlling Processes and Procedures

It is very important to be able to identify procedures in a very practical and rapid way. As all procedures involved in the activities performed are described, the list will grow, and simply having a list by name may at some point be impossible to manage. Therefore, it is advisable to create a coding system to name procedures by a shorter name that can be directly related to the department where it is performed.

At the authors' (FB & SE) ART Center, a coding system is used to facilitate this identification. For example, there is a procedure called ANDRO-DIAG-01. It stands for "Andrology Laboratory," "diagnosis test," number 01. All diagnosis tests follow the same base ANDRO-DIAG being numbered in order. Another example is CLIN-PROT-01, which stands for "clinical department," "protocol," number 01. A complete list with codes and names still exist, but this coding system facilitates control and management.

Another important identification is related to the version of the document in use. It is important to add the number of the last review and also the date, so that old and new documents do not get mixed up. It is very hard to keep that under control when working with printed documents, but when everything is in the computer, it is much easier.

See below the heading that can be included in all documents:

At the authors' (FB & SE) ART Center, there is a computer system with a main server that holds all documents and that can be accessed in all work stations. Each user has a password that grants access to different documents, according to their department. Documents do not allow edition or printing. Therefore, we can guarantee that employees have access only to the documents in use. The quality manager is responsible for keeping the original documents safe, for controlling reviews, and for saving new versions and making them available in the appropriate departments.

As with all medical documents, procedures and processes must be included in the backup system in place. Once they are only kept in the computer, no one can afford to lose them, and security is an important issue. Solutions of backup systems should be decided along with the informatics team and have to guarantee recovery of all documents in case of serious computer failure.

Final Considerations

Procedures and processes must be very well defined. How they are described is really not important, once you make sure all staff can understand them. Some countries' regulations determine how to do it; others do not. Follow the mandatory rules you may have to, or if your country lacks rules, use the model you feel most comfortable with. The most important thing is not to "do as the others do" but to find your own way of making things work.

Do not complicate by choosing complex models that will have to be extensively explained. Try to make it simple so everybody can understand and use, and later add more details and complexities while periodically revising your documents and training your staff. One of the basic concepts of a good quality management system is "continuous improvement." This concept has in itself a very comforting aspect that things can and should be improved with time. Therefore, do not stress yourself on making things perfect at first. In fact, if we really follow this concept, things should never be seen as perfect and have to be improved continuously.

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Chapter 5
Training Personnel

Fabiola Bento

The idea of a quality management system is to seek the continuous improvement of all procedures and processes. Most of its tools demand the participation of all staff, and most problem-solving groups and improvement groups have the participation of people from different departments. Because of that, enabling staff to work as a team and to have this broader view of all processes is one of the first training programs that should be offered. Once the staff has a complete view of "how things work" beyond their department, then they will be able to work with the quality management system.

Getting to Know Each Other

In all companies and clinics, people usually have the opportunity to interact and get to know each other in informal settings, such as during lunchtime and reunions. However, in the working place, due to the actual physical separation of departments and evidently different activities and responsibilities, people interact very little and tend to share only the essentials. Therefore, nobody knows exactly the activities performed by the other, unless they work together in the same department. The knowledge they have is very superficial and therefore insufficient to understand all nuances of their activities.

One of the best trainings to start with is the "presentation of departments." It is very simple. Each department prepares a presentation showing what they do, their responsibilities, difficulties, how their work impact their colleagues, patient satisfaction, etc. All important information should be presented, without mentioning the technical aspects of the procedures. The idea is not to train colleagues and enable them to do the job, but to show each other the activities performed and have a better understanding of the processes involved in the services the clinic provides.

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This training should not be done in a hurry. Let staff take their time to absorb all information presented and see how things work in everyday practice. Besides giving people a clearer view of the place they work at, this training tends to put an end to everyday comments and complaints, such as "why is it taking so long?" or "why did this happen?" or "why is the patient complaining?" or "why didn't he or she do it?" Understanding what the other does gives people the strength to unite themselves as a group and also to support each other when needed.

Interdepartmental Observations

Another very basic idea that can help is to let the staff observe each other at work. All training programs demand a certain amount of time, but this one is particularly more complicated as it has to be done during working hours and preferably during "busy" working hours to be effective. The idea is very simple: each team member spends a few hours observing a colleague from another department at work. This observation enables them to understand what the other does in a very realistic way and works even better if done after the first suggested training.

These interdepartmental observations are very effective because they are not limited to pure "conceptual" descriptions of one's work. Instead, they let people see the effort that has to be done and the energy that has to be spent to perform certain activities, besides letting people see the pressures involved and how their colleagues have to deal with them. Many procedures may look rather easy, specially looking from the outside. Therefore, it is quite explainable and honestly very normal for people to underestimate someone else's work and overestimate their own.

SWOT Analysis

A SWOT analysis is a good technique to be used after the previous training described. The staff already knows how all the department work, so now it is time to evaluate the whole system identifying what we do best and what can be improved; what we could do but are not doing at the moment; and what we have to fear and prepare ourselves to. It is a good way of analyzing the scenario and planning the future of the organization. It is also a simple technique that can help the staff have the broader view so necessary for the quality management system.

The creation of the SWOT analysis is credited to Albert Humphrey, a management consultant who devised it during his work at Stanford Research Institute in the 1960s and 1970s. The objective of the SWOT analysis is to identify the internal and external factors that have an impact on the organization's objectives. It may be used in decision-making situations, but also as a means to improve a procedure, a process, or the business as a whole. It depends on the subject of the analysis.

SWOT stands for *S*trengths, *W*eaknesses, *O*pportunities, and *T*hreats. The "strengths" are the internal characteristics that make a business and/or team unique and successful. It includes everything that is good and positive, for example, the

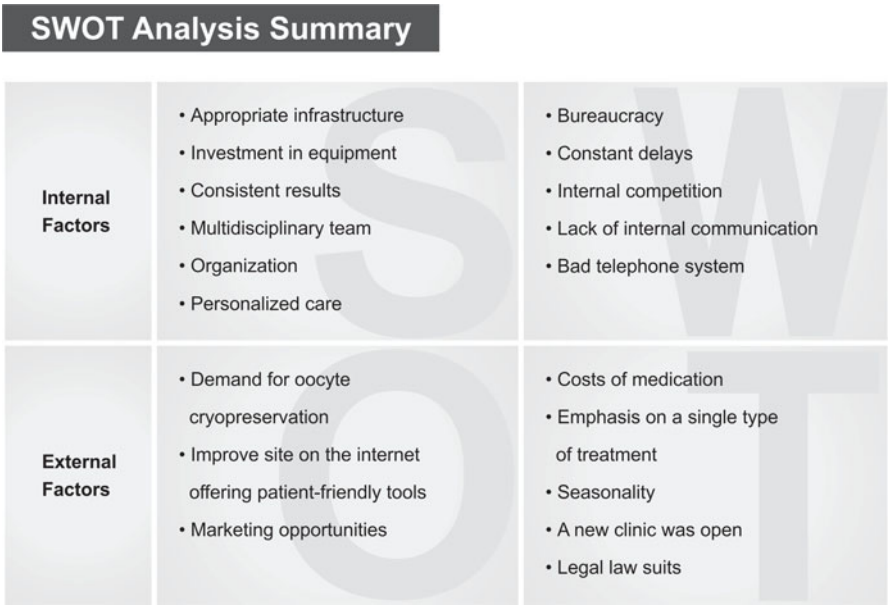

Fig. 5.1 SWOT analysis summary

appropriate infrastructure, or having a motivated team, or offering some type of service that is essential to patients, or the clinic's reputation. The "weaknesses," on the other hand, are the "bad" characteristics that represent a disadvantage a business and/or team has, such as a bad telephone system, or an internal communication system that does not work, or even the existence of too many forms and bureaucracy. These are all internal factors that influence performance directly. The strengths should always be used to our advantage and the weaknesses should be identified and seen as improvement opportunities.

Then, there are the other two aspects, which are external. The "opportunities" are the external chances of growth, more profits, or success. They include the demand for a certain type of service that can be developed, or the development of a new technique that can be absorbed and offered, for example. On the other hand, the "threats" are the external elements that may cause trouble or may harm performance, for example, the opening of another clinic that can represent a real competition or the increase in all materials prices that will impact the price of the service offered and so on.

A good way of offering this training is to divide it in two different days. On day 1, present the technique and explain the terms giving practical examples. Hand in templates to be filled in and give a few days, a week, for example, for the staff to think about it and come up with ideas. After everybody turns in their "homework," summarize the information and present it on day 2, when you can then work on suggestions and strategies to address the points that were raised. On day 2, you may end up with the summary shown in Fig. 5.1.

The results of this analysis may be surprisingly pleasant. People in different departments have different points of view, as our clients' points of view are most of the times different from ours. A lot can be learned from this exercise. Besides, it certainly makes the staff reflect about their own performance and how it affects the general performance. This is a good way to trigger self-evaluation and general improvement. From this analysis, new services can be developed and offered, procedures can be reviewed and improved, etc.

Ethical and Moral Values

Conceptually, companies are basically a group of people working together. As people behave according to their own individual "values," so do companies. Therefore, it is very important to define some "common" principles to modulate people's behavior inside the working place. A mission usually states the ethical values of a company but does not describe the everyday behaviors which show our moral values. So what a mission states can be interpreted and actually put into practice in very different ways according to each individual principles and values. For a mission to be fulfilled accordingly and uniformly, there must be some common shared values to guide your team.

During this training, the staff can define these values, discuss how to apply them, and analyze the implications of these values. Even though this training, which is more of a general discussion, may seem very unimportant, we must bear in mind that many countries around the world have very poor educational systems. Besides, having attended a good school or university does not guarantee good moral values, as it depends on individual family and life experiences. Moreover, the idea here is to build "common values," and it is impossible to assume people have the same principles simply based on their curriculums.

Values can be divided in values related to the internal public which is basically the staff and to the external public which is basically our patients. Read below a few examples of shared values which can be applied to both publics:

- Honesty and transparency
- Clear and immediate communication
- Respect people
- Respect patients' rights to parenthood
- Confidentiality
- Respect legislation

Just as an example, let us analyze the value "respect people" (Fig. 5.2). It is important to say that the values defined will only be followed if the "leaders" of the clinic set the example. A strong leadership is what guarantees real training results. The leaders must be directly involved and must be the first ones to follow what was established. As quality pioneer J.M. Juran said, "To my knowledge, no company has attained world-class quality without upper management leadership" [1]. A manager,

Example of Moral Value

RESPECT PEOPLE

WHO	HOW
Secretary / Receptionist	• Being cordial • Understanding patients' needs • Not letting patients wait • Being helpful • Informing patients of delays or any other problems • Trying to schedule appointments at the best time for patients
Nurse	• Being cordial • Treating patients according to their individual needs • Being helpful • Explaining procedures so as to calm patients • Understanding patients' worries and nervousness • Following correct technical procedures at all times
Laboratory Technician	• Being cordial • Doing everything possible to help patients accomplish their parenthood dream, for example, exhaustively search semen samples, working extra hours when necessary to finish procedures, etc • Giving clear explanations • Being honest and transparent • Following the described laboratory procedures • Communicating problems and deviations immediately
Physician	• Being cordial • Making an exhausting investigation • Explaining diagnosis and treatment clearly • Giving patients a choice based on well-explained treatment options and outcomes • Following correct technical procedures at all times • Admitting limitations

Fig. 5.2 Example of moral value

who does not respect his staff, does not listen to them, and does not help them, can never expect his staff to be helpful and respectful toward their colleagues or patients. They may be so, but it is impossible to demand something we do not do ourselves, at any level.

Besides, the way things are repeatedly done will determine the everyday behavior. If we always let our patients wait for hours in the reception area, this becomes a habit and will happen all the time as if this were something "normal." It does not

have to be normal unless we assume it is. Some recurrent problems are directly related to these repetitive behaviors, and some changes in principles and values may need to be analyzed to correct nonconformities. A simple review of a procedure may not guarantee the end of the problem.

In other words, we become what we do repetitively. An English proverb says that "practice makes perfect." However, its interpretation must be done with caution. A "good practice" may produce "perfect results," while a "bad practice" may well lead to "imperfection." Aristotle, the famous Greek philosopher, used to say that, "the moral virtues are produced in us neither by nature nor against nature. Nature, indeed, prepares in us the ground for their reception, but their complete formation is the product of habit."

Quality Management Training

This part of the training program will depend a lot on the quality management system that is being established. It is important to cover all aspects of the system and also train your staff about the specific guidelines that are going to be followed, if the case. For example, if an ISO 9001 will be used and, especially if a certification is part of the goal, give a specific training about it, so people can understand the process.

When procedures and processes are being described for the first time, involve your staff in the development of these documents and make sure they are trained. The staff must also be trained on how to use all tools created, such as the registration of nonconformity and how to find the root cause and suggest corrective actions. Specific training should be given to ensure the tools will be used, the procedures will be followed, etc. Figure 5.3 shows a few examples of quality management system training programs.

Evaluating Performance

Every training program given should be registered. One cannot evaluate results without properly controlling the information taught. Besides an attendance list, each team member should have a training file, where all internal and external training programs attended are registered (Figs. 5.4 and 5.5).

From these individual training forms, the staff can be evaluated. Was the training program effective? Was the new technique taught incorporated in daily work? Did the training improve performance? Is the tool presented being appropriately used? And so on. When an external training is offered, especially when it involves a degree or a specific course such as a language course, use the report cards of the institution as an evaluation document.

QMS Training Programs

TRAINING	DEPARTMENT
Mission Statement	All
Quality Policy Quality Indicators and Objectives	All
How to register a nonconformity and corrective actions	All
How to register preventive actions	All
How to describe procedures and processes	All
Procedures/Processes	Individualize by department
How to review procedures and processes	All
Internal Auditors	Only selected staff
Auditing Process	All
Internal Communication	All

Fig. 5.3 QMS training programs

Another way of evaluating the efficacy of a training program is by observing indicators already used. For example, if the secretaries attended a training program to better assist patients, check if the results of the satisfaction questionnaire on this specific item have improved, the efficacy of a laboratory training program can be checked on the laboratory indicators or results, and so on. When a training program does not produce the expected results or, in other words, is ineffective, a new training can be offered or, depending on the case, a closer analysis of the individual performance should be made to verify if the problem was with the training itself or with the person involved.

Giving Feedback

Feedback is the basis of all human relationships. It determines how people think, how they feel, how they interact, and in most cases how they face their daily responsibilities. We are generally very fast to point mistakes but usually very slow to recognize right actions and accomplishments [2]. In fact, we usually give only

TRAINING ATTENDANCE LIST

Date:
Time:
Training Description:

Objective:
Given by:

	Participants	Departament / Position	Signature
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

Fig. 5.4 Training attendance list

corrective and negative feedbacks, and even sometimes offensive, and tend to never give positive feedback.

The type of feedback we give determines the response we get. When a team is not working as we wanted or if we detect inappropriate behaviors, that may mean we are not giving enough feedback or the feedback we are giving is not appropriate. Giving feedback is an art and is one of the most important aspects of guiding a team toward common objectives. People need to know how they are doing regardless of their position in the hierarchy.

There are a few important aspects of giving feedback that should be observed:

1. Give feedback regularly establishing a periodicity.
2. Choose the appropriate time to give feedback. Feedback should be preferably given immediately; however, when dealing with corrective feedback, analyze the situation. Never give feedback if the working place or people involved are too tense, and never criticize someone in public.

INDIVIDUAL TRAINING RECORDS

Name: Departament/Position:

DATE	TRAINING	OBJECTIVE	COMMENTS	TRAINING EFFECTIVE?	
				YES	NO

Fig. 5.5 Individual training records

3. Plan your feedback in advance, so as to make it balanced (positive and corrective), to be objective, to describe the behaviors appropriately without false information or exaggerations, and to describe the behavior you want to see.
4. Be ready to listen. Especially when a corrective feedback is given, the person has the right to explain herself and tell you how she feels about it. This information may help you understand the problem, and the suggestions made can help find solutions.

Giving feedback is a big challenge. People react differently to different types of feedback. The better you know your team, the better you will become in giving feedback. Some people react well after receiving a corrective feedback because it actually triggers the motivation they need to improve. On the other hand, there are people who do not react well at all and get very frustrated about their work. Instead of inducing an appropriate behavior, it may produce a behavior even worse than the first one. The way you give your feedback has to be adapted to each personality trait.

Final Considerations

When creating your quality management system, make sure to deeply analyze your staff. Are they prepared for this? Most of the times they are not, and it is just not fair to blame them if the system does not work. As previously said, a quality management system is completely dependent on people, so preparing them is essential.

Besides, each team has different needs, and it is simply impossible for anyone to say the exact training programs that should be given to your team. Take some time reflecting about it, talk to your staff, talk to people who have already been through the process, read books and articles about it, and then decide what to do. There is no such thing as a "perfect" recipe to follow.

In short, dealing with a quality management system is ultimately dealing with people, and they are inevitably, as all human beings, different and full of imperfections. When forming a team, people interact differently too, and that is what makes teams so different and each working place so unique.

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Chapter 6
How To Get Information

Fabiola Bento

Information is the key element of a quality management system. There are two aspects involving information: how to gather information and how to pass on this information to the team. Information can be gathered in the form of reports, questionnaires, indicators, meetings, etc. A quality management system must always work on data and never on assumptions. Therefore, it is very important to be able to see exactly how things are going in terms of "numbers" and with realistic data, instead of impressions and isolated opinions. All data has to be quantified and its importance evidenced through reports and results.

Information must be passed on with a proper communication system. Without one, it becomes practically impossible to work as a team toward the same goal. All staff in all departments must have a common knowledge of what goes on inside the clinic to be able to understand their role and responsibility in everything that happens. Without communication, people are isolated in their "private worlds" and are unable to see the big picture. Without communication, people overestimate what they do, underestimate what others do, and cannot see improvement opportunities. Without communication, the quality management system is dead.

Regular Reports and Indicators

As part of the quality policy and objectives (see details in Chap. 3), many reports and indicators are periodically verified and analyzed. There should be a person responsible for collecting the information and preparing reports, especially when there is no quality manager. Moreover, a periodicity must be established and of course respected, so as to detect problems and deviations at a manageable time.

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These reports and indicators should be communicated internally to keep the staff informed of their performance and/or performance of different departments. Efforts and achievements must be recognized, and problems must be faced by the group as a cohesive team.

A good example is the data collected through satisfaction questionnaires (see details in Chap. 3). These questionnaires represent a direct communication with patients and that is when they can express what they think without having to interact with anyone. Through the results of satisfaction questionnaires, we can understand how we are really doing in terms of satisfying our clients. Therefore, it is very important to show our team the results of these questionnaires and also to discuss deviations and try to find solutions when a problem arises.

The results of Satisfaction Questionnaires can be publicized internally as follows (Fig. 6.1). Choose a form that everybody can understand. You can publicize a simple excel table with the data collected or graphs such as the ones given in the example. Make sure everybody can read and understand the results, instead of focusing on what is visually "more beautiful." Graphs can be great, but only if all your staff is familiar with them.

Internal Communication

It is very important to have a proper internal communication system to be used on a daily basis. There are many systems available, including free ones that can be obtained through the web. The important thing is to choose one that is easy to use and teach your staff how to use it. Immediate information can be passed on using this system, as not everything can wait until a formal meeting. Problems can be solved immediately and improvements can be made right away. Information can be passed on to the whole team at once, without having to gather everybody for a meeting. Besides, this system can provide more agility, can eliminate the communication that used to happen over the phone and took a longer time, and can restrain people from leaving their work stations to talk to someone else in another department. Everything can be made through the computer.

Improvement Groups

Continuous improvement is part of the quality management system. Even though improvement must be incorporated in the daily routine, specific aspects and situations can be studied by "improvement groups." An improvement group can be formed every time a situation does not have a simple solution and mainly when it involves more than one department. Meetings should be held regularly with the participation of one member from each department or departments involved. See below the example of an improvement group (Fig. 6.2).

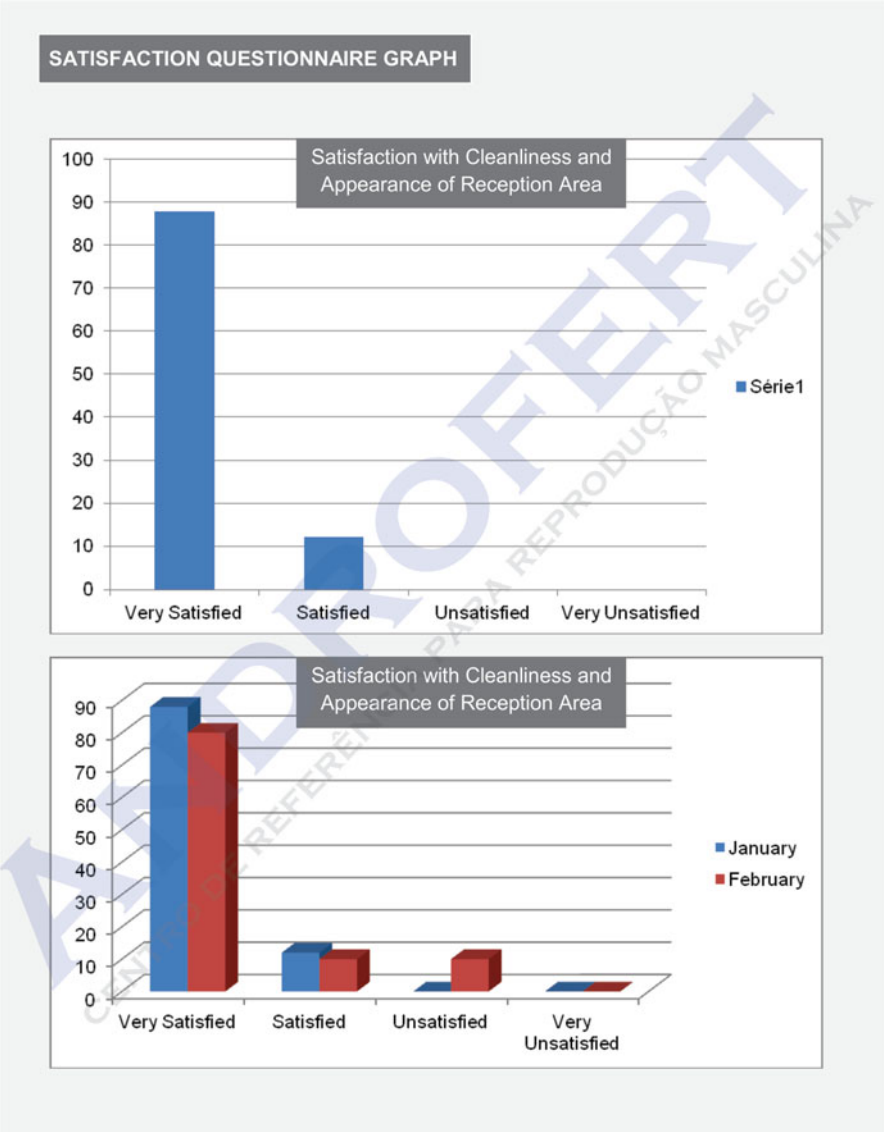

Fig. 6.1 Satisfaction questionnaire graph

Figure 6.2 shows only the "cycle" of an improvement group, determining the objectives of each meeting. Decisions as well as all suggestions and changes taken during these meetings need to be registered. The objective of an improvement group is not only to solve a problem but also to improve the way things work and anticipate future problems. Preventive actions may be taken, if that is the case, and should be appropriately registered.

IMPROVEMENT GROUP	
PROBLEM	Increase in costs will lead to an increase in treatment prices
QUESTION	How can we diminish costs making treatments more affordable?
PARTICIPANTS	Laboratory Supervisor, Chief Nurse, Chief Secretary, Chief of Cleaning and Maintenance, Manager, Quality Manager
DAY 1	Manager presents actual costs
	Brainstorm what can be changed without affecting quality
	General views and opinions
DAY 2	Practical suggestions of changes that can be made in each department
	Define what will be changed, how and when
DAY 3	Feedback on what was changed and impact on costs
	New changes needed? Restart cycle

Fig. 6.2 Example of improvement group

Internal Auditing

Auditing is part of any quality management system, regardless of its being a formal and certified one or not. In general, auditing happens at least once a year, even though it is advisable that it happens more frequently whenever possible. All staff must be trained on auditing; auditors should have previous training on how to audit, and the rest of the staff should learn what happens during the auditing process. It is important to understand that the system is not only audited to detect problems but mainly to verify compliance. Therefore, especially during an internal auditing process, the main idea is to verify compliance and consequently detect deviations and improvement opportunities.

The process of auditing should be documented as any other process. It must be systematic and documented to really promote quality improvements. All areas covered by the quality management system must be audited, from the cleaning to the laboratory processes. Before performing it, a plan must be established, with details such as date and time, department to be audited, auditor in charge, etc. (Fig. 6.3). This should be well communicated so that everybody knows when it is going to happen.

Before the auditing day, auditors should gather to discuss what will be evaluated and to "study" for the auditing day itself. It is important not to have auditors auditing the departments where they work. Therefore, auditors will have to read instructions and processes of the department they are going to audit before really doing it and also prepare checklists with critical aspects of each process (Fig. 6.4).

During the auditing process, auditors should present the objectives of the auditing to the employees involved and ask them to remain calm and act normally. The auditor can ask questions about the process being audited and also check documents and data. All observations should be documented to be analyzed later. As previously stated, the objective of the auditing process is to verify compliance and not focus on

AUDITING PLAN

DATE	TIME	AUDITOR	DEPARTMENT	PROCESSES

Fig. 6.3 Auditing plan

INTERNAL AUDITING CHECKLIST

Date:		**Time:**	**Auditor:**	
Department:			**Employees Involved:**	
Process/Instructions:			**ISO 9001 items (if the case):**	
No	Question/Critical Aspect		Evidence/Observations	CL
01				
02				
03				
04				
05				
06				
07				
08				
09				
10				

CL (classification): NC – non-conform; IO – improvement opportunity; C – conform.

Fig. 6.4 Internal auditing checklist

INTERNAL AUDITING FINAL REPORT

Auditors:

Departments audited:

Processes audited:

The non-conformities and improvement opportunities, if any, detected during the last auditing process were adequately treated? ↑yes ↑no

Comments:

#	Non-Conformities	*NC*
1		
2		
3		
4		
5		
#	Improvement Opportunities	*PA*
1		
2		
3		
4		
5		

Date:

Auditor Responsible for Final Report:

NC = non-conformity (insert number if non-conformity was registered)

PA = preventive action (insert number if preventive action was registered)

Fig. 6.5 Internal auditing final report

finding nonconformities. Of course, nonconformities may be found and should be documented, but the main objective is still to improve the system through a positive approach. The auditor should always try to give feedback right away, but it can be done at a later time if not possible.

After the auditing process itself, the auditor should write a final report of the auditing performed (Figs. 6.5 and 6.6), detailing nonconformities and improvement opportunities detected, suggesting preventive actions, etc. Depending on what is detected, additional meetings may have to be scheduled to discuss specific processes,

INTERNAL AUDITING FINAL REPORT

DEPARTMENT / PROCESS Refer toindividual checklist	AUDITING TEAM: CF, Fabiola Bento, SVJ, TV

The non-conformities and improvement opportunities, if any, detected during the last auditing process were adequately treated? (X) Yes ( )No

Comments_____

#	Non-conformities	NC
01	During the auditing process in the Andrology Lab, the auditor verified that the actual practice with regard to room temperature monitoring did not match the written policy of twice-a-day documentation.	201
02	During the auditing process in the Andrology Lab, the auditor verified that the warm-stage temperature was within acceptable limits in accordance to the defined range, but actual values have not been registered in the form.	201
03	During the procedure of sperm wash for ICSI, the auditor observed that the lab technician did not perform replicate counts for sperm number determination as described in the SOP ANDRO-TERA-01.	202
04	During the auditing process in the Operation Room, the auditor observed that that the scheduled diagnostic hysteroscopy was not performed because the patient had not received the pre-operatory information and didn't know about the anesthesia and necessary preparation.	203

#	Improvement Opportunities	PA
01	The auditor suggested that a more precise micropipette device be purchased to be used during Sperm Cromatin Integrity Assays which require 1 to 10 microliters pipetting.	50
02	The auditor suggested to review the SOP ANDRO-DIAG-02 because the actual practice of counting at least 200 spermatozoa in each replicate, taking the average, and determining the acceptability of results is not described in detail in the written policy.	-----
03	The auditor suggested that SOP FIV-PROT-12 could be improved with regard to communication between embryology and administrative staff whenever assisted hatching is carried out since it involves extra fees.	-----
04	The auditor suggested that SOP CLIN-PROT-14 could be improved by adding clear written instructions with regard to patient gowning before admission to the embryo transfer room.	-----

DATE: June 16, 2011	Fabiola Bento, MBA Quality Manager

Fig. 6.6 Internal auditing final report practical example

especially those involving technical aspects. Whatever is done, there should be appropriate documentation, and final decisions must be documented as well. Figure 6.6 shows a practical example of a final report with auditors' observations.

External Auditing

External auditing may have two different objectives:

1. Certification
2. Verification by an independent body

The importance of this type of auditing depends on the objective of one's quality management system. Some need a certification to comply with national regulations and, therefore, will obligatorily have an external auditing to be certified. Others may simply want to have experienced auditors, instead of own trained auditors, to perform regular auditing, to make sure their systems are working appropriately.

Regardless of one's choices and needs, the external auditing has the same objective of the internal auditing, that is, verify compliance. The only big difference is that when an external auditing is performed for certification, finding nonconformities may mean that certification will not be granted or actual certification may be canceled, depending on the gravity of the nonconformity found.

The periodicity of the external auditing is determined by the certification body. For example, companies ISO 9001 certified are audited annually to renew their certificates. If it is the simple verification by an independent body hired by the company, this periodicity may vary, especially when internal auditing is also used.

Regular Meetings

Another important way of gathering information is by holding regular meetings with your staff. These meetings should preferably be separated by departments and should have a reasonable periodicity to allow communication to happen. Meetings with the whole staff should happen only when necessary and to deal with very specific information, because they tend to turn into long and nonproductive meetings. Department meetings are usually more productive because issues are dealt with in a more direct and practical way.

The periodicity of these meetings depends on the amount and type of work of each department, but it is advisable to hold them at least once a month. In the beginning, meetings are usually long, especially for lack of experience, but with time and focus on objectivity, these meetings will be shorter and more productive. If they are frequent, they will be even better, for there will be no "accumulated" subjects to be discussed.

All meetings should be registered (Fig. 6.7). The meeting's minutes should be written and saved in a proper place so everybody involved can read what was decided

IVF LABORTORY MEETING		
Date:__/__/__	Time: ___:___	
Participants:		
	PENDING SUBJECTS	DECISIONS, IF ANY
1		
2		
3		
4		
5		
	SUBJECTS/DATA DISCUSSED	DECISIONS, IF ANY
1		
2		
3		
4		
5		
	PRESENTED NEXT MEETING	
1		
2		
3		
4		
5		

Fig. 6.7 IVF laboratory meeting minutes

and also check on any pending subject or responsibility. It is also important to have these meetings registered in case an employee is absent on the day of the meeting. He can then read what was discussed and be able to follow any new orientation determined in the meeting.

Conclusion

As previously said, information is the key element of a quality management system. How data will be collected and how communication will happen is a personal choice, based on the size, profile, and needs of all professionals who work in a particular setting. It is difficult to dictate a rule or say what the best way is. This chapter only presented some basic ideas about what is usually advised and should not be seen as "all that can be done." It is definitely a good start though.

As every aspect of a quality management system is interrelated, communication is what feeds the QMS and brings it to life. It becomes impossible to make decisions and expect the team's involvement when results and outcomes are not known. As Dr. Diane L. Kelly said in her book, a good communication process "which ensure individuals and teams have the information they need, when they need it, to make effective and timely clinical and organizational decisions" should be designed and implemented [1]. Even though communication is not usually directly mentioned in regulations and directives, it is what will, in the end, determine the success of your quality management system.

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Part II
Reproductive Laboratories

Chapter 7
The Role of Reproductive Laboratories in the ART Clinic

Sandro Esteves and Ashok Agarwal

Reproductive laboratories (RL) are key elements of clinics performing assisted reproductive technology (ART). They include both the andrology and the embryology clinical laboratories, which may also work in association with other laboratories, such as genetic, endocrine, and pathology.

Reproductive laboratories' main goals are to meet patients and physicians' needs. Specific functions include proper identification, transportation, storage, processing, and examination of human gametes with subsequent reporting of results. Reproductive laboratories attempting to accomplish the above-cited tasks in a quality management philosophy should address three questions that constitute the primary pillars of quality, that is, (1) what do you do? (2) how do you do it? and (3) how do you make sure that what you do is being done in the proper manner? (Fig. 7.1).

The concept of quality management (QM) can be described as a systematic program that monitors and evaluates the quality of services being provided to make sure they meet or exceed customers' expectations. A quality management system designed for reproductive laboratories should integrate all quality-related functions and activities at all levels, which includes quality control (QC), quality assurance (QA), and quality improvement (QI), and it should involve all employees and other people associated with the laboratory processes. Quality control is the establishment of quality specifications for each piece of equipment and/or procedure and involves ensuring that they conform to established limits and standards. Quality control activities begin before any sample is collected and end with the presentation of results and communication to patients/clinicians. Quality assurance focus on documentation to

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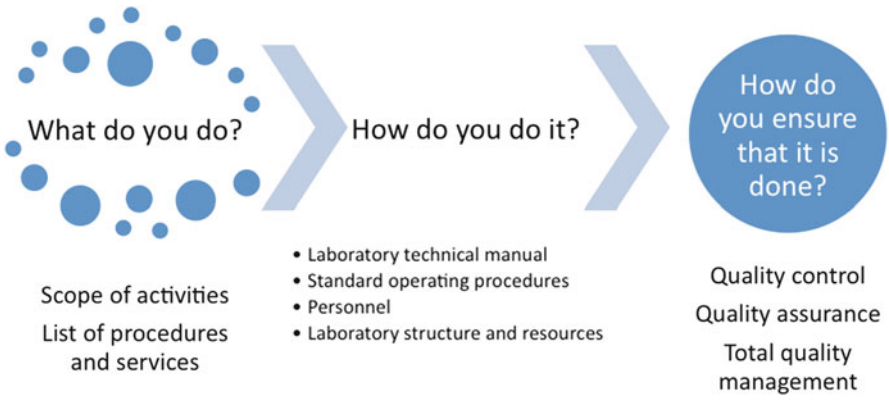

Fig. 7.1 The three pillars of quality for reproductive laboratories

ensure that a product or service satisfy its required quality characteristics, while QI focuses on the progressive increase in the quality and efficiency of each aspect of the work and activities related to patient care and internal production [1].

Despite not being universally mandatory for ART clinics, implementation of a quality management system has been enforced by regulatory/accreditation agencies in several countries. Specific recommendations for accreditation of ART clinics and certification of its employees have been designed with the purpose to protect public health and to ensure safety in assisted reproductive techniques. As examples, in the United States three agencies regulate ART [2]. At the federal level, the Centers for Disease Control and Prevention (CDC), which is concerned with public health and safety, collects and publishes data on ART procedures. The CDC provides education and information to enhance health care decisions, including best practices in laboratory medicine. The Food and Drug Administration (FDA) controls approval and use of drugs, biological products, and medical devices and has jurisdiction over screening and testing of reproductive tissues, such as donor eggs and sperm, while the Centers for Medicare and Medicaid Services (CMS) is responsible for implementation of the Clinical Laboratory Improvement Act (CLIA) to ensure the quality of laboratory testing [3]. Laboratory testing for the diagnosis of infertility, such as semen and blood analyses, is covered by CLIA. Embryology procedures are not considered diagnostic and do not fall under CLIA's mandate. Therefore, the College of American Pathologists (CAP) in collaboration with the American Society for Reproductive Medicine (ASRM) developed the Reproductive Laboratory Accreditation Program (RLAP), which provides accreditation and standards for reproductive laboratories such as andrology and embryology laboratories [4, 5].

Activities of reproductive laboratories are regulated in other countries as well. Within the European Union, the European Parliament has issued directives concerned with increasing quality and safety in application of human tissues and cells to the human body. These requirements were laid down in a single original directive (2004/23/EC) and two subsequent technical directives (2206/17/EC and 2006/86/EC) [6].

In South America, the Brazilian Sanitary Surveillance Agency issued similar directives in 2006 (RDC33), which was subsequently revised in 2011 (RDC23) [7]. Both the European and Brazilian directives aim at increasing quality through mandatory implementation of a comprehensive and validated quality management system that involves the presence of adequately trained and certified staff, full documentation and formulation of standard operating procedures, and quality control and quality assurance at all units performing assisted reproduction.

Independent of its origin, the requirements issued by different regulatory agencies and accreditation programs attempt to promote accuracy and reproducibility of methods and results as well as to minimize the risks of transmitting infectious and other potential risk factors for both patients and their offspring. In this section, we provide an overview of how reproductive laboratories can be integrated in a quality management system. We also provide tools and practical examples that will aid in the development of a quality management plan for both andrology and embryology clinical laboratories.

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Chapter 8
Defining What Reproductive Laboratories Do

Sandro Esteves and Ashok Agarwal

Reproductive laboratories should define the list of procedures under their scope of activity (see example in Table 8.1). Even though the embryology laboratory is the core of ART clinics, the roles of the andrology laboratory cannot be underestimated as it comes into play not only in the diagnosis of male factor infertility, which is contributory in 50–60% of infertile couples [1] but also in infertility treatments.

The typical clinical andrology laboratory performs some or all of the following diagnostic and therapeutic procedures: routine semen analysis, computer assisted semen analysis (CASA), semen biochemical tests, presence and quantification of seminal leukocytes, detection and quantification of antisperm antibodies in the semen, serum or cervical mucus, tests of sperm function (sperm membrane integrity, reactive oxygen species [ROS], seminal antioxidant capacity, sperm DNA integrity, acrosome reaction and sperm penetration assays), cryopreservation of spermatozoa (either ejaculated or surgically-retrieved), and preparation of sperm for intrauterine insemination or in vitro fertilization. Semen is a complex biological fluid and its assessment requires several tests and technical skills. Critical factors to diagnostic testing performed by andrology laboratories include accuracy (degree to which the measurement reflects the actual or true value) as well as precision (reproducibility of results). High-quality andrology laboratories have experienced technologists and a quality system in place to ensure accuracy and precision. Accuracy is a challenge for the modern andrology laboratory as many semen tests still require manual microscopic skills. It has been reported that the coefficient of variation is high when different andrology laboratories evaluate the same semen specimen [2, 3].

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Table 8.1 Sample of scope, description, and list of procedures performed by clinical reproductive laboratories at Androfert

Andrology laboratory	Embryology laboratory
Scope and description	
The andrology lab performs the following activities: (1) diagnostic testing on semen, seminal plasma, and cervical mucus; (2) sperm cryopreservation; and (3) sperm processing for therapeutic procedures	The embryology lab performs procedures involving human reproductive tissues, gametes, and embryos for therapeutic purposes
The andrology lab is a controlled environment with a dedicated and independent air filtration and positive pressurization system. An air compressor generates positive pressure (702 m^3/h) by insufflating external air through a series of filters (prefilters [G3[a]+F8[b]], impregnated activated carbon filters, and high-efficiency particulate air [HEPA][c] filter). Laboratory access for maintenance and replacement of equipment and materials is restricted, and the access door (with viewer) is equipped with an electronic password controlled system monitored by external surveillance. Technical personnel access to the laboratory is made through an antechamber with an area for dressing and hand-washing. The air filtration system is certified biannually by a third party company according to the official regulatory requirements. Laboratory constructive materials meet the standards required by the national regulatory agency and are detailed in the clinic descriptive manual. The workstations have been ergonomically designed to optimize comfort during routine workload. Chairs are comfortable and adjustable to the height and backrest, and microscopes have height adjustable eyepieces. The andrology lab has an individual air cooling/heating system	The embryology laboratory and its adjacent areas (operating room, dressing room, and embryo transfer room) were designed as an integrated cleanroom[e] facility controlled by a dedicated central air-handling system for humidification, cooling/heating, and filtering particulates and volatile organic compounds. Technical personnel access to the laboratory is made through an antechamber with an area for dressing and hand-washing. A separate antechamber is used for cleanroom gowning. Laboratory access is permitted by an electronic password control system monitored 24 h a day by external surveillance. Cleanrooms are certified biannually by a third party company according to the national regulatory requirements. Laboratory design and constructive materials meet the standards required by regulatory agency and are detailed in the clinic descriptive manual. The embryology lab is equipped with stainless steel workstations designed to optimize comfort and cleaning during routine workload. Chairs are comfortable and adjustable to the height and backrest, and microscopes have height adjustable eyepieces. There is no source of ultraviolet or ionizing radiation and illumination is made by using controlled intensity incandescent lamps only. A remote alarm system monitors ambient lab temperature and noise levels, power supply, and incubators 24 h a day. The laboratory and adjacent areas have an emergency power backup system with 120 h autonomy. Carbon dioxide tanks are located outside the laboratory and incubators are fed with CO_2 using a dual system stainless steel pipelines
Sperm cryopreservation and processing of sperm for therapeutic procedures are carried out inside a biological safety cabinet—class II, type A1[d]	
Activities	
Diagnostic procedures	Therapeutic procedures
Standard semen analysis Macroscopic parameters (color, volume, pH, viscosity, liquefaction, and agglutination) Microscopic parameters (sperm concentration, total and progressive motility, morphology, presence of round cells)	*Preparation of dishes for embryo culture and gamete handling*
Detection of leukocytes in semen Myeloperoxidase test (Endtz)	*Follicular fluid and oocyte handling* Examination of follicular aspirates Oocyte identification

Sperm vitality and membrane integrity
- Eosin-nigrosin test
- Hypo-osmotic swelling test (HOS)

Sperm washing and analysis
- Discontinuous colloidal gradient centrifugation
- Swim-up method
- Simple wash
- Retrograde ejaculation specimens

Biochemical seminal analysis
- Fructose qualitative

Antisperm antibody assessment
- Direct antisperm antibodies test on sperm
- Indirect antisperm antibodies testing (seminal plasma, serum or cervical mucus)

Azoospermia screen procedure

Sperm DNA damage testing
- Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)
- Sperm chromatin dispersion technique

Therapeutic procedures

Sperm preparation for intrauterine insemination (IUI)
Sperm preparation of conventional in vitro fertilization (IVF)
Sperm preparation for intracytoplasmic sperm injection (ICSI)
Retrograde ejaculation sperm preparation for ART
Preparation of cryopreserved sperm for IUI, IVF, and ICSI
Semen cryopreservation

- Oocyte handling
- Oocyte quality and maturity grading
- Insemination of oocytes

Sperm handling for IVF/ICSI
- Semen processing for IVF/ICSI
- PESA, TESA, TESE, micro-TESE sperm processing for ICSI
- Sperm selection for ICSI

In vitro fertilization and micromanipulation techniques

Zygote handling
- Determination of fertilization
- Zygote quality evaluation

Digital imaging recording

Embryo handling
- Embryo culture and grading
- Embryo biopsy
- Assisted hatching
- Preparation of embryos for transfer

Cryopreservation

Surgically retrieved spermatozoa from the epididymides/testes
Oocytes
Zygotes and embryos
Reproductive tissues
Thawing procedures

Source: Androfert—Andrology and Human Reproduction Clinic, Brazil, with permission

[a] Filter G3: primary filter to collect coarse dust with a dust spot efficiency of 80–90%

[b] Filter F8: secondary filter to collect and retain small particle dust with a spot efficiency of 90–95%

[c] HEPA (high-efficiency particulate air filter): small particulate air filter with 99.97% minimum particle-collective efficiency for particles as small as 0.3 μm

[d] A class II, type A1 cabinet meets requirements for the protection of product, personnel, and the environment. This cabinet recirculates approximately 70% of the air through a supply filter and exhausts approximately 30% of the air through an exhaust filter to the room

[e] A cleanroom is a controlled environment in which the concentration of airborne contaminants is controlled to specified limits

These skills improve with daily use, use of quality control standards, as well as continuing proficiency testing (also known as external quality control). When both accuracy and precision are assured, the clinician is able to rely upon the values provided by the andrology laboratory and safely direct further work-up, diagnosis, and counseling of the infertile male. For the tertiary referral center, it is important to offer a broad spectrum of specialized semen testing performed on-site as this provides timely results. However, this is not true for all centers as the benefits of quick turnaround for testing are outweighed by the cost of performing the tests, quality assurance, and maintaining trained personnel for specialized tests. Even though accreditations are available for andrology laboratories, it should be noted that most facilities associated with ART clinics perform only standard semen analysis and have a significant lack of standardization in both the performance and reporting of semen analysis results [4].

The embryology laboratory performs some or all of the following: culture medium preparation, examination of follicular aspirates with oocyte identification, oocyte quality and maturity grading, sperm preparation, sperm selection, insemination of oocytes, determination of fertilization and zygote quality evaluation, embryo culture and embryo grading, embryo biopsy, assisted hatching, preparation of embryos for transfer, oocyte/embryo/sperm cryopreservation, and micromanipulation of human oocytes and/or embryos. Progress in the field of ART has expanded greatly in the last decades. Better techniques and equipment have made it possible to improve ART outcomes while reducing multiple pregnancies. It is now possible to cryopreserve both gametes and embryos with much better efficiency than in past years and to genetically screen embryos before transfer. All of these advancements pose increasing challenges for ART laboratories in terms of quality control and quality assurance as they should have reproducible processes from 1 day to the other in order to maintain sustainable results without jeopardizing the health of offspring.

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Chapter 9
Explaining How Reproductive Laboratories Work

Sandro Esteves and Ashok Agarwal

In order to perform the procedures under their scope of activities, reproductive laboratories shall have the following (1) written instructions of how procedures are to be carried out, (2) personnel to perform procedures and routines, and (3) resources and facilities to allow procedures to be performed.

Laboratory Manuals

The development of the laboratory procedure manual defines all aspects of work in a standardized manner. In theory, most procedures performed by RLs are fairly well standardized. These procedures have been designed to either diagnose or treat conditions that impair the reproductive potential of a given couple. In daily practice, however, there is a wide variation in the procedures adopted by different laboratories and even by different personnel working in the same facility [1]. As such, the accuracy and reliability of reported results are compromised, and it is also difficult to compare intra- and interlaboratory data. It also makes an evidence-based problem-solving approach very difficult due to the shortcomings imposed by this lack of standardization. For example, if there are no systematic daily reports on incubator temperature, CO_2, and culture media pH, it would be impossible to determine if a sudden drop in fertilization rates is due to the culture environment or other conditions. Along the same lines, if there is a lack of quality control for the plasticware used, it will be difficult to determine if a reduction in sperm recovery and

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Table 9.1 Standard operating procedure (SOP) table of contents checklist

General information
Name of test or procedure
Principles (goals and more general information about the test/procedure)
Pre-analytic information
Patient instruction for test/procedure preparation
Specimen collection instructions (including specimen container if appropriate)
Specimen labeling
Transport
Specimen referral
Specimen acceptability (including rejection criteria)
Analytic information
Equipment and materials
Reagents
Conditions required (e.g., use of laminar flow safety cabinet)
Instrument calibration and verification
Quality control (negative and positive control if required)
Step-by-step procedure description
Assay performance limitations(inter- and intra-assay, variability of the control, sensitivity)
Troubleshooting
Post-analytic information
Calculations (if required)
Normal ranges (reference intervals for normality or expected results)
Policy for handling alert or panic values (if applicable)
Patient report
References (articles published, current literature, in-house elaboration)

motility after sperm processing are due to plastic toxicity of a new lot of containers or other factors.

The reproductive laboratory procedure manual development process should start with the elaboration of complete standard operating procedures (SOPs) that should be followed by each and every personnel involved in patient testing and specimen handling. SOPs should be well elaborated, objective, and repeatable since they also play an important role in quality control. The procedure manual should be available to laboratory personnel at all times. Minimum requirements for SOP include relevant pre- and post-analytic considerations, as well as the analytic activities that represent the laboratory's path of workflow. An efficient SOP includes all necessary information for the test to be reproducible and to be performed efficiently. It shall include but may not be limited to the topics presented in Table 9.1.

The specific style and format are at the discretion of the laboratory director although elaboration of SOPs should follow preestablished formats and standards published by national or international agencies [2]. Templates may be obtained from many sources such as the "Clinical and Laboratory Standards Institute" (http://www.clsi.org) and can be used as a starting point for creating a laboratory-specific procedure manual. Figures 9.1 and 9.2 provide simplified samples of standard operating procedures used in reproductive laboratories.

In addition to SOPs for testing/examining/processing fluids, cells, and tissues, reproductive laboratories shall have a technical manual that includes detailed

I. Introduction

Prolonged exposure of sperm to seminal plasma results in a marked decline in both motility and viability. Sperm incubated in synthetic culture medium free of seminal plasma show no such declines. It is essential, therefore, that spermatozoa for clinical procedures such as in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) be separated from the seminal environment as soon as possible after ejaculation.

II. Principle of procedure

Colloidal density gradient centrifugation is a common method of sperm processing for ART purposes. Density gradient centrifugation selects the highly motile sperm subpopulation from the net specimen, and it allows the elimination of leukocytes and other microorganisms which are trapped by the gradient interphases.

III. Specimen collection

Semen specimens are obtained by masturbation. Refer to SOP on specimen collection for proper instructions.

IV. Equipment and materials

Sterile disposable serological pipettes (1, 2, 5 and 10 mL)

Disposable polystyrene round-bottom centrifuge tubes (sterile) with caps

Disposable transfer pipets (sterile)

Pipettor 1 to 200 microliters and sterile tips

Pipetting device

Sterile centrifuge polystyrene tubes (6 mL) with caps

Counting chamber

Fine point permanent marker pen

Laminar flow cabinet

37°C incubator

Centrifuge

V. Reagents

HEPES-buffered sperm washing medium

Human serum albumin (HSA)

Colloidal density gradient (colloidal suspension of silica particles stabilized with covalently bonded hydrophilic silane supplied in HEPES), lower and upper phases

VI. Quality control

New lots of contact disposable materials and reagents should be tested for toxicity using the sperm viability bioassay. Only commercially-manufactured and approved (by national regulatory agency) reagents should be used. Certificate of analysis including pH, osmolality, sterility assurance level, bacterial endotoxin level and mouse embryo bioassay results should be obtained for all reagents used in this procedure. Reagents should be stored in the refrigerator between 4-8°C degrees and used up to one week before expiration date. Reagent lot number should be documented for each individual procedure.

VII. Procedure description

Prepare Reagents

1. Bring all components of the gradient kit (upper and lower phase) and semen samples to 37°C, for 20 minutes, in the incubator.

2. Transfer 1 mL (volume of gradient may be reduced) of the lower phase colloidal gradient into a sterile conical bottom disposable centrifuge tube.

3. Layer 1 mL upper phase on top of the lower phase using a transfer pipet. Slowly dispense the upper phase lifting the pipet up the side of the tube as the level of the upper phase rises. A distinct line separating the two layers will be observed. This two-layer gradient is stable for up to two hours.

4. Label 15 mL centrifuge tube(s) with patient's name.

Analyze and Wash Specimen

Note: Sterile techniques should be used throughout specimen processing. Sperm processing should be performed inside a Laminar flow cabinet (e.g. Class II Bio-safety cabinet)

1. Semen specimen should be allowed to liquefy completely for 15 to 30 minutes in the 37°C incubator before processing.

2. Measure volume using a sterile pipet.

3. Remove a drop of semen using sterile technique and asses count, motility and round cell count.

4. Gently place up to 2 mL of liquefied semen onto the upper phase. If volume is greater than 2 mL, it may be necessary to split the specimen into two tubes before processing.

5. Centrifuge for 20 minutes at x300g.

6. The supernatant should be removed with a sterile transfer pipette to the level directly below the second layer.

7. Using a transfer pipet, add 1.5 to 2 mL of HEPES-buffered sperm wash media supplemented with 5% HSA and resuspend pellet. Mix gently with pipet until sperm pellet is in suspension.

8. Centrifuge for 7 minutes at x300g.

9. Remove supernatant from the centrifuge tube using a transfer pipet down to the pellet.

10. Resuspend the final pellet in a volume of 0.5 mL sperm wash medium using a 1 mL sterile pipet. Record the final volume. Perform a routine post-wash semen analysis for count and motility.

VIII. Panic values

Perform a pre-wash analysis. While examining the specimen, pay particular attention to extraneous round cells, debris, and bacteria that may be present. If the number of round cells are >1 million/mL, perform Endtz test immediately. A positive Endtz test should be reported to the lab director immediately.

Either the presence of only immotile sperm or the absence of sperm at all at the post-wash analysis should be reported to the lab director immediately.

IX. Assay performance

Buffered-medium (HEPES or similar) is to be used with atmospheric air 37°C incubators, and the tubes' caps should be tightly closed. If the 37°C incubator atmosphere is 5% (v/v) CO2 in air, then the medium should be buffered with sodium bicarbonate or a similar buffer, and the tubes'caps should be loose to allow gas exchange. Adherence to these principles will ensure that the culture pH is compatible with sperm survival.

X. References

Esteves SC. Semen Preparation: Ejaculated Sperm for ICSI. In: Malik S & Agarwal A, Eds. A Workshop on Human Spermatozoa and Assisted Conception, 1st ed. New Delhi, Jaypee Brothers Medical Publishers, 2011, pp. 31-37.

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Fig. 9.1 Simplified sample of standard operating procedure for semen processing by colloidal gradient centrifugation

information on how to identify, transport, store, and report results of all specimens handled under their scope of activity. Table 9.2 lists the contents of typical reproductive laboratories technical manual.

I. Introduction

Several sperm retrieval methods have been developed to collect epididymal and testicular sperm for intracytoplasmic sperm injection (ICSI) in azoospermic men. Testicular sperm aspiration (TESA) can be used to retrieve sperm from the testes both in men with obstructive azoospermia (OA) who fail PESA as well as in those with non-obstructive azoospermia (NOA). Testicular sperm extraction (TESE) using single or multiple open biopsies, and more recently microsurgery (micro-TESE), are indicated for men with NOA.

II. Principle of procedure

Processing of surgically retrieved-spermatozoa differs from the commonly used methods for processing ejaculates. Sperm processing should not only ease the selection of the best quality spermatozoa for ICSI but also optimize their fertilizing ability, whenever possible. In order to achieve their goals, laboratory personnel should: (i) Receive the best quality surgically-retrieved specimen possible, with minimal or no contaminants such as red blood cells and noxious micro-organisms, (ii) Minimize the iatrogenic cellular damage during sperm processing by mastering technical skills and controlling several factors, including centrifugation force and duration, exposure to ultraviolet light and temperature variation, laboratory air quality conditions, dilution and washing steps, quality of reagents, culture media and disposable materials, and (iii) Improve the sperm fertilizing potential, if possible, by using stimulants or selecting viable sperm for ICSI when only immotile spermatozoa are available.

III. Specimen collection

Testicular specimens are obtained by the surgeon either using percutaneous aspiration or open biopsy. Please refer to SOPs on sperm retrieval techniques for more information.

IV. Equipment and materials

50 × 9 mm and 60 × 15 mm petri dishes (sterile)

Disposable (sterile) serological pipettes (5.0 mL)

Pipettor 1 to 200 microliters and sterile tips

Pipetting device

6 mL sterile centrifuge polystyrene tubes with caps

0.7 × 25 mm needles (26 gauge) and tuberculin syringes (sterile)

Fine point permanent marker pen

Injection micropipettes

Laminar flow cabinet

Warming plates

Stereomicroscope

Centrifuge

Inverted microscope equipped with Hoffman modulation phase contrast and electro-hydraulic micromanipulators.

V. Reagents

HEPES-buffered sperm washing medium

Mineral oil

PVP solution

Human serum albumin

VI. Quality control

New lots of disposable materials and reagents should be tested for toxicity using the sperm viability bioassay. Only commercially-manufactured and approved (by national regulatory agency) reagents should be used. Certificate of analysis including pH, osmolality, sterility assurance level, bacterial endotoxin level and mouse embryo bioassay results should be obtained for all reagents used in this procedure. Reagents should be stored in the refrigerator between 4-8 Celsius degrees and used up to one week before expiration date. Reagent lot number should be documented for each individual procedure.

VII. Procedure description

Laboratory setup

Note: Use sterile handling conditions under a laminar flow cabinet or cleanroom environment during all laboratory steps.

1. Prepare 20 mL of HEPES-buffered and protein supplemented (5% HSA) sperm medium, and keep it at 37°C.
2. Transfer a 5 mL aliquot of protein-supplemented sperm culture medium to a 6 mL polystyrene tube and send it to the operating room (sperm media is used to flush the aspirating system before aspiration and to incubate testicular specimens upon collection).
3. Prepare four 2-well petri dishes by transferring 0.5 mL and 1.0 mL sperm medium-aliquots to the inner and outer-dish wells, respectively. Place two of them onto a warm surface (37°C) inside the workstation, and send the others to the operating room.
4. Mount two tuberculin syringes connected with 26-gauge needles (to be used as tools for mincing and squeezing seminiferous tubules).

Procedure

1. Transfer testicular parenchyma fragments to the outer-dish well. Under stereomicroscopy, identify seminiferous tubules and remove blood clots using the needled-tuberculin syringes.
2. Transfer seminiferous tubules to the inner-dish well containing fresh sperm medium. Perform mechanical dispersion of the tubules by mincing repeatedly using both needled-tuberculin syringes (use one to hold tubules in place at the bottom of the dish and the other to squeeze and open them). Repeat this step until no intact tubules are seen.
3. Examine the homogenate to confirm the presence of sperm using the inverted microscope at x400 magnification. Inform the surgeon promptly if an adequate number of sperm for ICSI is available. This step should take no more than 10 minutes because the patient is kept under anesthesia until a decision of continuing or finishing the surgical retrieval is made. If other specimens are taken, carry out the initial processing steps described above.
4. Aspirate and transfer the cell suspension from the inner-well dish to a sterile centrifuge tube. Dilute the aspirate with 3 mL of fresh sperm medium and centrifuge it at x300g for 7 minutes. Discharge the supernatant and resuspend the pellet in 0.2 mL of sperm medium. When a processed specimen is still contaminated with an excessive number of red blood cells, dilution and centrifugation with erythrocyte lising buffer may be required (see SOP "use of erythrocyte lysing buffer for surgically-retrieved specimens).
5. Prepare a petri dish containing a series of microdrops under mineral oil for sperm pick-up from a processed testicular cell suspension (see SOP "Sperm pick-up from a processed testicular cell suspension").
6. Load 1 to 4 µL sperm suspension aliquot to each 10 µL peripheral microdrop of sperm medium for search and selection of motile sperm. First aspirate a small volume of PVP into the injection micropipette to improve control during sperm pick-up and to avoid blowing air bubbles during ejection of selected sperm into the PVP droplet. Transfer sperm from the cell suspension to the PVP drop using the microinjection pipette.
7. After finishing to pick-up sperm from the processed sample, free the injection micropipette off any debris using the PVP droplet.
8. Make a final morphologic sperm assessment under x800 magnification in the group of preselected spermatozoa for ICSI. Perform intracytoplasm sperm injection using current SOP. Consider cryopreservation of left-over testicular aspirates.

VIII. Panic values

Either the presence of only immotile sperm or the absence of sperm at all at the post-processed testicular suspension should be reported to the lab director immediately. If only immotile spermatozoa are obtained after processing, different strategies may be used to differentiate live immotile spermatozoa from dead ones, thus aiding in the selection of viable gametes for ICSI (See SOP "Methods for selecting viable immotile sperm for ICSI).

IX. Assay performance

Dishes with microdrops containing testicular suspensions can be incubated up to 48 hours before ICSI at room temperature in an attempt to improve testicular sperm motility. Buffered-medium (HEPES or similar) is to be used in such cases.

X. References

Esteves SC; Agarwal A: Sperm Retrieval Techniques. In: Gardner D et al, Eds. Human Assisted Reproductive Technology: Future Trends in Laboratory and Clinical Practice, 1sr ed. Cambridge, Cambridge University Press, 2011, v. 1, pp. 41-53.

Esteves SC. Semen Preparation: Sperm Extraction for ICSI. In: Malik S & Agarwal A, Eds. A Workshop on Human Spermatozoa and Assisted Conception, 1st ed. New Delhi, Jaypee Brothers Medical Publishers, 2011, pp. 37-47.

Fig. 9.2 Simplified sample of standard operating procedure for surgically-retrieved testicular sperm processing

Table 9.2 Sample of reproductive laboratories' technical manual table of contents at Androfert

Coding	Name
BCTG-MTO-01	Donor Selection Criteria
BCTG-MTO-02	Specimen Collection
BCTG-MTO-03	Specimen Transport and Distribution
BCTG-MTO-04	Specimen Processing
BCTG-MTO-05	Specimen Storage
BCTG-MTO-06	Specimen Release
BCTG-MTO-07	Specimen Discard
BCTG-MTO-08	Specimen Registry and Traceability
BCTG-MTO-09	Staff Qualifications and Responsibilities
BCTG-MTO-10	Non-conformities and Follow-up
BCTG-MTO-11	Biosafety Norms
BCTG-MTO-12	Document Record and Control
BCTG-MTO-13	Availability of Technical and Operating Procedure Manuals
BCTG-MTO-14	Data Collection and Storage System
BCTG-MTO-15	Biological Waste Management Plan
BCTG-MTO-16	Germinative Tissues and Cell Bank Competencies
BCTG-MTO-17	Preventive Action Record
CRIO-MTO-01	Cryobiology Laboratory Description
CRIO-MTO-02	Cryobiology Laboratory Rules of Operation
CRIO-MTO-03	Cryobiology Biosafety Norms
CRIO-MTO-04	Cryobiology Laboratory Quality Control Guidelines
CRIO-MTO-05	Specimen Cryopreservation
CRIO-MTO-06	Liquid Nitrogen Container Handling in Cases of Accident
ANDRO-MTO-01	Andrology Laboratory Description
ANDRO-MTO-02	Andrology Laboratory Rules of Operation
ANDRO-MTO-03	Semen Specimen Collection, Identification and Labeling
ANDRO-MTO-04	Andrology Laboratory Set-up for Testing
ANDRO-MTO-05	Andrology Laboratory Biosafety Norms
ANDRO-MTO-06	Andrology Laboratory Quality Control Guidelines
ANDRO-MTO-07	Andrology Laboratory Utensil Washing Procedure
ANDRO-MTO-08	Detergent Residue Testing Procedure
ANDRO-MTO-09	Plasticware Utensils Sperm Viability Testing Procedure
ANDRO-MTO-10	Procedure in Cases of Biohazard Substance Accident
ANDRO-MTO-11	Andrology Lab Routines and Checklists
FIV-MTO-01	Embryology Laboratory Description
FIV-MTO-02	Embryology Lab Characterization and Standardization
FIV-MTO-03	Embryology Laboratory Quality Control Guidelines
FIV-MTO-04	Embryology Lab Routines and Checklists
FIV-MTO-05	Fyrite Gas Analyzer for CO_2 Incubator
FIV-MTO-06	Electronic Bacharach Analyzer for CO_2 Incubator
FIV-MTO-07	Culture Media Quality Control and pH Determination
FIV-MTO-08	Incubator Cleaning and Sterilization Procedure
FIV-MTO-09	Incubator Water Tray and Shelves Exchange Procedure
FIV-MTO-10	Warm Plates Quality Control
FIV-MTO-11	Embryology Laboratory Microbiological Control
FIV-MTO-12	Embryology Lab Biohazard Substance Accident Procedure
FIV-MTO-13	Embryology Laboratory Maintenance and Cleaning
FIV-MTO-14	Embryology Laboratory Quality Improvement Program

From Androfert—Andrology and Human Reproduction Clinic, Brazil

Personnel

Apart from technical and SOP manuals, reproductive laboratories shall have proper personnel to fulfill their responsibilities. Regulatory agencies and/or professional societies set the minimum standards to be followed regarding laboratory staffing [3–5]. For countries without formal regulatory guidelines, preestablished formats are available, such as those recommended by the College of American Pathologists Reproductive Laboratory Accreditation Program [6].

In general terms, reproductive laboratories should have adequate personnel to provide all services under their scope of activities in a timely manner, with a mechanism in place to provide backup for personnel. The vast majority of tests/procedures performed by RLs fall in the category of high complexity as they involve troubleshooting, interpretation, and judgment that require advanced knowledge and skills. According to the guidelines proposed by the American Society for Reproductive Medicine, a minimum of two qualified persons are needed who should be able to perform all technical services [3]. However, number and personnel levels should be appropriate for the laboratory size and complexity. Personnel requirements with regard to andrology laboratories may follow different criteria in countries where such laboratories are subjected to federal, state, or local regulations. In the USA, for instance, high-complexity andrology diagnostic testing such as the manual assessment of sperm concentration and morphology falls under the CLIA regulation which requires that andrology laboratories have personnel at five different levels, that is, laboratory director, clinical consultant, technical supervisor, general supervisor, and testing personnel, although one person may hold more than one position if qualified [7].

In most ART-regulated countries, qualifications and responsibilities for three positions, that is, director, supervisor, and technologist, are usually required. Requirements for laboratory directors vary according to countries/regions, as in some he/she must hold a physician degree while in others he/she may be either a physician or a qualified scientist with expertise in biochemistry, biology, and physiology of reproduction [3–6, 8]. Experience in experimental design, statistics, and problem solving is expected from lab directors. The lab director shall be prepared to fulfill several professional, organizational, administrative, consultative, scientific, and educational responsibilities for the services provided. The director is also responsible for maintaining the standards, documenting compliance, and implementing the requirements of the regulatory agencies. Laboratory supervisors and technologists should be qualified by education and experience and be in adequate number for the size and volume of the program. Laboratory supervisors' responsibilities include daily supervision of activities and oversight of RLs while technologists should be able to perform and report results of all routine technical activities. The Practice Committee of the American Society of Reproductive Medicine (ASRM) recommends that a minimum of two technologists are required to perform up to 150 in vitro fertilization (IVF) cycles in the embryology laboratory [3]. However, additional staff should be provided in programs performing larger number of IVF cycles

and for those including andrology duties. In our program, each IVF and andrology technologist should be able to hold, annually, 200 IVF (fresh and cryopreservation) cycles and 800 andrology procedures (semen analysis, sperm functional assays, sperm preparation for ART-related procedures, and cryopreservation), respectively.

Other staffing of different levels, such as technicians, nurses, medical assistants, and administrative and support personnel, is critical for midsize reproductive laboratories or above. In our program, registered nurses and medical assistants with specialized training in assisted reproduction are responsible for providing (1) nursing care to couples undergoing ART-related procedures such as oocyte retrieval, surgical sperm retrieval, and embryo transfer; (2) technical assistance to physicians performing oocyte/sperm collection and embryo transfer; and (3) education, counseling, and support for infertile couples.

Despite the fact that quality management responsibilities are fulfilled by laboratory directors in most cases, a dedicated quality manager should ideally be part of the staff in reproductive laboratories engaged in a quality management philosophy. Among several tasks, the quality manager ensures that the laboratory director's and other personnel's responsibilities are fulfilled. He/she also facilitates effective interaction of all individuals who work within the laboratory. The quality manager is responsible for implementing a program that monitor and evaluates the quality of services that are being provided to patients. The quality manager work in close interaction with the lab director and technical personnel to identify problems and to find solutions as well as ensuring that the quality of laboratory services (quality assurance) satisfies their required quality characteristics. The likely outcome of such integrated team work is the progressive improvement in the quality and efficiency of each aspect of the work and activities related to patient care and internal production (quality improvement). Figure 9.3 depicts reproductive laboratories' responsibilities and staff required to fulfilling specific tasks.

Structure and Resources

Reproductive laboratories should have adequate space to provide safe and comfortable working conditions and be designed in accordance to the volume and spectrum of testing/procedures performed. Laboratories must maintain or have full access to all equipment necessary to perform those services offered. It is out of the scope of this chapter to describe in detail the technical requirements and the infrastructure to set up reproductive laboratories. However, a short synopsis is warranted, and the information on the basic requirements of reproductive laboratories with regard to design, resources, and safety is provided below.

The minimum standards for laboratory infrastructure, equipment, and supplies have been published by professional societies and/or regulatory agencies and can be found elsewhere [3–8]. Standards vary from region to region, and conformity to these requirements is now mandatory by regulatory agencies in countries such as those within the European Union and Brazil.

Main responsibilities	Interpretation	Staff involved
Clinical significance, interpretation, and results correlation	Interpret and make judgments about the clinical significance of laboratory data	Director, supervisors, embryologists and andrology lab technicians
Consultations	Provide consultations to physicians and other practitioners regarding the clinical significance of laboratory findings	Director and supervisors
Interaction	Interact effectively with accrediting and regulatory agencies, appropriate administrative officials, healthcare community, and patient population	All
Standards of performance	Carry out procedures according to laboratory SOPs	Embryologists and lab technicians *(Director and quality manager shall define, implement, and monitor standards of performance in quality control)*
Proficiency	Enroll in the institution proficiency testing program	Embryologists and technicians
Monitoring	Monitor work performed in the lab to determine that clinically reliable data are being generated	Director, supervisors and quality manager
Correlation of lab data	Correlate laboratory data for diagnosis and patient management	Director
Quality Management	Adhere to the quality management policy and participate as members of the institution's quality improvement committee	All *(quality manager assumes responsibility for implementation of the quality management plan)*
Personnel	Ensure that there are sufficient qualified personnel with adequate documented training and experience to perform the lab workload	Director
Education	Participate in continuing educational programs	All *(director shall provide educational direction for the laboratory staff)*
Reference laboratories	Select and monitor all reference laboratories for quality of service	Director and quality manager
Safety	Adhere to the safety laboratory environment policy in compliance with good practice and applicable regulations	All *(director and quality managers are responsible for implementing the lab safety plan)*
Selection of equipment, methods, and reagents	Provide input into the selection of the most appropriate tools to assess a patient's diagnosis or status	Director and supervisors
Record keeping	Report and keep records in the laboratory	Embryologists and technicians *(Supervisor/director monitor adequacy of system of record keeping in the laboratory)*
Compliance	All laboratory personnel must be in compliance with applicable federal, state, and local laws and regulations	All
Administration and Management	Provide effective and efficient administration of the laboratory service, including budget planning and control with responsible financial management, in accordance with regulatory requirements and institutional assignment of such responsibilities	Quality manager and director
Development	Plan and direct development appropriate to the facility.	Quality manager and director

Fig. 9.3 Overview of the main responsibilities of reproductive laboratories' staff

Ideally, reproductive laboratories should be conveniently located in low traffic and secure areas. Laboratory design, air-quality control, illumination, safety, and technical resources should be appropriate for the performance of high-quality laboratory work in adherence to the local regulations. It is recommended that nontoxic disposable materials should be used for all therapeutic procedures [1, 3–8]. Chemicals and reagents must be properly labeled and stored. Use of toxic chemicals or radioisotopes is not permitted inside the embryology laboratory. Technical, maintenance, and policy manuals, as well as reference material, should be readily accessible for all laboratory personnel. The embryology laboratory should be as paper free as possible to avoid contamination. The use of electronic manuals, documents, and forms is fully granted as well as intranet communication and other computerized tools such as digital imaging. However, procedures must be available to laboratory personnel when the electronic versions are inaccessible (e.g., laboratory information system or network downtime); as such, laboratories must maintain either paper or electronic copies that can be easily accessed. A separate office may be shared by the reproductive laboratories for administrative functions.

Andrology Laboratory

While the andrology laboratory may share physical space with other laboratory activity, it should have distinct areas for diagnostic and therapeutic procedures. Therapeutic procedures such as sperm processing for ART and semen cryopreservation are performed using aseptic techniques within sterile environments. The optimal cost-effectiveness for performing therapeutic andrology procedures into a sterile environment is by using biological safety cabinets, which is designed to provide protection at three different levels (1) personnel protection from potentially harmful agents inside the cabinet; (2) product protection to avoid contamination of the work, experiment, or process; and (3) environmental protection from contaminants contained within the cabinet. Biological cabinets are classified according to biosafety levels. Due to the low contamination risk of reproductive cells/tissues to personnel and ambient and the absence of hazard vapors or gases, a class II type A unit is appropriate (Fig. 9.4). The common features of a class II, type A biological safety cabinet include (1) front access opening with maintained inward airflow; (2) high-efficiency particulate (HEPA)-filtered, vertical, and unidirectional airflow within the work area; and (3) HEPA-filtered exhaust air to the room or exhaust to a facility exhaust system. An internal fan draws room air into the cabinet through the front opening and into the front intake grill. The supply air then passes through a HEPA filter before flowing downward over the work surface. As the air flows downward, it "splits" about 6–18 cm from the work surface, one half of the downward flowing air passing through the front exhaust grill and the other half passing through the rear exhaust grill. Any aerosol particles generated at the work surface are immediately captured in this downward airflow and passed through the front or rear exhaust grills, thereby providing the highest level of product and personnel protection. The air is

Fig. 9.4 Class II type A biological safety cabinet

then discharged through the rear plenum into the space between the supply and exhaust filters located at the top of the cabinet. Owing to the relative size of these filters, about 70% of the air recirculates through the supply HEPA filter back into the work zone; the remaining 30% passes through the exhaust filter into the room or to the outside. More information on biosafety cabinetry can be found at the website of the National Sanitation Foundation (http://www.nsf.org).

Regulatory agencies may or may not require ambient air quality control in addition to biological safety cabinetry for andrology laboratories performing therapeutic procedures. In Brazil, for instance, andrology laboratories performing sperm processing for therapeutic purposes shall have positive pressure air filtration for coarse particles [4].

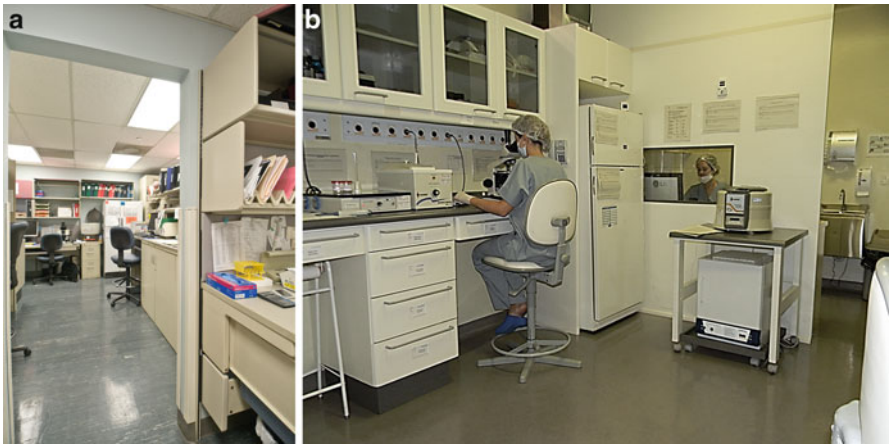

Fig. 9.5 (**a**, **b**) Andrology laboratory space organization

The laboratory physical area should be determined according to the number and type of tests/procedures to be performed. This will determine the number of technicians and the needed equipment. Figure 9.5a, b illustrates space organization in typical andrology laboratories. For new laboratories, it is important to keep in mind that it is much easier to expand if an existing space is available; as such, leaving unused space may help future expansion although even small physical areas can have its space optimized according to its organization.

Semen collection rooms are integral part of reproductive laboratories. They must be located in a quiet and private area in proximity to the andrology laboratory (Fig. 9.6). The room has to be equipped with proper furniture and be supplied with a sink or a washing station for use before and after collection. Ideally, semen collection rooms shall have urinals rather than toilets. Patients are asked to void their bladders but not the bowel in order to avoid contamination of the collected specimen. Instructions for collection, magazines, and/or videos should be also available. A simple electronic bell of intercom system may be used to warn the nurse or technician that the patient finished collection.

For practical purposes, workstations can be set up according to test and procedure. As an example, a workstation for routine semen analysis shall be equipped with phase-contrast optical microscope, cell counter, warm plate, and the necessary supplies and reagents (Fig. 9.7).

Separate workstations can be set up for staining and sperm morphology assessment and antisperm antibodies testing. The same biological safety cabinet can be used for both semen processing and cryopreservation procedures (Fig. 9.8), and a dark room workstation is needed for tests involving the use of fluorescence microscopy (Fig. 9.9). A list of materials commonly used in the andrology laboratory is provided in Appendix.

Fig. 9.6 Andrology laboratory collection room

Fig. 9.7 Andrology laboratory workstation for semen analysis

Fig. 9.8 Andrology laboratory workstation for semen processing and cryopreservation procedures

Embryology Laboratory

The embryology laboratory is a dedicated facility for handling gametes and embryos fully integrated with other ART clinic critical areas. The embryology laboratory main goals are to offer an optimal environment for manipulation and culture of gametes and embryos under strict conditions of contamination control and risk management.

Fig. 9.9 Andrology laboratory workstation for assays involving fluorescence microscopy

Human gametes and embryos are extremely sensitive to oscillations in temperature, humidity, light exposure, contaminants, and physical trauma. As such, the embryology laboratory has to meet several requirements with regard to design, constructive materials, equipment, furniture, illumination, temperature and humidity, safety, and air-quality control and monitoring, making it a unique environment in biomedical sciences.

The embryology laboratory environment shall minimize the risk of contamination to the gametes and embryos while optimizing the full potential of spermatozoa and oocytes for zygote formation and embryo development. Although lab personnel and utensils are the main sources of contamination involving microorganisms, other sources of contamination include inert and organic particles in air suspension and volatile gases. Contamination may be avoided or minimized by adhering to good laboratory practices and strict air-quality control. Effective measures include (1) the restriction in the number of embryologists working inside the laboratory and a carefully planned workflow, (2) strict adherence to safety and high-quality laboratory standards, (3) laboratory design and construction, and (4) control of air particulate and volatile organic compounds (VOCs) contamination. While the first two issues will be addressed in another section, an overview of the importance of laboratory design/construction and air-quality control is provided below.

Design and Construction

The design and construction of the embryology laboratory should ensure aseptic and optimal handling of gametes, zygotes, and embryos during all phases of treatment. Ideally, its location and physical area should be integrated to other ART clinic/hospital facilities in which clinical procedures are performed, such as the procedure

rooms for oocyte and sperm retrieval, embryo transfer, as well as the andrology lab and cryopreservation storage facilities. The laboratory should be as close as possible to the embryo transfer room to minimize temperature fluctuations during embryo transportation. A time interval of <2 min between loading the embryo(s) into the transfer catheter and displacement into the uterine cavity seems to be ideal [9].

Attention should be given not only to the incorporation of the most advanced materials when designing and constructing the laboratory but also to ergonomics aspects of furniture and equipment. Requirements may include but are not limited to:

- Use of controlled intensity incandescent lights or ultraviolet-free fluorescent illumination.
- Use of low-odor epoxy for walls and ceiling painting.
- Stainless steel workstations are ideal for cleaning and disinfection.
- Dressing rooms equipped with hand-washing facilities should be available in close proximity to the laboratory.
- Pass-through chambers for materials and specimens transfer to and from the laboratory are recommended.
- Location of storage areas should be logically planned for efficiency and safety within each working area.

Critical items such as incubators should be appropriately alarmed and monitored. Commercially available web-based remote monitoring devices have built-in ability to monitor for power shutdown and ambient noise levels. Moreover, external inputs can be connected to incubators' sensors to monitor critical conditions such as temperature, CO_2, and humidity levels that may fall outside normal ranges. When an alarm condition is detected, the device is programmed to notify laboratory personnel by sending out e-mail alarm messages or text messages. An automatic emergency energy generator backup in the event of power failure is mandatory. A minimum of two incubators is recommended [5], but the ideal number depends on the program complexity and volume. In our program, a maximum of four IVF cases are placed inside each incubator simultaneously. Moreover, we have dedicated incubators for blastocyst culture and to handling culture media prior to the IVF case. Overloading tissue culture incubators with several IVF cases may impact embryo development by creating internal chamber instability due to multiple door openings [10]. Gas cylinders should be located outside or in a separate room with an automatic backup system. Warm plates and heating blocks are crucial for temperature maintenance when gametes, zygotes, and embryos are handled outside incubators. A list of equipment, materials, and reagents commonly used in the embryology laboratory is included in Appendix. Figure 9.10 illustrates an embryology laboratory space organization.

Air-Quality Control

Several reports suggest that toxicants [e.g., bacteria, particulate matter, dust, and chemicals (VOCs)] may impact fertilization and embryo development (Table 9.3) [11–23]. Although the need of specific technical requirements relating to air quality

Fig. 9.10 Embryology laboratory space organization

in human in vitro fertilization (IVF) has been extensively debated, most practitioners acknowledge that more rigorous laboratory management is better practice and minimum standards toward air quality should be implemented [21, 24–27]. It is still a matter of debate how high the standards for laboratory air quality should be set, but animal experiments suggest that embryo development improve by cultivating embryos in cleanroom environments [28]. In humans, it has been demonstrated that cultivating embryos in cleanroom facilities is not detrimental to fertilization and embryo development [17–23]. On the contrary, results of the aforementioned studies suggest that strict control of air-quality conditions inside the embryology laboratory may optimize reproductive outcomes (Table 9.3).

Due to the critical role of ambient air quality in laboratories performing testing, processing, preservation, storage, and distribution of human tissues and cells, which includes laboratories performing ART, regulatory agencies in many countries have issued directives which include specific requirements for air-quality standards [4, 8, 29] (Table 9.4). These documents take into account the premises of the "precautionary principle" to safeguard public health in the prevention of transmission of infectious diseases via transplanted tissues and cells. The precautionary principle is used when measures are needed in the face of a possible danger to human health where scientific data do not permit a complete evaluation of the risk [30].

Air-quality control is achieved by using air filtration systems, which are designed to both reduce particulates in air and to decrease VOC levels.

Table 9.3 Characteristics and main outcomes of studies assessing the impact of laboratory air quality on in vitro fertilization

Author	Year	Study design	Study population	Method	Outcome
Little and Mirkes	1990	Basic research; animal study	In vitro cultured rat embryos	Protein and DNA analysis	High levels of acrolein (volatile organic compound) associated to embryotoxicity
Cohen et al.	1997	Basic research; analytical measurement procedure	None	Air sampling and VOC determination in human IVF laboratories	Higher levels of VOC (mainly toluene and isopropyl alcohol) in HEPA-filtered laboratory ambient air and incubators compared to outside unfiltered ambient air
Schimmel et al.	1997	Basic research; analytical measurement procedure	None	Air sampling and VOC determination in human IVF laboratories	Higher levels of VOC found in CO_2 tanks and incubators compared to outside air; air filtration using carbon activated and potassium permanganate reduced VOC levels
Hall et al.	1998	Basic research; analytical measurement procedure and animal study	Mouse model	Air sampling and VOC determination in human IVF laboratories; acrolein bioassay using 2-cell mouse embryos	Increased levels of VOC observed in ambient air of IVF laboratories. Reduction in aldehyde levels by air filtration using carbon-activated and permanganate. In vitro mouse embryo development, implantation and post-implantation development inversely correlated with acrolein concentration
Mayer et al.	1999	Clinical research; prospective randomized crossover study	Infertile couples undergoing IVF	Embryo culture in CO_2 incubators with and without VOC filtration	Higher pregnancy rates in couples whose embryos were cultured in incubators equipped with VOC air filters
Racowsky et al.	1999	Clinical research; observational study	Infertile couples undergoing IVF	IVF and embryo culture in laboratories and incubators with and without VOC filtration	Reduction of spontaneous abortion rate in IVF cycles performed in laboratory and incubators equipped with carbon-activated filters
Boone et al.	1999	Clinical research; observational study	Infertile couples undergoing IVF	Construction of cleanrooms for IVF, oocyte retrieval and embryo transfer	Reduction in air particles and increase in the number of high-quality embryos for uterine transfer
Worrilow et al.	2000	Basic research; analytical measurement procedure	None	Design of a highly purified, high velocity air control (HVAC) system and IVF laboratory with VOC air filtration	All areas within the IVF laboratory and accompanying procedure rooms qualified as class 100 areas. No VOCs were found at concentrations above detectable limits or >0.1 parts per billion

(continued)

Table 9.3 (continued)

Author	Year	Study design	Study population	Method	Outcome
Worrilow et al.	2002	Clinical research; observational study	Infertile couples undergoing IVF	IVF performed in cleanroom laboratories with VOC filtration. Outside ambient air temperature/ humidity and inside airborne particle counts and the presence of over 90,000 VOCs were assessed over a 2-year period	A seasonal correlation was observed between temperature and humidity of the outside ambient air serving the IVF high velocity air control system (HAVC) and an influx of VOCs into the IVF with significant impact on implantation rates
Esteves et al.	2004	Clinical research; observational study	Infertile couples undergoing IVF	Design and construction of cleanrooms with VOC air filtration for IVF, oocyte retrieval, and embryo transfer	Increase in the proportion of high-quality embryos and clinical pregnancy rates, and reduction of spontaneous abortion rate in IVF cycles performed in cleanroom IVF laboratory and adjacent rooms
Von Wyl and Bersinger	2004	Clinical research; analytical measurement procedure and observational study	None	VOC and air particle determination in an old (in use) IVF laboratory and in a newly built facility with positive-pressure air filtration for particles	Air concentrations of the measured compounds were lower in the new over pressurized IVF laboratory; fertilization and pregnancy rates did not differ between the old and new facilities
Esteves et al.	2006	Clinical research; observational study	Infertile couples with severe male factor infertility undergoing IVF	Sperm and oocyte retrieval, micromanipulation, embryo culture and embryo transfer performed in cleanroom facilities with VOC filtration	Increase in the proportion of high-quality embryos and clinical pregnancy rates, and reduction of spontaneous abortion rate in ICSI cycles performed in cleanroom laboratory and adjacent procedure rooms
Knaggs et al.	2007	Clinical research; observational study		The laboratory facility was designed to meet the European Union tissues and cell directive (2004/23/EC). Analysis of various key performance indicators in a limited period prior to and after the move into the new embryology facility	Performing embryology procedures in a cleanroom environment have not adversely affected key performance indicators routinely measured in the embryology laboratory. Implantation and pregnancy rates increased after the move into the cleanroom

IVF in vitro fertilization, *VOC* volatile organic compound, *HEPA* high-efficiency particulate air

Table 9.4 Ambient air-quality requirements for assisted reproduction laboratories operating under regulatory directives in the United States, European Union, and Brazil

Region (directive)	United States (FDA code of Federal regulation 21CFR1271.195 for human cells and tissues)[a]	European Union[b] (EU directive 2004/23/EC; 2006/86/EC)	Brazil (Anvisa RDC33/2006; RDC23/2011)
Particle filtration	Process-based; specifications not defined	Equivalent to GMP[c] Grade A air quality in the critical areas[d] with a background environment[e] at least equivalent to Grade D (exceptions apply[f])	At least equivalent to ISO class 5 (NBR/ISO 14644–1) in the critical areas[g]
Microbial contamination	Process-based; specifications not defined	Microbial colony counts equivalent to those of Grade A as defined in the current GMC guide[h] with a background environment at least equivalent to Grade D	Microbiological monitoring required; specifications not defined
Volatile organic compounds filtration	Not required	Not required	Ventilation systems should be equipped with filters imbedded with activated charcoal

[a]Where environmental conditions could reasonably be expected to cause contamination or cross contamination of human cells and tissues or equipment, or accidental exposure of human cells and tissues to communicable disease agents, environmental conditions must be adequately controlled and proper conditions for operation should be provided. Where appropriate, air filtration and environmental monitoring for microorganisms should be provided

[b]European Union member states are Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom

[c]GMP: European commission guide to good manufacturing practice revision to annex 1 (EU 2003/94/EC); Grades A and D air quality for particulates are equivalent to international standard ISO 14644-1 classes 5 and 8, respectively (see Table 9.5)

[d]Where tissues or cells are exposed to the environment during processing

[e]Background environment: clean areas for carrying out less critical stages. A filtered air supply should maintain a positive pressure and an airflow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively

[f]A less stringent environment may be acceptable in the following cases: (1) where it is demonstrated that exposure in a Grade A environment has a detrimental effect on the required properties of the tissue or cell concerned, (2) where it is demonstrated that the mode and route of application of the tissue or cell to the recipient implies a significantly lower risk of transmitting bacterial or fungal infection to the recipient than with cell and tissue transplantation, and (3) where it is not technically possible to carry out the required process in a Grade A environment (e.g., due to requirements for specific equipment in the processing area that is not fully compatible with Grade A)

[g]RDC33/2006 recommends one of the following methods to achieve such conditions: (1) biologic safety cabinet class II type A, (2) unidirectional laminar flow workstation, and (3) at least equivalent ISO 5 cleanroom

[h]Maximum colony forming units (cfu) in respectively Grades A and D environments are as follows: air sample (cfu/m3: <1 and 200), 90-mm-diameter settle plates (cfu/4 h: <1 and 100), 50-mm-diameter contact plates (cfu/plate: <1 and 50), and 5-finger glove print (cfu/glove: <1 and "not defined")

Control of Particles

Contaminant particles are generated by laboratory personnel, process, facilities, and equipment. Air particles may be in constant (e.g., viruses, bacteria, spores, and other inert submicron particles measuring <1 μm) or temporary suspension (e.g., residues of cleaning agents, clothing, and skin shedding measuring 1–100 μm). In reproductive laboratories, particles of interest measure between 0.1 and 10 μm. However, it is well accepted that particles of 0.3 μm or larger should be the target with regard to particulate contamination control in the IVF setting. Because bacteria and other contaminants can attach themselves to particles, a decrease in particles equates to an increase in air quality.

A cleanroom is an environment in which the concentration of airborne particles is controlled to specified limits. The level to which these particles need to be removed depends upon the standards required. The most frequently used is the international standard ISO 14644-1 which establishes classes of air cleanliness for airborne particulate levels in cleanrooms and clean zones [31] (Table 9.5). While particle counts may not be directly related to fertilization or pregnancy outcome, there are some indirect data to indicate that as laboratory air becomes cleaner (reduced particle counts), there is improvement in ART outcome [17, 21, 23]. Removal of airborne particulates involves the forced movement of air using positive air pressurization through a series of filters of increasing efficiency. Filter efficiency is achieved by decreasing membrane pores diameter. First, air filtration eliminates larger particles such as dust, and subsequently, high-efficiency particulate air (HEPA) or ultra-low penetration air (ULPA) filters trap small particulates, fungi, spores, and bacteria, thus decreasing microbiological contamination [32, 33]. HEPA air filters have 99.97% minimum particle-collective efficiency for particles as small as 0.3 μm and 99.99% of particles of greater or smaller size. This enables the HEPA filter to effectively trap all known infectious agents and ensure that only microbe-free air come into the room.

Table 9.5 Classes of air cleanliness for airborne particulate levels in cleanrooms and clean zones according to the International Standardization Organization (ISO) norm 14644-1

Particles/m^3 by size: ISO 14644-1						
	0.1 μm	0.2 μm	0.3 μm	0.5 μm	1 μm	5 μm
ISO 1	10	2				
ISO 2	100	24	10	4		
ISO 3	1,000	237	102	35	8	
ISO 4	10,000	2,370	1,020	352	83	
ISO 5	100,000	23,700	10,200	3,520	832	29
ISO 6	1,000,000	237,000	102,000	35,200	8,320	293
ISO 7				352,000	83,200	2,930
ISO 8				3,520,000	832,000	29,300
ISO 9				35,200,000	8,320,000	293,000

In addition to air filtration, strict rules and procedures are followed to control or eliminate particle sources whenever possible. They include proper cleanroom design and construction as well as cleaning procedures and personnel training.

Control of VOCs

Organic chemical compounds are everywhere in both indoor and outdoor environments because they have become essential ingredients in many products and materials. VOCs are organic chemical compounds whose composition makes it possible for them to evaporate under normal indoor atmospheric conditions of temperature and pressure [34]. Indoor VOCs react with the indoor ozone and the chemical reactions produce submicron sized particles and harmful by-products that may be associated with adverse health effects in some sensitive populations.

Analytical measurements of common air constituents and their concentrations estimate that the total VOC concentration in typical outdoor air of urban areas ranges from 330 to 2240 μg/m^3 (±636 μg/m^3) of total VOC [35]. An early study conducted in seven ART clinics showed that air quality deteriorated with regard to VOC contamination as it passed from the exterior of the buildings to inside the embryology laboratory and deteriorated further inside incubators. The numbers ranged from an average 533 μg/m^3] for outside air VOCs to 2,769 μg/m^3 inside incubators, representing a fivefold increase in VOC concentration.

As aforesaid, VOCs have been linked to reduced outcome in ART. Aromatic hydrocarbons (benzene, toluene, and xylene), alcohols (ethanol, propanol, and phenol), alkanes (propane and hexane), and aldehydes (nonanal and decanal) are VOCs that can be found in dyes, paint thinners, printing solutions, flues, perfumes, and flavorings used in food products. In the ART setting, it has been shown that benzene is found in CO_2 gas cylinders [36] while ethylbenzene and benzaldehyde are emitted from plasticware [12]. Elevated levels of other VOCs, such as toluene, formaldehyde coming from insulation used in air-handling systems, refrigerant gases, isopropyl alcohol fumes, and aliphatic hydrocarbons, have been described in ART laboratories [12, 18, 36]. Laboratory cleaning agents and writing instruments generally produce VOCs [21, 37].

VOCs, which are 100–1,000 times smaller than the effective pore size of HEPA filters, are not trapped by HEPA air filtration but can be eliminated by filters containing activated carbon. The spaces between the carbon particles contain a cloud of delocalized electrons that act as electronic glue, thus forcing the chemical contaminants to bind to the carbon. Alcohols and ketones are not easily removed by carbon, but they can be oxidized, and thereby detoxified, by potassium permanganate. Therefore, to protect gametes and embryos from VOCs in the laboratory, ventilation systems can be equipped with filters imbedded with activated carbon and potassium permanganate [14]. Activated carbon traps such compounds as benzene and formaldehyde, while potassium permanganate oxidizes alcohols and ketones. Furthermore, oil overlays of culture media can act as sinks to capture VOCs because VOCs are oil soluble [38].

Measurement and Instrumentation of Air Quality

Important measurements related to contamination control in reproductive laboratories include particle count, airflow and velocity, VOC emission, humidity, temperature, and surface cleanliness (Fig. 9.11a, b). Personnel are the primary source of contamination by body regenerative process (skin flakes, oils, perspiration, and hair), behavior (rate of movement, sneezing, and coughing), and attitude (work habits and communication between workers). Facilities should have specific standards and/or instruments to measure these factors. Additionally, procedures can be measured or validated by third party certification organizations.

Particle counts are the standard means for assessing air quality [39]. The particle counter draws a sample of air across a laser beam and then determines particle size and number (Fig. 9.11a). The number of particles of a specified size in a specific volume of air determines the room cleanliness (see Table 9.5).

VOCs can be measured by adsorption from air on Tenax TA, thermal desorption, gas chromatographic separation over a 100% nonpolar column (dimethylpolysiloxane), or mass spectroscopy [12]. Current measurement technology for VOCs requires sophisticated equipment and lacks the prospect for rapid real-time monitoring. Alternatively, VOCs can be detected based on different principles and interactions between the organic compounds and sensor components. There are electronic devices that can detect parts per million (ppm) concentrations. Others can predict with reasonable accuracy the molecular structure of VOCs in the environment or enclosed atmospheres and could be used as accurate monitors of the chemical fingerprint and further as health monitoring devices. Holographic sensors, for example, can provide direct reading of the analyte concentration as a color change [40]. The main limitation of using sensors to measure VOC levels is concerned with their detection limits. Devices usually detect VOCs as ppm that is inadequate to measure individual harmful VOCs present in much lower concentrations in assisted reproduction laboratories. Measurements devices with lower detection limits as parts per billion would be more adequate for monitoring VOC levels in the IVF setting [12]. It is then important to understand that measurement for VOC in indoor air is highly dependent on how they are measured. All available measurement methods are selective in their ability to identify and quantify accurately, and none are capable of measuring all VOCs. For example, benzene and toluene are measured by a different method than formaldehyde and other similar compounds. The range of measurement methods and analytical instruments is large and will determine the sensitivity of the measurements as well as their selectivity or biases. This is why any statement about VOCs that are present in a given environment needs to be accompanied by a description of how the VOCs were measured so that the results can be interpreted correctly. It is our opinion that using VOC-reducing technology, such as the incorporation of filters imbedded with activated carbon and potassium permanganate in the air ventilation system [28, 29], offers a more practical solution compared to the expensive and labor-intensive VOC testing as currently performed.

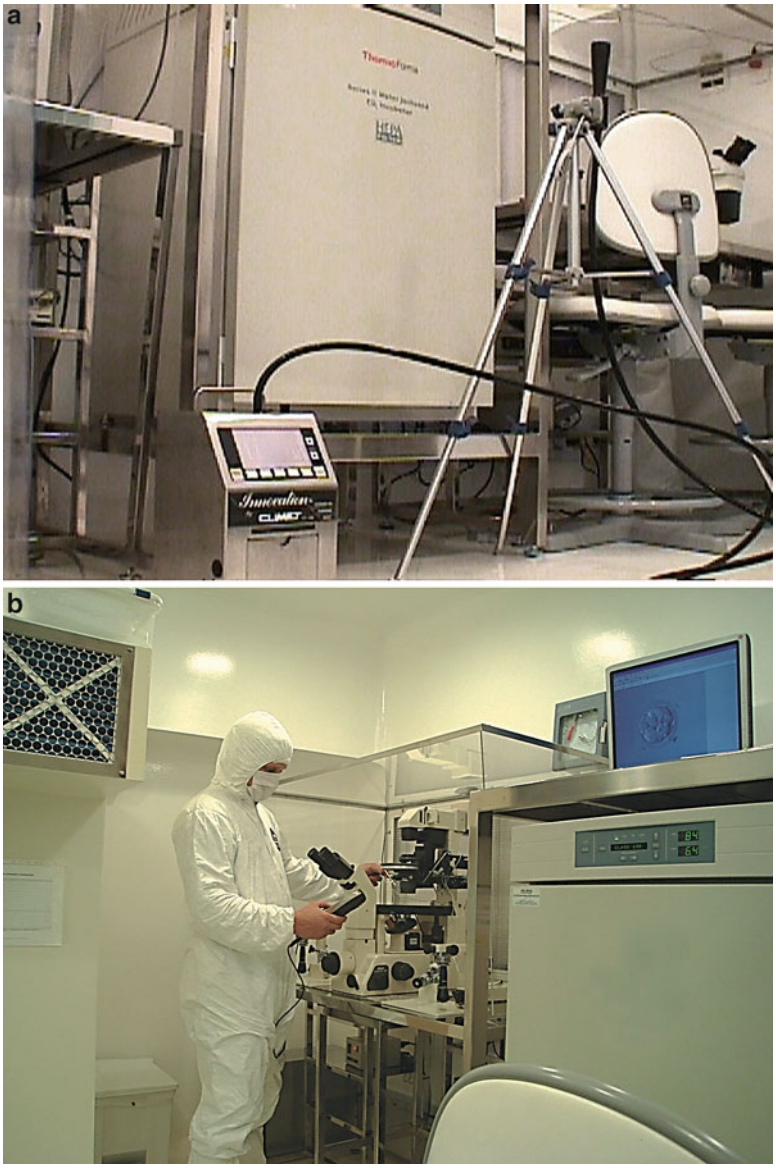

Fig. 9.11 Cleanroom validation testing: (**a**) airborne particle count monitoring, (**b**) air volume flow and velocity assessment

Fig. 9.12 Cryoroom

Cryoroom

Both andrology and embryology reproductive laboratories can share the same room for storage of cryopreserved specimens. A "cryoroom" is a dedicated facility for the storage of preserved samples and the supply of liquid nitrogen to them (Fig. 9.12).

Typical features of a properly designed dedicated cryoroom with best risk management standards include:

- External storage of liquid nitrogen.
- Transfer pipeline for liquid nitrogen into the cryoroom.
- Integrated battery-operated low-level liquid nitrogen alarm system.
- Oxygen depletion alarm system installed in the vicinity of potential nitrogen leak sources. The sensor permanently monitor the area, and the control panel displays

the oxygen levels and provides alarm in the event of a sensor reporting a reduced concentration of oxygen. Oxygen depletion alarms are usually set at 19% volume.
- Negative pressure ventilation system to exhaust the nitrogen in case of low oxygen levels.
- Interlock door system that allows escape but prevent access in emergency conditions.
- Extensive maintenance routine covering all aspects of the system.

Additional best practice measures include (1) access permission to the containers' room to lab personnel only, (2) adequate space for liquid nitrogen (LN_2) containers and/or freezer systems which should be identified according to the type of specimen they hold, and (3) inventory system (preferable electronic with proper backup) readily accessible from both andrology and embryology laboratories' computer network. In addition to low-level LN_2 alarm system, it is also important to manually check liquid nitrogen levels in case unpressurized dewars are used for storage. Evaporation rates can be calculated for each tank based on the manufacturer specifications and frequency of lid opening (Table 9.6). Information obtained from these calculations can be used to define a rank of priority for liquid nitrogen tank refilling.

Cryorooms should be designed and equipped with proper safety ventilation and oxygen-monitoring precautions due to the chemical properties of LN_2. Liquid nitrogen is safe under normal usage, but it undergoes a large volume expansion as it returns to the gaseous form by evaporation (e.g., through spillage)—1 L of liquid nitrogen produces approximately 680 L of nitrogen gas. This expansion ratio will quickly displace the atmosphere within a confined space and can cause oxygen depletion if control measures are not in place. As such, cryostorage rooms should be equipped with systems to both monitor oxygen in ambient air and to exhaust air under negative pressure equivalent to at least 75 $m^3/h/m^2$ [4]. An emergency plan is also mandatory for handling cryopreserved specimens in cases of disaster or vessel leakage.

Case Study: How to Design and Implement Reproductive Laboratory Facilities with Air-Quality Control

In this section we describe how we designed and implemented our reproductive laboratories and related areas with air-quality control [41]. We also present results of air-quality monitoring within the clean areas and retrospective data of culturing human embryos in our cleanroom facilities.

Cleanrooms are defined by ISO14644-1 as "rooms in which the concentration of airborne particles is controlled, and which are constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room and in which other relevant parameters, e.g., temperature, humidity, and pressure, are also controlled as needed." In the ART context, however, other filtration mechanisms rather than particle elimination alone through coarse, fine, and high-efficiency particulate air (HEPA) and/or ultra-low particulate air (ULPA) filtration are required to control contamination. In this sense, it is essential to remove VOCs that are con-

Table 9.6 Liquid nitrogen tank evaporation rates in operational conditions at Androfert, and calculation of critical levels for tank refilling

Liquid nitrogen tank	Height (cm)	Volume (L)	Ratio L/cm	Evaporation rate (cm/month)	Evaporation rate (L/month)	Evaporation rate (L/day)	Critical low LN_2 level (cm)	Critical low LN_2 level (L)	Days to reach critical low LN2 level
YDS-65	46	65	1.41	16	22.61	0.75	28	39.57	34
Volta-34	40	34	0.85	15	12.75	0.43	15	12.75	50
Volta-20	42	20	0.48	12	5.71	0.19	25	11.90	42
SX-44	40	44	1.10	12	13.20	0.44	25	27.50	37
XC-47	42	47	1.12	12	13.43	0.45	25	27.98	42
VHC-35	40	35	0.88	12	10.50	0.35	25	21.88	37
YDS-47	42	47	1.12	10	11.19	0.37	15	16.79	81
HC-35	40	35	0.88	13	11.38	0.38	25	21.88	35

stantly being generated by materials and cleaning agents used inside the laboratory. Removal of VOC is achieved by potassium permanganate-impregnated-pelletized coconut-based activated carbon filters. As such, a better definition for ART cleanrooms would be as "a room in which the concentration of airborne particles and VOCs is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles and VOC inside the room, and in which temperature, humidity and pressure are also controlled."

Embryology Laboratory and Related Facilities

Construction Details

All surfaces, including ceilings, walls, and floors, were made of smooth, impervious, and non-shedding materials and free from cracks and crevices. The junctures of the ceiling to the walls are coved. Walls surface were covered with low odor epoxy-based paint, and floors were made of sheet vinyl with heat-welded seams and a coved base, with the exception of the embryology laboratory in which polyurethane-based coatings were used for walls and floor finishes. Lighting fixtures are flush mounted with the ceiling and sealed, and no sinks or floor drains are present in the cleanroom. Additionally, we selected materials with reduced VOC off-gassing potential. As examples, fiberglass, wood and plastic-based materials were not used, and prefabricated site-assembled construction materials were avoided. Instead, in situ wet construction with applied surface finishes was preferred. Stainless steel and anodized aluminum were used in doors, windows, air vents and diffusers, as well as in workstations. Water-based low VOC adhesives were used when needed.

Only the minimum amount of furniture, equipment, and supplies are brought into the cleanrooms. Furthermore, furniture and equipment are non-permeable, non-shedding, cleanable, and resistant to frequent cleaning and disinfecting.

Air-Handling Ventilation Unit Room

The Air-Handling Ventilation Unit (AHVU) room [2.1 m width × 3.9 m length × 2.5 m height (20.5 m^3)] includes a rooftop air-handling unit (model UAECA-300, Veco Campinas, Brazil) that draws outside air through coarse (G4) and carbon activated prefilters before it enters the main ventilation unit. A free-standing main ventilation unit (model UVCA-3000; Veco, Campinas, Brazil) pulls prefiltered outside air and cleanrooms return air through coarse (G3) filters (1st stage filtration), past a 16-unit potassium permanganate-impregnated-pelletized coconut shell-based activated carbon filters (2nd stage filtration), and then through fine (F8) dust filters (3rd stage filtration). Filters type G3 are primary filters to collect coarse dust with a dust spot efficiency of 80–90% while type F8 are secondary filters to collect and retain small particle dust with a spot efficiency of 90–95%. Lastly, filtered air enters the cleanrooms through HEPA-filter air diffusers (Fig. 9.13). Floor- and ceiling-level vents in the cleanrooms return air to the main ventilation unit, to be remixed with existing air.

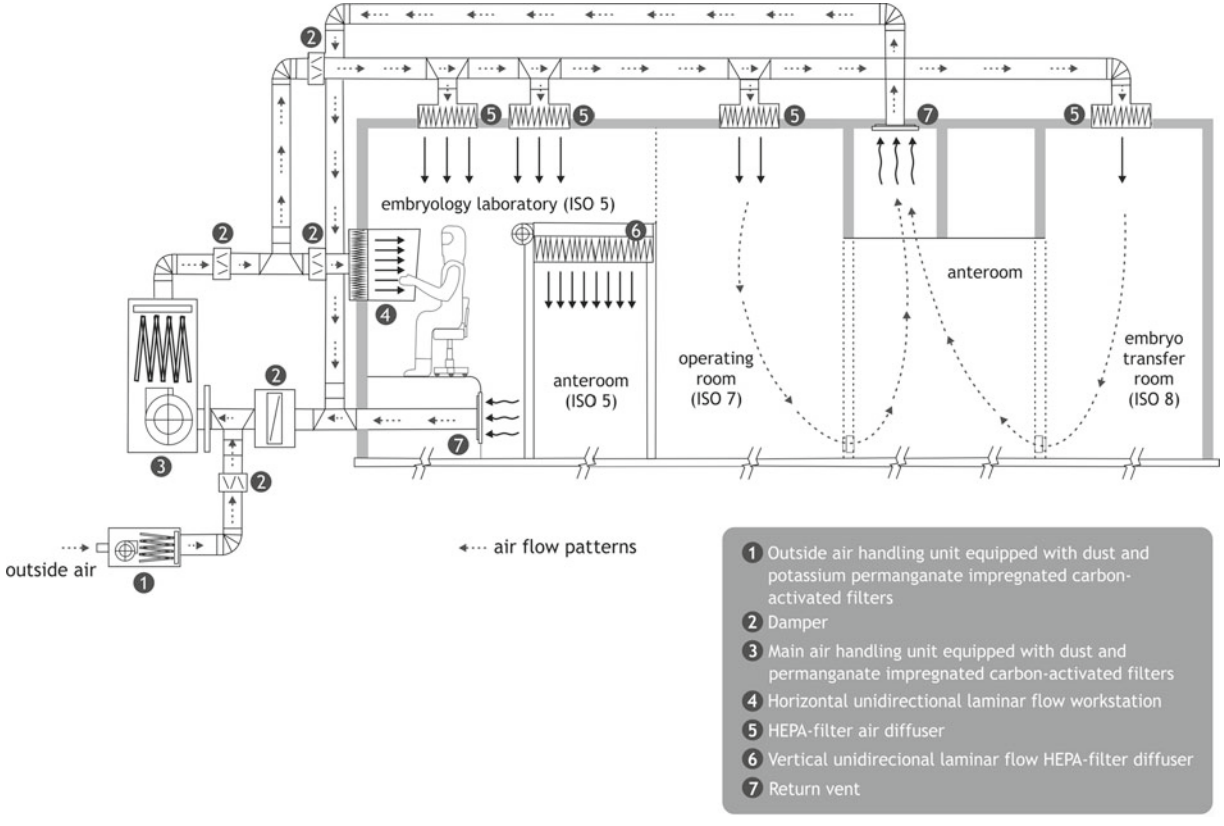

Fig. 9.13 Cleanroom assisted reproduction laboratory and related clean areas

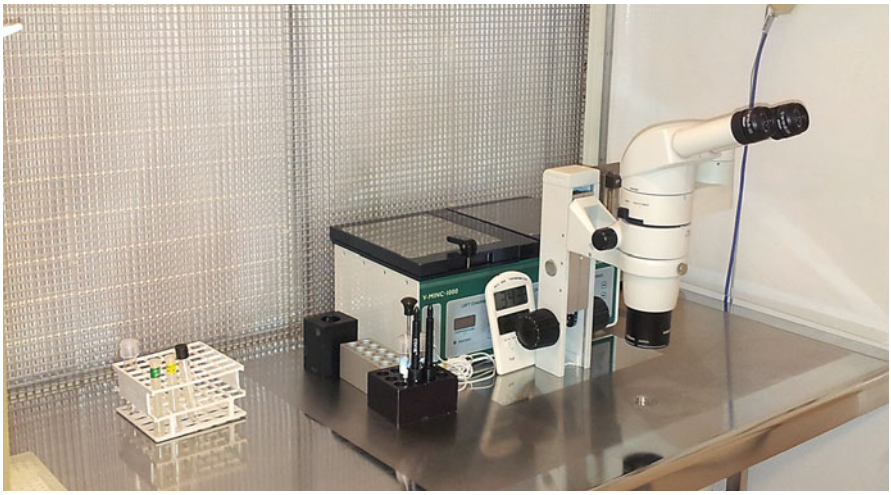

Fig. 9.14 Workstation for incoming oocytes and outgoing embryos

Fig. 9.15 Micromanipulation workstation

Embryology Laboratory

The cleanroom embryology lab [3.5 m width × 3.9 m length × 2.5 m height (34.1 m^3)] has two ceiling HEPA-filter air diffusers and two wall-mounted HEPA-filter diffusers that provide horizontal unidirectional laminar airflow to workstations for incoming oocytes and outgoing embryos and micromanipulation (Figs. 9.14 and 9.15).

Four vents at the floor level return air to the main air-handling ventilation unit. Access to the cleanroom is made through an anteroom equipped with two ceiling HEPA-filter air diffusers that draw cleanroom air and provide vertical unidirectional laminar airflow to the entire anteroom. The anteroom has a clean closet to store face masks, safety glasses, hoods, coveralls, boots, and disposable laboratory supplies and is used as a gowning room. The anteroom is also the pass-through for specimen transfer from the adjacent operating room to the embryology laboratory. The anteroom and cleanroom undergo 499 and 103 air exchanges per hour, respectively.

Operating Room

The operating room [4.7 m width × 3.6 length × 2.8 m height (47.4 m^3)] has a unique ceiling HEPA-filter diffuser and a return vent in the wall at floor level (Fig. 9.16).

Using these passageways, the air in the room undergoes 12 exchanges per hour (Fig. 9.13). In addition, the operating room has a portable minihood containing a high-efficiency particulate air (HEPA) filter (model DM-66, Veco, Campinas, Brazil) (Fig. 9.17). During oocyte and sperm retrieval, the tubing heating system is place inside the minihood which is used to improve air quality directly over the area where capping and uncapping of tubes occurs. Access to the operating room is made through an anteroom where personnel perform hand hygiene and complete other high-particulate-generating activities. Also, the anteroom is a transition area that constantly maintains air pressure relationships between the operating and dressing rooms, ensuring air flows from clean to dirty areas and reducing the need for the HVAC control system to respond to significant disturbances.

Embryo Transfer Room

The embryo transfer room [3.0 m width × 3.2 length × 2.6 m height (24.9 m^3)], which is adjacent to the operating room, has a unique ceiling HEPA-filter diffuser and a return vent in the wall at floor level (Figs. 9.13 and 9.18). The embryo transfer room undergoes nine air exchanges per hour.

Positive Pressure

Positive-pressure differential is maintained among the rooms. The embryology laboratory/anteroom is positive to the operating room [2.1 mm water column differential (mmWC)], which is positive to the embryo transfer room (0.7 mmWC). The operating room is also positive to the dressing room/hallways (0.5 mmWC).

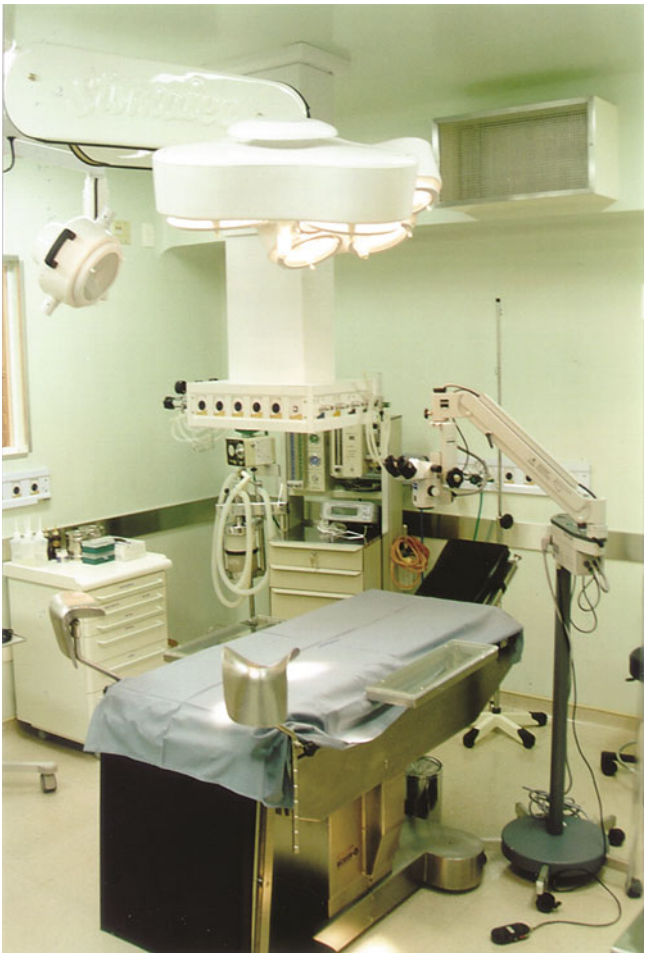

Fig. 9.16 Operating room with ceiling HEPA-filter diffuser

Andrology Laboratory and Cryopreservation Storage Room

Construction Details

Similarly to the embryology laboratory, all andrology and cryoroom surfaces were made of smooth, impervious, and non-shedding materials, and the junctures of the ceiling to the walls are coved. Walls were painted with low-odor epoxy paint, and floors were made of sheet vinyl with heat-welded seams and a coved base. Furniture and equipment are non-permeable, non-shedding, cleanable, and resistant to frequent cleaning and disinfecting.

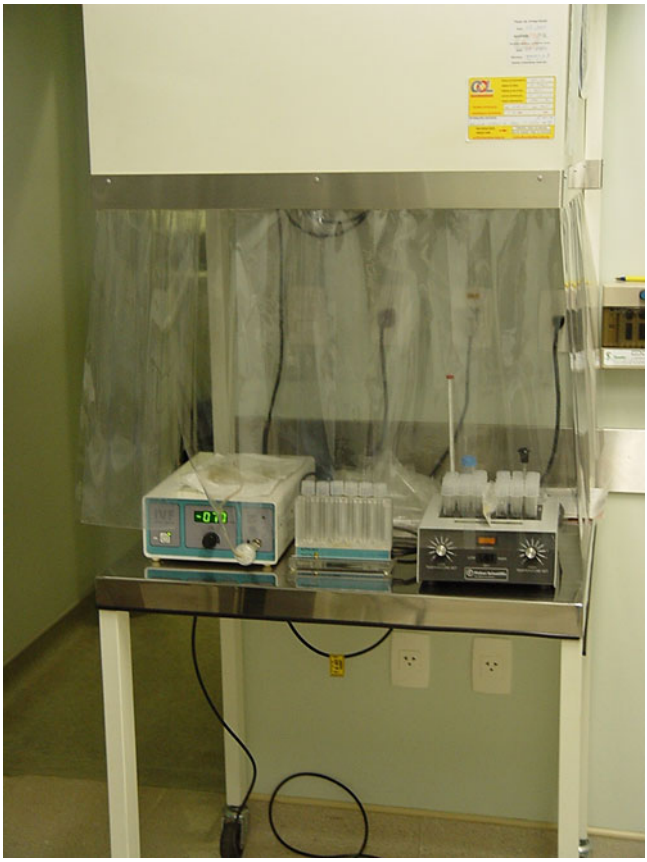

Fig. 9.17 Portable minihood containing a high-efficiency particulate air (HEPA) filter

Andrology Laboratory

The andrology lab [3.5 m width × 5.1 length × 2.8 m height (50.0 m^3)] has a rooftop air-handling unit (model UAECA-300, Veco Campinas, Brazil) that draws outside air through coarse (G3 and F8) and carbon activated filters before it enters the unique ceiling HEPA-filter air diffuser that distributes filtered air to the laboratory under positive pressure at 702 m^3/h (Fig. 9.18). The laboratory is equipped with a class II type A1 biological safety cabinet (model Bioseg-09, Veco, Campinas, Brazil) where sperm handling for therapeutic purposes and cryopreservation takes place. Access to the andrology lab is made through an anteroom where personnel dress and perform hand hygiene.

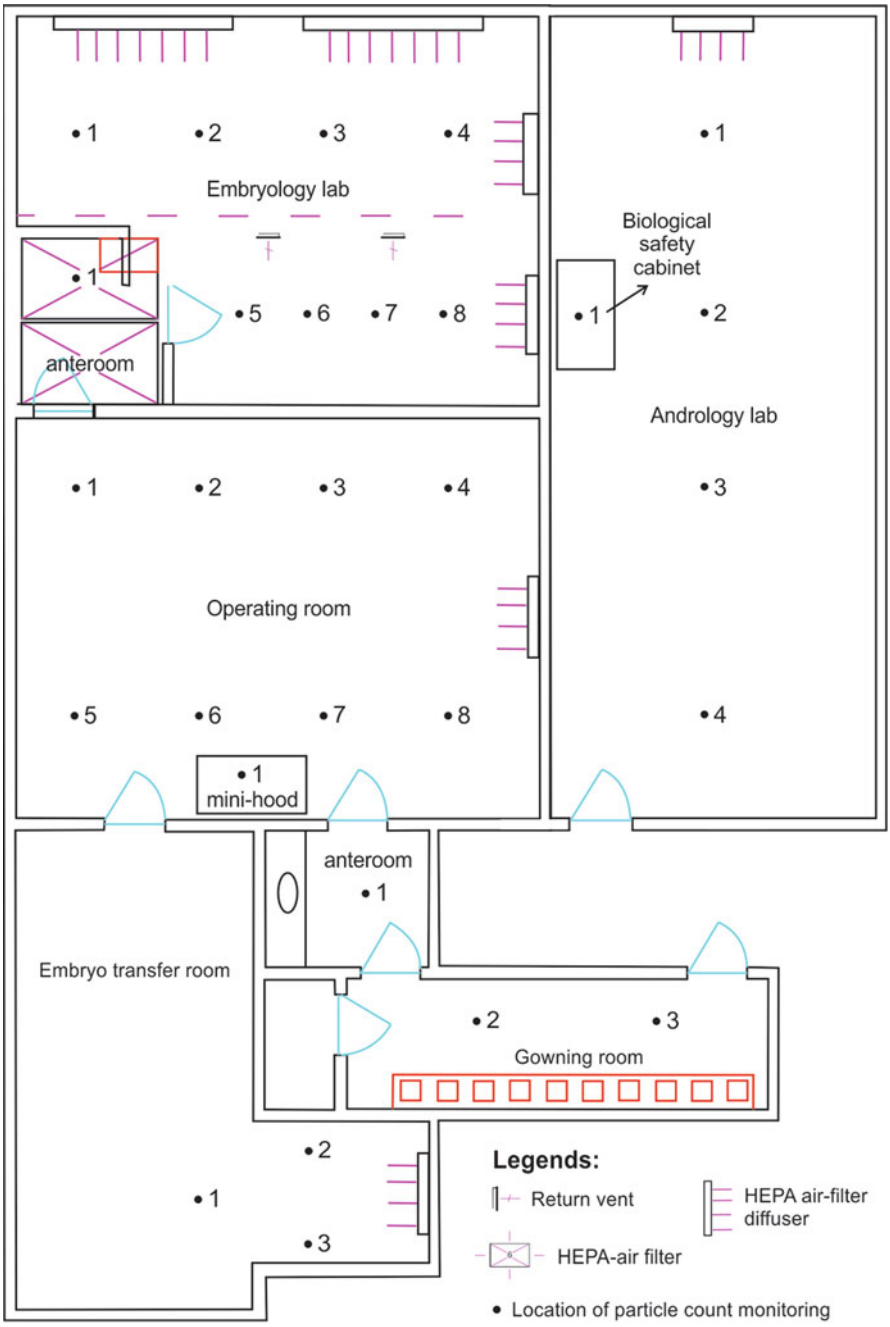

Fig. 9.18 Layout of reproductive laboratories and related facilities

Cryopreservation Storage Room

Liquid nitrogen tanks containing cryopreserved specimens are stored in the cryoroom room [2.1 m width × 3.5 length × 3.0 m height (22.1 m^3)]. The cryoroom is equipped with an oxygen depletion alarm unit and a ventilation system (model UE 500, Veco Campinas, Brazil) to exhaust ambient air under negative pressure at 150 $m^3/h/m^2$. Access to the cryoroom is made through the andrology laboratory.

Mechanisms to Reduce Contamination

In addition to the construction details, choice of furniture, equipment, and supplies, several measures are taken to reduce contamination. Personnel access to reproductive laboratories is limited, and it is made through an anteroom equipped with a gowning room chamber and hand-hygiene area. All personnel entering reproductive laboratories or adjacent areas (operating room and embryo transfer room) are required to gown up with a scrub suit, face mask, surgical cap, and operating room shoes. Furthermore, personnel are required to step on adhesive covered mats that remove dirt and dust from the soles of shoes when they are walked upon. An anteroom between the embryology laboratory and the operating room allows for passage of gametes and embryos between these two locations and minimizes the mixing of air between the embryology lab and the adjacent operating room. Embryology laboratory personnel wear non-shedding Dacron coveralls, hoods, and shoe covers, as well as masks and gloves. Gowning up prior to embryology lab entrance takes place in an anteroom between the lab itself and the operating room (Fig. 9.19).

Care is taken to selecting and using commodity items within the embryology lab. Lint-free wipes, cleanroom paper, and pencils only are allowed. Many cosmetics contain sodium, magnesium, silicon, calcium, potassium, or iron and may emit VOC. These chemicals are banned from our reproductive laboratories.

Cleaning is an essential element of our contamination control system. A list of cleaning tasks that are performed on a daily basis both in reproductive laboratories and adjacent critical areas include cleaning of all work surfaces as well as equipment and vents, emptying of trash and waste, cleaning of the doors, door frames, and lockers in the pre-staging area and gowning areas using isopropyl alcohol, and mop all room floors. Moreover, all equipment, materials, and containers introduced into the reproductive laboratories area are cleaned prior to entrance. On a monthly basis, rooms and incubators are "term-cleaned." Annually, rooms are sanitized with 2% sodium hypochlorite solutions.

As part of quality control, rooms' and incubators' temperature and humidity values are obtained twice daily. Semiannually, microbiological monitoring is carried out. Settle plates, surface sampling (e.g., swabs and contact plates), and glove printing are obtained from critical areas. Inhibitive mold agar Petri dishes (for molds/fungus) and a blood agar Petri dish (for bacteria) are labeled with the room, location, and date, placed into a biohazard bag, and sent to microbiological analysis.

Fig. 9.19 Embryology laboratory anteroom and gowned staff

Air-Quality Monitoring

Semiannual validation testing is carried out by a third party certification company (CCL, Campinas, Brazil). Although particle counts are the standard means for assessing air quality, several other tests which include air volume flow and velocity, filter integrity leak testing, air pressure differential measurement between rooms, ambient air temperature, and humidity are performed as well (Table 9.7 and Figs. 9.11a, b).

Particle counts are performed in various locations within the embryology laboratory and other critical areas. For this experiment, eight locations each in the embryology and operating room, one location in each anteroom, one location in each operating room and andrology lab laminar flow cabinets, three locations in the embryo transfer room and four at the andrology lab, and two dressing room locations are monitored (Fig. 9.18).

Table 9.7 Tests and equipment used for cleanroom validation

Validation test	Equipment
Air volume flow rate	Termoanemometer
Air exchange rate measurements	Termoanemometer
Air and room pressure differential measurement	Microanemometer and balometer
HEPA-filter integrity leak testing	Aerosol generator
Airborne particle cleanliness counts	Electronic particle counter
Recovery performance testing	Smoke generator
Lighting level measurement	Luxmeter
Noise level measurement	Decibelmeter
Temperature and humidity monitoring	Thermometer and hygrometer

Tests are performed according to the IEST 006.2 standards

Ten particle count cycles are performed at each of the nine sites both at rest conditions and with personnel performing daily activities (at operation). The results are pooled to provide individual and mean counts for each site for three different particle sizes (0.3, 0.5, and 5.0 μm). We routinely use particle counts at operating conditions for determining our cleanroom classification. Reports are compared and monitored for any trends of increased particulates and other validation measurements (Table 9.8). The certification company provides a report with a list of recommendations to maintain or improve air-quality conditions at the end of each semiannual validation. Prefilters are replaced semiannually, and HEPA filters are replaced as needed based on particle counts and filter integrity testing results. If particle counts are not within limits, the laboratory director and supervisor evaluate the procedures used in that specific area to identify potential sources of contamination. As previously discussed, VOC emission is not assessed during validation procedures due to technical limitations of currently available testing procedures. We routinely replace all filters imbedded with activated carbon and potassium permanganate semiannually.

Clinical Results

Retrospective data of culturing human embryos in cleanroom environments and clinical results of ART is presented in Table 9.9. Pregnancy and live birth rates significantly increased in the first triennium (24% and 37%, respectively) while miscarriage rates decreased (30%) after installation of the cleanrooms. Embryo development also improved over that period while fertilization rates were almost identical. These results were achieved by transferring similar number of embryos despite the fact that female age was lower in the former group. Thereafter, miscarriage rates remained unchanged, although pregnancy and live birth rates slightly decreased mainly due to the practice of transferring lower number of embryos adopted by our group. In addition, during these same years, the mean age of females who sought IVF increased significantly. It should be noted, however, that the

Table 9.8 Sample document of validation testing results for reproductive laboratories (RL) and associated critical areas

Facility	ISO 14644–1 cleanroom classification	Air particle count			Ambient air humidity (%)	Room temperature (°C)	Noise level (dBA)	Air volume flow rate (m^3/h)	Number of air exchange rate per hour
		0.3 $\mu m/m^{3a}$	0.5 $\mu m/m^{3a}$	5 $\mu m/m^{3a}$					
Embryology lab	ISO 5	2,877 ± 1,381	649 ± 354	0 ± 0	43.1 ± 6.8	25.5 ± 0.5	64	3,509	103
Embryology lab anteroom	ISO 5	1,429 ± 1,015	596 ± 597	0 ± 0	–	–	62	1,593	499
Operating room (OR)	ISO 6	99,472 ± 26,870	1,626 ± 523	85 ± 64	46.3 ± 5.9	25.8 ± 0.7	66	593	12
OR and RL anteroom	ISO 7	80,472 ± 12,084	2,098 ± 466	2,282 ± 107	–	–	67	–	–
Embryo transfer room	ISO 7	84,657 ± 10.683	1,239 ± 781	1,741 ± 616	49.2 ± 4.7	25.2 ± 1.5	58	224	9
Andrology laboratory	ISO 7	–	313,980 ± 38,759	350 ± 86	47.5 ± 6.3	25.1 ± 1.7	66	702	14
P value[b]	–	<0.001	<0.001	<0.001	–	–	–	–	–

Semiannual validation testing performed by third party company (CCL, Campinas, BRAZIL), July 2011

[a]Airborne particle mean counts obtained "at operation"

[b]Values are means ± standard deviation. Ten particle counts cycles were performed at each location with personnel performing daily activities (at operation). One-way ANOVA was used for particle count comparisons. A *p* value of below 0.05 was considered significant. Other cleanroom validation measurements (air humidity, room temperature, noise level, air volume flow rate, and air exchange per hour) are descriptive only

Table 9.9 Patient characteristics and main outcome measures of Assisted Reproductive Technology Program (Androfert, Brazil) in consecutive years (1999–2010)

	1999–2001[a]	2002–2004[a]	2005–2007[a]	2008–2010[a]	*P* value[b]
Number of cycles[c]	255	389	632	1039	–
Mean female age, years (±SD)[d]	30.2±5.2	32.8±5.4	34.7±5.1	34.4±4.9	<0.001
Indication for ICSI, %[e]					
Male	28.2%	29.2%	30.0%	26.5%	0.11
Female	44.6%	31.1%	30.5%	38.4%	
Both	27.2%	39.7%	39.5%	35.1%	
Mean number of retrieved oocytes, *n*[e]	10.8±6.9	10.7±6.6	9.9±7.3	10.3±7.2	0.89
Mean MII oocytes, *n*[e]	8.9±5.6	8.9±5.7	8.0±5.8	8.4±6.0	0.76
Mean fertilization rate 2PN, %[e]	69.4±25.3	70.3±33.0	65.4±37.5	65.0 ±31.9	0.11
Top quality embryos on transfer day, %[f]	36.4±29.2	46.9±30.6	45.8±33.5	52.3±35.2	<0.001
Mean number of transferred embryos per patient[g]	3.3±1.8	3.4 ±1.5	2.9±1.4	2.3±1.1	<0.001
Clinical pregnancy rate per transfer, %[h]	36.2%	44.8%	38.0%	38.1%	0.03
Spontaneous abortion, %[i]	28.9%	20.1%	22.8%	22.3%	0.04
Live birth rate, %[j]	25.7%	35.2%	31.3%	31.1%	0.02

Center began reporting to Latin American Registry (REDLARA) in 2002

Data includes fresh embryo transfer only

ICSI intracytoplasmic sperm injection

[a]Cycles prior to 2002, when construction of cleanroom facilities and implementation of strict air-quality control for particulates and volatile organic compounds began, were performed at a conventional facility from the same practice

[b] Chi-square test, one-way ANOVA, and Kruskal–Wallis test were used for comparisons. A p value of below 0.05 was considered significant

[c] Total number of ICSI cycles reported to REDLARA is 2,060

[d] 1999–2001 versus all others, $P<0.001$; 2002–2004 versus 2005–2007 and 2008–2010, $P=0.01$; 2005–2007 versus 2008–2010, $P>0.05$

[e] 1999–2001 versus all others, $P>0.05$

[f] 1999–2001 versus all others, $P<0.001$; 2002–2004 versus 2005–2007, $P>0.05$; 2002–2004 and 2005–2007 versus 2008–2010, $P=0.007$

[g] 1999–2001 versus 2002–2004, $P>0.05$; 1999–2001 and 2002–2004 versus all others, $P<0.001$; 2005–2007 versus 2008–2010, $P=0.01$

[h] 2002–2004 versus all others, $P=0.03$; all others pairwise comparisons, $P>0.05$

[i] 1999–2001 versus all others, $P=0.04$; all others pairwise comparisons, $P>0.05$

[j] 2002–2004 versus all others, $P=0.02$; all others pairwise comparisons, $P>0.05$

proportion of cleavage-stage embryos classified as having high quality at the day of transfer is steadily increasing over the last years. Over this same period, there was no appreciable difference in embryo culture techniques. Furthermore, the reasons patients underwent ART (male factor, female factor, or combined) did not significantly change after the installation of the cleanrooms.

In earlier studies, we have also compared IVF outcomes performed in different cleanroom laboratories. In one report, we evaluated 468 consecutive ICSI cycles performed in our general IVF population [20], whereas in another series, we assessed ICSI outcomes in a subgroup of couples in which the indication for treatment was severe male factor infertility [22]. In both studies, oocyte retrievals, gamete micromanipulation, embryo culture, and transfers were performed within two different ART facilities as follows: one was equipped with cleanrooms in which strict air-quality control for particles and VOCs within the embryology laboratory and adjacent critical areas was undertaken while the other had minimum standards of air-quality control within the embryology laboratory only. In both series, embryo development and pregnancy rates were significantly higher for ART cycles performed in cleanroom facilities compared to conventional ones, while miscarriage rates were markedly reduced in the former. In these series, female age, duration of ovarian stimulation, amount of gonadotropin required per cycle, number of oocytes retrieved, and proportion of ICSI cycles involving microinjection of epididymal or testicular spermatozoa were not statistically different between groups.

Our experience has been consistent with an association between the presence of air contaminants in the IVF laboratory and ART outcome. Attention to this important technical aspect may aid in the optimization of treatment results [42].

Laboratory Safety

Reproductive laboratories should focus on measures to protect the health not only of lab personnel but also of biological specimens handled. The latter is of particular importance when performing therapeutic procedures. Adequate laboratory facilities and resources are of utmost importance for safety. Facilities' design should aim to optimize efficiency of their operation and minimize the risks of injury and occupational illness of their occupants.

Facility resources include space design, which is crucial to optimize workflow, instruments, furnishings, communication systems, supplies, ventilation, piped gases and water, public utilities, and security. The environment within the laboratory should be favorable for the effective performance of its personnel. Bench and storage space for the proper handling of specimens and housing of equipment and supplies should be adequate and convenient. Special work areas should be provided for testing systems that require a controlled environment. Work areas should be arranged for ease of communication and smooth workflow [6]. In addition, patients and visitors should be protected from recognized hazards.

Human error, poor laboratory techniques, and misuse of equipment cause the majority of laboratory injuries and work-related infections. Technical methods that are designed to avoid or minimize the most commonly reported problems of this nature include (1) safe handling of specimens in the laboratory; (2) use of pipettes and pipetting aids; (3) avoiding the dispersal of potentially infectious materials; (4) use of biological safety cabinets; (5) avoiding accidental ingestion of potentially infectious materials and contact with skin and eyes; (6) avoiding accidental injection of infectious materials; (7) care when using centrifuges, refrigerators, and freezers; and (8) standard precautions with blood, other body fluids, and tissues. A detailed description of the technical methods listed above is provided elsewhere [43].

Reproductive laboratories mainly deal with biologic fluids, reagents, chemicals, and disposable utensils. As such, they are classified as basic "biosafety level 2" facilities [43]. Biosafety level designations are based on a composite of the design features, construction, containment facilities, equipment, practices, and operational procedures required for working with agents from the various risk groups. Biologic fluids may be contaminated with bacteria, virus, or fungi. The most important infectious microorganisms found in seminal and follicular fluids are HIV and hepatitis B and C viruses (HBV and HCV). These microorganisms are classified as "risk 2" pathogens, which means that laboratory exposures to these agents may cause serious infection but effective treatment and preventive measures are available and the risk of spread of infection is limited. The assignment of an agent to a biosafety level with regard to laboratory work is based on risk assessment. Such assessment will take the risk group into consideration, as well as other factors, to establishing the appropriate biosafety level. Reproductive laboratories that are not intentionally handling contaminated specimens such as those tested positive for HIV, HTLV, HBC, or HCV are assigned to risk group 2 and usually require biosafety level 2 facilities, equipment, practices, and procedures for safe conduct of work. Controlled ventilation air-handling system and biological safety cabinets are desirable as safety precautions for biosafety level 2 laboratories. However, biosafety level 3 facilities are more appropriate to provide the necessary degree of safety for infected specimens.

An overview of safety procedures applied to reproductive laboratories is depicted in Table 9.10.

Laboratory Personnel Safety Procedures

Reproductive laboratories should create and adopt a safety manual that identifies known and potential hazards and specifies practices and procedures to eliminate or minimize such hazards. An effective safety program will ensure that safe laboratory practices and procedures are integrated into the basic training of employees. Employees should be introduced to the code of practice and to local guidelines, including safety or operating manuals. As an example, standard operating procedures for proper disposal of all waste materials, including biological fluids, cells, and tissues, should be readily available. Safety SOP should be consistent with regulatory

Table 9.10 Reproductive laboratories' safety procedures

Laboratory personnel	Laboratory equipment
All laboratory personnel should be immunized against hepatitis B	Work surfaces and non-disposable vessels that have come into contact with biological samples or containers should be disinfected with 70% isopropyl alcohol on a daily basis. Disinfection should be carried out at the completion of daily activities and after spillage
Eating, drinking, smoking, using cosmetics, or storing food in the andrology is strictly forbidden	On a daily basis, equipment, doors, and door frames should be cleaned and room floors mopped using 70% isopropyl alcohol
Mouth-pipetting should not be permitted. Instead, mechanical pipetting devices should always be used for the manipulation of liquids	All equipment, materials, and containers introduced into the reproductive laboratories should be cleaned using 70% isopropyl alcohol prior to entrance
All laboratory personnel should be properly gowned in the laboratory and remove it upon leaving	On a monthly basis, rooms (including walls and ceiling) and incubators should be "term-cleaned" using 70% isopropyl alcohol
Laboratory personnel should wear disposable gloves when handling specimens and/or their containers. Gloves must be removed and discarded when staff leave the laboratory or use the telephone or computer. Gloves cannot be reused	Annually, rooms should be sanitized with 2% sodium hypochlorite solution and then rinsed with sterile water
Personnel should wash their hands regularly, especially before entering the laboratory and after removing gowns and gloves	
Personnel should take precautions to prevent accidental wounds from sharp instruments that may be contaminated with biological fluids, and avoid contact of such fluids with open skin, cuts, abrasions, or lesions	
Measures should be taken to prevent, and where necessary contain, spillages of biological fluids	
All sharp objects (needles, blades, etc.) should be placed in a proper container after use. The container should be sealed before it becomes full and disposed of in the same way as other dangerous laboratory items	
All potentially hazardous items (gloves, specimen containers, plasticware) should be disposed appropriately after use	
Face masks or surgical masks should be worn by all staff performing procedures	
Staff should wear protective safety goggles, insulated gloves, and closed shoes when necessary, for example, when handling liquid nitrogen	

requirements guidelines. Employees shall be trained to prevent or contain the adverse effects of reasonably anticipated accidents and disasters.

ART programs recommend that patients should be serum-screened for HIV, hepatitis B and C, and HTLV virus, as well as syphilis, before enrolling in ART treatments [3–5]. Despite these precautions, there is a low risk of not detecting infections within the "immunological window," and guidelines do not provide recommendations regarding the ideal time interval between screening and ART treatment. Along the same lines, semen from males enrolling in ART is routinely screened for bacterial contamination which includes aerobic bacteria, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, and *Neisseria gonorrhoeae*, but not for virus or fungi [3, 4]. However, neither patients providing semen specimens

for diagnostic procedures nor patients' specimens to be used for therapeutic procedures are screened for microbial contamination. As such, all body fluids shall be handled with precautions as if they are potentially contaminated [3–5]. Standard precautions should always be followed which includes appropriate barrier protections (gloves, gowns, eye protection) whenever samples are obtained from patients. In addition, all laboratory personnel should be immunized against hepatitis B.

Andrology laboratory personnel may be exposed to chemical hazards. It is important that they have proper knowledge of the toxic effects of these chemicals, the routes of exposure, and the hazards that may be associated with handling and storage [43]. Material safety data sheets or other chemical hazard information are available from chemical manufacturers and/or suppliers. These should be accessible as part of safety or operating manuals. In addition, reproductive laboratories' personnel should take precaution measures when handling liquid nitrogen which include (1) use of approved tanks only and tongs to withdraw objects immersed in liquid nitrogen; (2) eye protection with a face shield or safety goggles; (3) avoid touching non-insulated pipes and never allow unprotected parts of the body to touch pipes or vessels containing liquid nitrogen. Hand protection with insulated gloves and feet protection with closed shoes are mandatory. Liquid nitrogen spill on the skin can produce an effect similar to a burn, and the gas issuing from the liquid is extremely cold. Delicate tissues, such as those of the eyes, can be damaged by even a brief exposure to the gas, which may not affect the skin of the face or hands; (4) working in well-ventilated or negative-pressurized areas. A small amount of liquid nitrogen forms a large amount of gas. If nitrogen gas evaporates from the liquid in a closed room, the percentage of oxygen in the air may become low and create a risk of asphyxiation. Oxygen detectors, which trigger an alarm when the oxygen level falls below 19% (v/v), should be used where liquid nitrogen is stored; (5) use of tubes and straws especially made for freezing in liquid nitrogen only. Care should always be taken because even those can explode as they become warm.

Laboratory personnel may also confront other hazards posed by forms of energy including fire and electricity. Fire-fighting equipment should be placed near room doors and at strategic points in corridors and hallways. Fire extinguishers should be regularly inspected and maintained, and their shelf life kept up to date. Training of laboratory staff in fire prevention and immediate action in case of fire and the use of fire-fighting equipment is desirable. Fire warnings, instructions, and escape routes should be displayed prominently in each laboratory room and in corridors and hallways.

Laboratory Equipment Safety Procedures

Work surfaces and non-disposable vessels that have come into contact with semen, follicular fluid, or other biological samples should be sterilized or disinfected. Cleaning agents routinely used in reproductive laboratories are mainly limited to 70% alcohol. Ethanol and isopropyl alcohol have similar disinfectant properties.

They are active against vegetative bacteria, fungi, and lipid-containing viruses but not against spores. Their action on non-lipid viruses is variable. For highest effectiveness, they should be used at concentrations of approximately 70% (v/v) in water: higher or lower concentrations may not be as germicidal. A major advantage of aqueous solutions of alcohols is that they do not leave any residue on treated items. However, alcohol is volatile and harmful to gametes and embryos. As such, one should allow proper time for evaporation and room ventilation before handling gametes and/or embryos.

Sanitization of the laboratory space, its furniture, and its equipment requires stronger agents than alcohol. Surfaces can be decontaminated using a solution of sodium hypochlorite; a solution containing 1 g/L available chlorine is suitable for typical reproductive laboratories. Sodium hypochlorite is a fast-acting oxidant and is widely used as a broad-spectrum chemical germicide. Due to the volatile and toxic properties of sodium hypochlorite, term cleaning of reproductive laboratories using this agent is often limited to an annual basis. Clinical procedures are cancelled during cleaning and for a few days thereafter. Sodium chloride residues should be removed by wiping laboratory surfaces and equipment with a solution of 70% alcohol or sterile water.

Biological Specimens Safety Issues

In general, reagents, chemicals, and utensils used in the embryology lab do not pose a hazardous risk. Most laboratories use commercial culture media and supplies. Currently, major manufacturers comply with international regulations regarding safety and quality. However, laboratories should require manufacturers' certificates of analysis for each lot of culture media and for other reagents purchased, and define tolerance limits for accepting media and reagents with regard to packing conditions and refrigeration. For several countries, culture media and other reagents are shipped overseas; as such, a strict control of temperature from the site of origin to the destination should be provided. In our setting, we request that a temperature data logger is included with each culture media shipment. Upon arrival, we check for packing conditions and temperature fluctuations during transportation. If the fluctuation of temperature during shipment was above or below the ceiling and threshold levels, respectively, supplies are returned to the manufacturer.

Nowadays, sterile, nonpyrogenic, embryotoxicity-tested, single-use plasticware rather than glassware is used in most reproductive laboratories. Products labeled nonpyrogenic have been validated by the United States Pharmacopeia (USP) Bacterial Endotoxins (Limulus Amebocyte Lysate Test; LAL) testing for medical devices. The acceptance level is <0.1 endotoxin units per milliliter (EU/mL) or 5 EU/device [44]. Endotoxins are heat-stable polysaccharides anchored to lipids of the outer membrane of gram-negative bacteria. Endotoxins, which are shed during bacterial growth and released on cell lysis, can be biologically active even after autoclave sterilization [45]. Products labeled for in vitro fertilization have been tested for

embryotoxicity using the mouse 1-cell non-embryotoxicity assay. At least 75% of both test and control embryos must reach the hatched and/or expanded blastocyst stage in order for test products to be deemed non-embryotoxic. Despite being the most popular method to assess toxicity of contact materials, mouse embryo bioassays have several limitations due to the too great differences between mice and human embryos [46]. In addition, caution should be taken with the lids of Petri dishes which are not routinely tested for embryotoxicity [44]. Nowadays, protein source for culture media supplementation is routinely obtained from commercial suppliers which provide documentation for transmissible infectious diseases testing.

Appendix. Equipment, Supplies, and Reagents Commonly Used in Clinical Reproductive Laboratories

	Andrology lab	Embryology lab	Cryopreservation and storage
Equipment	Phase-contrast microscopes with 10×, 20×, 40× objectives Optical microscope with 100× objective Cell counters (single and multiple channel) Counting chambers Humidified chamber Centrifuges (with adjustable speed and time) Refrigerator and freezer Vortex mixer Aliquot mixer Plate shaker Automatic pipettors (rechargeable) Air-displacement micropipettes with different ranges Analytical balance Warm and hot plates Water baths pH meter Spectrophotometer Luminometer Flow cytometer Fluorescence microscope Absorbance microplate reader Thermometers Incubator Laminar flow cabinet	Workstations for micromanipulation and gametes/embryo handling Inverted phase-contrast microscope with 10×, 20×, 40× objectives Stereomicroscopes Warm stages Tube heaters CO_2 Incubators Electrohydraulic micromanipulators Laser system for embryo biopsy/hatching Refrigerator and freezer Centrifuge Thermometers Automatic pipettors (rechargeable) Air-displacement micropipettes with different ranges (5–500 μL) pH meter Incubator carbon dioxide measurement device Laminar flow cabinet or cleanroom environment Software for image capture and recording Data loggers Monitoring and alarm notification system	Automated-cryopreservation system Aliquot mixer Cryovials barcode identification system and reader Cryovial sealing device Liquid nitrogen containers Liquid nitrogen container alarm system Oxygen monitor Thermometers

Supplies	Sterile semen specimen containers (tested against sperm toxicity) Graduated serological pipettes (1–10 ml) Test tube racks Polystyrene graduated centrifuge tubes Glass microscope slides and coverslips pH paper Filter paper Transfer pipettes (Pasteur pipettes) Microcentrifuge tubes Micropipette tips Marker Pen Nontoxic powder-free latex gloves Protective eye glasses Glassware (beaker, Erlenmeyer flasks, glass funnels) Catheters for intrauterine insemination	Graduated serological pipettes (1–10 ml) Culture dishes and flasks Syringes and syringe filter units Test tube racks Polystyrene centrifuge tubes Transfer pipettes (Pasteur pipettes) Micropipettes tips Micromanipulation pipettes Denuding pipette and tips Catheters for embryo transfer Sterile wipes Laboratory cryomarkers (nontoxic) Sterile nontoxic powder-free gloves	Plastic cryosleeves Cryovials Cryocanes Laboratory cryomarkers (nontoxic) Liquid nitrogen Cryogloves Protective eye glasses
Reagents	Immersion oil Tyrode's salt solution Modified human tubal fluid medium Phosphate buffered saline solution 1× Stain for sperm morphology Eosin Y and nigrosin stains Peroxidase staining Ethanol, 96% Benzidine 3% H_2O_2 Sodium citrate D-fructose Distilled and deionized water Resorcinol Concentrated HCl Bovine and human serum albumin Immunobead rabbit anti-human Ig (H & L) reagent IgA, IgG, IgM immunobeads Dimethyl sulfoxide (DMSO) Luminol (5-amino-2,3 dehydro-1,4 phthalazinedione) Aluminum foil Oxidative stress assay kit Commercial kit for DNA integrity testing Isopropyl alcohol 70% Sterile wipes Lower and upper phase colloidal gradient Sperm wash media	Culture media Mineral oil Human serum albumin or synthetic serum substitute Sperm wash media Rinsing media Polyvynilpirrolidone Hyaluronidase Embryo biopsy media, microscope slides and fixatives Sterile distilled water Isopropyl alcohol 70%	Freezing media Thawing media

Vary according to the scope of activities, procedures, and protocols

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Chapter 10
Ensuring that Reproductive Laboratories Provide High-Quality Services

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Several tests and procedures under reproductive laboratory (RL) scope of activities are complex and not easy to standardize. As a consequence, results can vary widely within and between laboratories, which may ultimately impact on health-care decisions and treatment outcome. In order to ensure that results are accurate, precise, and reproducible, and that results from one laboratory can be compared with those provided by others, every RL, regardless of its location, complexity, and size, should implement a quality management (QM) program as a solution for the lack of standardization of actions and procedures.

In the context of reproductive medicine, laboratory QM can be described as a systematic program that monitors and evaluates the quality of services provided to infertile couples and their treating clinicians. Quality management integrates quality activities such as quality control (QC), quality assurance (QA), and quality improvement (QI) which aid in not only identifying problems but also finding their solutions as well as ensuring and optimizing the quality of laboratory services [1, 2].

Quality control is the establishment of quality specifications for equipment, procedures, and staff, thus ascertaining that they conform to established limits and standards. Quality assurance involves activities to ensure that a product or service will satisfy its required quality characteristics. Quality improvement focuses on the progressive increase in the quality and efficiency of each aspect of the work and activities related to patient care and internal production [1].

The importance of QM programs for reproductive laboratories has increased in recent years, and in many countries QM is now mandatory or required by regulatory and/or accreditation authorities [2–4].

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A comprehensive QM program applied to reproductive laboratories must cover all laboratory areas and should include pre-analytic, analytic, and post-analytic components. Pre-analytic processes include any step involved in the process prior to the testing or procedure (e.g., physicians' orders, patient instructions for semen and oocyte collection, patient identification, sample transport, specimen acceptance criteria, and specimen identification). Analytic processes include the examination of specimens and/or the processes involved in the production of viable embryos and healthy offspring. Post-analytic variables include any steps involved in the completion of the analytic phase and reporting results (e.g., turnaround time, quality and interpretability of reports, outcome data). A review of errors, complaints, number of incidents, patient satisfaction, and personnel complaints and suggestions during a certain predetermined period (at least annually) should be analyzed [1, 2].

In practical terms, the QM program should be described in the quality manual and can be viewed as a "plan-do-check-act" cycle [1, 5]. The first step is planning, which is followed by implementation. Results are then checked, and action is taken to improve the process. In the planning step, laboratory scope of activities and critical quality indicators to patient outcomes should be defined. Implementation involves standardization of procedures (SOPs) and quality specifications for materials, reagents, equipment, personnel training, and proficiency assessment. A control system should be implemented for facilitating the checking step. It should include recording test/procedure data, identification of personnel responsible for each processing/testing step, and definition of critical values. Lastly, a critical analysis of results and competency is undertaken to guide the action step. Action may involve troubleshooting nonconformities, personnel retraining, and implementation of novel aspects aiming to increase quality and efficiency of each aspect of work and activities related to patient care and internal production [1, 5]. This cycle is a never ending and dynamic ongoing activity, as summarized in Fig. 10.1.

Quality indicators for typical reproductive laboratories are provided in Table 10.1. Although threshold values may vary among laboratories due to protocol heterogeneity, they should ideally take into account the likely impact of a defined protocol on outcome and the importance of a particular indicator on quality care. As such, each laboratory should define its tolerance limits; nonetheless, indicators measuring serious events should be set at very low or zero levels [6].

Quality Control

Quality control includes all activities or operational techniques carried out to meet the quality requirements for a particular process. It includes laboratory resources (instruments, equipment, supplies, and personnel) and how these resources are used (SOPs, maintenance, documentation, and record keeping). Quality control should begin before any sample is collected and end with results reporting to the final customer (clinician and/or patient) [2, 7].

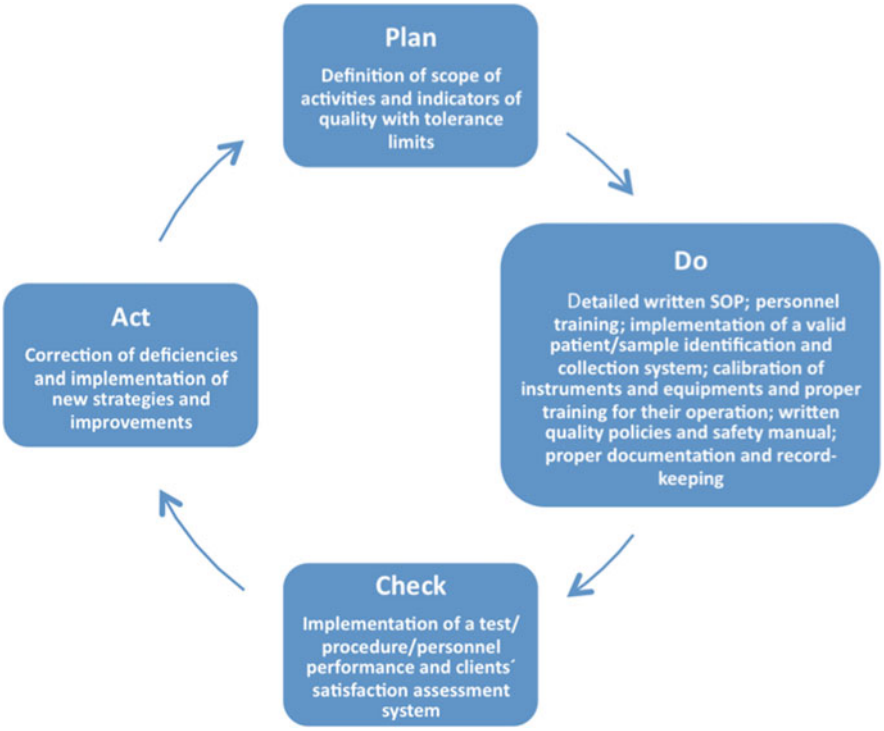

Fig. 10.1 Reproductive laboratory quality management program as viewed as a "plan-do-act" cycle

A QC program should have written goals, policies, procedures, delegation of functions, and regular review by appropriate personnel. The QC program should include tolerance limits and corrective actions when limits are exceeded. Standard operating procedures (SOPs) are important elements in a QC program as they offer all necessary information for the test/procedure to be reproducible and to be efficiently performed (see Chap. 9).

A simple example of a QC activity is temperature monitoring (e.g., warming plates, refrigerators, and incubators). Documented measurements should be analyzed to ascertain that are within previously defined tolerance limits. This ensures that a particular element is properly functioning, and if not, corrective actions should be readily available to improve or replace its function. Another example of QC activity in andrology laboratories is the use of positive/negative controls for tests such as antisperm antibodies and DNA integrity which should be run in parallel to the actual patient testing.

It should be noted that QC activities do not measure laboratory performance as a whole; it treats each element as a unit [8]. The QC program goals are to prevent, detect, and correct errors throughout pre-analytic, analytic, and post-analytic

Table 10.1 Quality indicators commonly used by typical clinical reproductive laboratories

Andrology laboratory	Embryology laboratory
Patient preparation, specimen collection, labeling, preservation, and transportation incidents rate	Maintenance of optimal environment (microbial and air quality control)
Test requisition inaccuracy rate	Patient preparation, specimen collection, labeling, preservation, and transportation incidents rate
Specimen rejection rate	2PN fertilization rate
Untimely reporting of test results rate	Abnormal fertilization rate
Improper paperwork and clerical errors rate	Post-ICSI oocyte degeneration rate
Post-processing motile sperm recovery rate	Percentage of high-quality embryos on days 2, 3, and 5 of culture
Post-thawing sperm survival rate	Blastulation rate
Outcome following intrauterine insemination using processed sperm:	Post-biopsy embryo development grading
Biochemical and pregnancy rates	Post-thaw oocyte/embryo survival rate
Miscarriage and ectopic pregnancy rates	Retained embryos in transfer catheter rate
Live birth rates	Implantation rate
Malformation rates	Biochemical and clinical pregnancy rates
Safety incidents involving lab personnel	Miscarriage and ectopic pregnancy rates
Serious events rate:	Live birth rates
Mislabeled specimens	Multiparity rates
Insemination mix-up	Malformation rates
	Safety incidents involving lab personnel
	Serious events rate:
	Mislabeled specimens
	Insemination mix-up
	Thaw error
	Transfer mix-up
Commentaries	
Post-processing sperm recovery may be assessed according to the type of gradient and initial sample quality. Post-thaw sperm survival may be evaluated according to pre-freezing sperm quality categories	Results may be assessed according to female age, sperm source (ejaculated, epididymis, testicular sperm, fresh or frozen counterparts), type of azoospermia (obstructive or nonobstructive), and the use of fresh or frozen embryos
Thresholds should be established for each quality indicator, and data should be collected and analyzed	

Source: Androfert Brazil, with permission
PN pronuclei, *ICSI* intracytoplasmic sperm injection

processes. A detailed description of andrology and embryology laboratories' quality control technical aspects can be found elsewhere [8–10]. In its 5th edition, the World Health Organization (WHO) laboratory manual for the examination of human semen provides detailed suggestions on how to improve quality in laboratory performing semen analyses [8]. It includes information on how to make and use quality control samples for assessing sperm concentration, sperm motility, sperm morphology and vitality, as well as the statistical procedures for analyzing and reporting within- and between-technician systematic and random errors.

Although a comprehensive QC program may not be implemented in all reproductive laboratories, a quality control program for semen analysis and sperm

processing techniques, identification of oocytes, maintenance of the developmental capacity of oocytes and spermatozoa during the procedures of fertilization, embryo culture, and embryo transfer should be in place as minimum standards. A summarized quality control checklist for reproductive laboratories seeking accreditation, as required by the College of American Pathologists [10], is provided in Table 10.2. These elements are aimed to ensure quality throughout the pre-analytic, analytic, and post-analytic phases of testing/procedures. Tables 10.3 and 10.4, respectively, list QC activities commonly used in the andrology and embryology laboratories.

Table 10.2 Quality control checklist to be accomplished for laboratories seeking accreditation by the College of American Pathologists Reproductive Laboratory Accreditation Program

QC area	Checklist
Procedure manual	A complete procedure manual should be available and readily accessible to the personnel in the laboratory
	Laboratory policies and procedures should be reviewed (at least annually) and approved by the laboratory director; lab personnel should have full knowledge about the contents of procedure manuals (including changes) relevant to the scope of their activities
Reagents, culture media, and material	Reagents and solutions should be properly labeled (content, quantity, or concentration as applicable; date prepared or reconstituted/opened; expiration date), stored according to the storage requirements, and used within their indicated expiration date
	A documented method for quality control of reagents/media and contact material should exist *(documentation of media and materials pretested by the manufacturer with an appropriate bioassay is acceptable)*
Instruments and equipment	A schedule or system should be available at the instrument for the regular checking of the critical operating characteristics
	Temperature and CO_2 concentration of CO_2 incubators should be checked daily using an independent measuring device *(laboratory may verify acceptable incubator culture conditions by monitoring and documenting checks for media pH)*
	A system should be available for emergency backup of power to critical equipment (refrigerators, freezers, incubators) and to detect and prevent gas failure of laboratory's CO_2 incubators *(in-house and remote alarms should be monitored 24 h/day)*
	A validated system for monitoring and maintaining liquid nitrogen levels in storage tanks should be available
Records	Laboratory records should be generated for each individual or patient's treatment cycle. The following information should be available: results of oocyte retrieval procedure, semen analysis before and after processing, outcome of insemination/fertilization and embryo culture, timing of protocol events, personnel performing each laboratory step, and proper data record to allow for the tracking of the disposition for gametes or embryos handled or stored
	Information with respect to all critical reagents, supplies, and equipment used in collection and processing of gametes and embryos, including lot numbers and expiration dates, should be recorded to allow for traceability

(continued)

Table 10.2 (continued)

QC area	Checklist
Requisitions, specimen receipt, and result reporting	Patient instructions for collection and delivery of semen samples to the laboratory, documented criteria for rejection of unacceptable specimens or handling of suboptimal specimens, and semen specimens information with regard to method of collection, type of specimen container, days of abstinence, collection or transport problems, time of specimen receipt, and analysis should be available and/or recorded
	Patient results should be timely reported with accompanying reference (normal) intervals or clinical interpretations
Semen analysis	Policies of quality control and calibration should be in place for automated analysis of semen characteristics
	Analysis should be performed at established standard specimen temperature range (for motility assessment) using good quality instruments, including counting chambers, and duplicate counting should be carried out for samples assessed using a standard hemocytometer
	A procedure for the accurate distinction of leukocytes from other round cells should exist, and for azoospermic specimens, as well as postvasectomy checks for reproductive sterility, a centrifugation technique should be employed on the seminal fluid
	Percent and progressive sperm motility should be evaluated in a standardized manner, using internal quality control, within 1 h of collection, and viability testing should be carried out in semen specimens with percent motility of <30%
	Sperm morphology smears should be of good quality and adequately identified. Stains, which have to be checked for contamination and reactivity each day of use, must be used to facilitate classification of cell types. The method used for morphology classification should be indicated on the report, and a documented system must exist to ensure consistency of morphologic observations among personnel performing microscopic morphologic classification. Slides should be retained for at least 30 days for future reference
	For biochemical tests such as fructose, positive and negative controls should be run with each assay
	Serum and follicular fluid specimens used for indirect ASA testing should be heat-inactivated before use, and positive and negative controls should be included with each assay. Testing for ASA requiring motile sperm should be assayed with minimal delay
Therapeutic sperm processing	Proper handling instructions for insemination specimens should be defined and followed, including aseptic technique for processing, the method for concentrating motile sperm, and a system to verify and maintain the identity of the specimen throughout receipt, storage, processing, and disposition

(continued)

Table 10.2 (continued)

QC area	Checklist
Sperm, oocyte, embryo handling, and culture	Sterile techniques should be employed in the handling, assessment, culturing, and transfer of sperm, oocytes, and embryos
	Documented criteria for oocyte insemination and evaluation of oocyte maturity and embryo quality should be in place, including the definition of periods for examination as well as policies for the disposition of oocytes with an abnormal number of pronuclei. A process to verify proficiency in the laboratory's ability to assess the quality of embryos before transfer should exist
	A documented program for personnel training and competency evaluation to perform micromanipulation should be in place, and a system to ensure that micromanipulation procedures are performed at an acceptable levels should exist (including fertilization, cleavage, and pregnancy rates)
	A documented program should be available to train and evaluate personnel competence in the performance of embryo biopsy and blastomere fixation
Embryo transfer	Laboratory should document the length of time that embryos are cultured as well as the quality of embryos before transfer
	A system should be in place to check the patient specimen identity (sperm or embryos) against the identity of the patient prior to transfer or insemination
	The laboratory should have policies to check the catheter for any embryos left after transfer
Cryopreservation of sperm, oocytes, and embryos	Laboratory should have reliable and documented procedure(s) for sperm, oocytes, and/or embryos cryopreservation, as well as for labeling, storage, and recording/tracking such specimens
	The laboratory should be able to document the current inventory of all specimens that have been banked, and a policy with regard to inventoried samples that cannot be located in the bank should exist
	Procedures should be adequate to verify specimen identity and integrity throughout the entire process of cryopreservation
	The laboratory should have a program to ensure that its cryopreservation program is capable of providing acceptable recovery rates
	A documented procedure to cover length of storage, informed consent, and long-term disposition of cryopreserved gametes or embryos should also exist
Personnel	Laboratory director and all other personnel should meet the requirements described by regulatory agencies
	Laboratories should be able to provide backup laboratory personnel as needed, to ensure timely andrology and embryology services
Physical facilities	Space for administrative functions, clerical and technical work, shelf and refrigerator/freezer/liquid nitrogen tank storage space should be adequate
	Laboratory design and space should be adequate to ensure quality of work *(including quality control activities) and safety of personnel (important elements include cleanliness and maintenance of floors and benches; presence of water taps, sinks, drains, and electrical outlets in proper quantity and location; ventilation, lighting, temperature/humidity control, and communication devices)*

Table 10.3 Sample of quality control activities time schedule for andrology laboratories

Frequency	Activity
Daily	Temperature (room, refrigerators, freezers, incubators, warm stages)
	Ambient air humidity
	Microscopes (optics, cleaning, covering)
	Surveillance and correlation of semen analysis results for sperm concentration, motility, vitality, and morphology within samples
Daily/weekly	Level of liquid nitrogen in storage tanks
As used	Cleaning (equipment, instruments, workstations, and laminar flow hood)
	Water baths (temperature and water levels)
As used/weekly	Staining solutions and reagents (contamination, debris, color, expiration date)
Weekly	Cleaning (incubators, centrifuge, refrigerator, balance)
	pH meter (level of electrolytes in electrodes, calibration, membrane cleaning)
	Incubators and water bath (change water in tray)
	Automated semen analyzer (beads calibration, motility QC, review of settings)
Weekly/monthly	Filling of liquid nitrogen tanks
Monthly	Microscopes (check mechanic system, illumination system, and phase contrast)
	Spectrophotometer (wavelength, clean interior and exterior, absorbance, and linearity) and other specific equipment used for sperm function tests (e.g., luminometer)
Quarterly	Analysis of replicate measurements for sperm concentration, motility, vitality, and morphology by different technicians and analysis of mean results (internal quality control)[a]
Biannually	Certification (biosafety cabinets/laminar flow hoods)
	Participation in proficiency testing program
Annually	Calibration (thermometers, timers, sensors, centrifuge, pipettes, balance)
As received	Supplies, culture media, and reagents (receiving date, product characteristics such as temperature during transportation and during arrival, opening date, expiration date, storage requirements, certification of analysis, toxicity testing for every new lot of plasticware used in contact with gametes)

[a]Internal quality control (IQC) monitors precision and indicates, through results outside the control limits, when the assay may be faulty. The QC procedure used depends on the assessment to be controlled since different assessments are sensitive to different types of errors. Quality control samples should be analyzed as part of routine laboratory work and not treated in a special way, which could provide a more precise and accurate result than that for routine samples. The types of IQC material used to monitor within- and between-technician variation can be purchased or made in the laboratory. Commercial QC samples are provided with a mean and known extent of variation established by the manufacturer. They can be used to both assess accuracy and precision but may be not universally available. Their advantage is that target values are provided by manufacturers by multiple assessments, computer-aided sperm analysis, or consensus values. Alternatively, laboratories can produce their own QC samples. In these cases, target values are unknown, and therefore, multiple assessments should be performed to at least estimate values and minimize random errors. Random errors affect precision and occur by chance in different readings or sampling performed by the same observer using the same equipment. However, laboratory-produced QC slides are limited in their ability to identify systematic errors, which originates from the observer and/or equipment used to perform analyses, unless an external quality control program is in place. Laboratory-made QC samples for sperm concentration, motility, vitality, and morphology can be generated. Aliquots of diluted semen samples with varying sperm concentrations can be stored frozen, or at 4°C with a preservative, and analyzed at intervals for sperm concentration. Video-recorded specimens can be made and used for motility, morphology, and vitality IQC [8].

Table 10.4 Sample of quality control activities time schedule for embryology laboratories

Frequency	Activity
Daily	Temperature (room, refrigerator, incubators, warm stages)
	Humidity (room, incubators)
	Microscopes (optics, cleaning, covering)
	CO_2 concentration (incubators) using independent devices
Daily/weekly	pH of culture media kept in incubators
As used	Cleaning (equipment, instruments, workstations, and laminar flow hood)
	Temperature of media kept in incubators and warm stages
As used/weekly	Solutions, mineral oil, culture media, and reagents (contamination, debris, color, expiration date)
Weekly	Cleaning (incubators, refrigerator)
	pH meter (level of electrolytes in electrodes, calibration, membrane cleaning)
	Incubators and water bath (change water in tray)
	Cleaning (floor, walls, ceiling, and furniture)
Monthly	Microscopes (system checking: mechanic, illumination, and optics)
Biannually	Certification and validation (biosafety cabinets, laminar flow hoods, air filters, air quality)
	Microbiological control (quantitative and qualitative analysis of colony-forming units of bacteria and fungi on laboratory surfaces, as well as in incubators and laboratory air)
	Participation in proficiency testing program
Annually	Calibration (thermometers, timers, sensors, pipettes)
As received	Supplies, culture media, and reagents (receiving date, product characteristics such as temperature during transportation and during arrival, opening date, expiration date, storage requirements, certification of analysis, toxicity testing for every new lot of plasticware and materials with contact to gametes and embryos)

Proficiency Testing

Proficiency testing (PT), defined as the determination of laboratory testing performance by means of interlaboratory comparisons, is an integral element of quality control [1, 2, 10]. Laboratories involved in PT programs periodically receive specimens from a central laboratory/regulatory agency for analysis and/or identification. In-house technicians assess specimens/slides and send their results to the central laboratory which then compares laboratory's results with those of other laboratories in the group and/or with an assigned value. Interlaboratory communication is prohibited among members of PT programs, and PT samples should be integrated within the routine workload, which means that they should be treated as patient specimens. Personnel who routinely test patient samples will be required to analyze the PT samples using the same protocol as for patient samples [10].

Proficiency testing applied to embryology laboratories mainly involves embryo grading and determination of the suitability of culture media for embryo culture. In the former, embryo grading is carried out using videos with embryos at different days of culture. Participants are asked to score embryos according to several parameters (grade, stage, cell number, % cytoplasmic fragmentation, symmetry, blastocyst features such as inner cell mass, trophectoderm, and compaction) and report their results using a multiple-choice-answers' questionnaire [11]. In the latter, culture media specimens are sent to participants to be used with their preferred bioassay (mouse embryo, hamster sperm motility, human sperm survival). Participants should perform the bioassay and determine the suitability of the distributed media for in vitro embryo culture. In andrology, PT involves the periodic distribution of material (to assess sperm concentration, vitality, morphology, antisperm antibodies, as well as videos to grade sperm motility) by a central laboratory/agency which is analyzed by each PT participating laboratory. Material received can be stored and used as internal quality control, but one should be aware of its shortcomings since the values are already known.

Proficiency testing results are returned to the central laboratory/agency where data from different laboratories are compiled and sent out to participants together with comments and suggestions. For quantitative analytes, the calculated results should be within acceptable limits for technicians to be considered proficient in a given testing. According to the ISO 13528:2005, there are four types of criteria to assess acceptable variability (1) ±3 standard deviations (SD) of the compiled results of all participating laboratories; (2) ±3 SD of the compiled results of all expert laboratories; (3) quality specifications based on expert opinion, state-of-the-art guidelines, and biological variability; and (4) previous-cited quality specifications adjusted for the uncertainty of assigned values [12]. For qualitative results, such as embryo grading, the degree of agreement on embryo classification among laboratories has been considered a valid measurement [11]. A high degree of agreement is achieved when over 75% of participating laboratories produce similar embryo scores which match quality specifications [11].

Corrective actions should be implemented in case of unacceptable PT results and may include instrument calibration, change in procedures, personnel retraining, or other measures. Regardless of the method used for assessing acceptable variability limits, it is important that they provide clinically useful ranges, that is, a value within the variability limits should have a minimum effect of clinical decision [8]. A sample report of PT testing for andrology laboratories is provided in Table 10.5. Additional information on agencies providing proficiency testing and external quality control can be found elsewhere [8, 13].

Since PT programs are not universally available, alternative external quality control may be used to determine laboratory testing performance. Examples of such methods are split sample analysis with reference or other laboratories, split samples with an established in-house method, assayed material, regional pools, validation by chart review, and participation in ungraded/educational proficiency testing programs [8].

Table 10.5 Sample of proficiency testing (PT) report for andrology laboratories

Laboratory test	Calculated result[a]	Expected results[b]	Comment	Corrective action
Sperm count	34.6 M/mL	46.9 ± 12.8 M/mL	Results within acceptable mean ± SD	Not required
Sperm motility	25%	26 ± 8%	Results within acceptable mean ± SD	Not required
Strict criteria sperm morphology	5%	8 ± 4%	Results within acceptable mean ± SD	Not required
Sperm viability (eosin–nigrosin test)	44%	49 ± 6%	Results within acceptable mean ± SD	Not required
Antisperm antibody (immunobead testing)	Positive	Positive	Correct result reported	Not required

Source: Andrology laboratory and reproductive tissue bank, Cleveland Clinic, with permission
SD standard deviation
[a]Indicate testing results for an individual technologist performing each laboratory testing under PT guidelines
[b]Compiled results of all participating laboratories in PT program

Quality Assurance

The quality assurance (QA) program looks at the laboratory as a whole. It is designed to identify problems or errors with the goal of improving the entire process [1, 2, 6, 7]. The main goal of the QA program is to identify errors and areas of low laboratory performance.

Typical components of QA programs include QC activities, continuing educational activities and training for personnel, safety issues for laboratory personnel and patients, and enrollment in external quality QC (proficiency) programs. In summary, QA is the overall surveillance of all laboratory activities related to quality and includes monitoring of outcomes, reporting accuracy, and assessment of feedback from patients and personnel. As such, QA is not simply restricted to the analytical laboratory aspects but to all aspects of the process: from referring the patient for testing/procedures and specimen collection (pre-analytical phase) to performing the laboratory tests/procedures (analytical phase) and then reporting and interpreting the results (post-analytical phase) [7]. Documentation of all of the above is an important part of QA.

The importance of QA lays on the fact that most errors detected in certified medical laboratories do not occur during the analytical phase. In one study involving an ISO-certified medical laboratory, the distribution of errors was 85%, 4%, and 11% in pre-analytical, analytical, and post-analytical phases, respectively [14]. As a practical example, a trained technician will precisely measure the volume of a given ejaculate; however, the results of such analysis would be inaccurate if there was a partial loss of the ejaculated specimen during collection, and this loss was not reported.

An andrology laboratory with a dedicated QA program provides clear guidelines for proper specimen collection and monitors pre-analytical errors to ensure that non-laboratory personnel report all confounders that may impact on outcomes. In the aforementioned example, the laboratory must ascertain that the patient specimen is a complete ejaculate, and in the case of being incomplete, the laboratory should have written criteria either for specimen rejection or collection error reporting. QA prevents this type of inaccuracy (abnormal ejaculate volume due to an error in reporting and/or documenting loss of part of specimen) that could mislead the clinician to order unnecessary testing in an attempt to further evaluate the hypothesis of an existing reproductive tract obstruction. An example of quality assurance report for andrology laboratories is provided in Table 10.6.

Quality Improvement

Quality improvement (QI) is a comprehensive-monitoring program designed not only to detect and eliminate problems but also to enhance laboratory performance by exploring innovation and developing flexibility and effectiveness in all processes [5]. QI focuses on the progressive increase in the quality and efficiency of each aspect of the work and activities related not only to internal production but also to patient care, employees, physicians, and the entire community it is related with [6, 7].

The goals of quality improvement are twofold, that is, the improvement of identified poor laboratory performance areas and the proactive optimization of activities that are within expected levels but that could potentially impact patient care if improved. As an example, improvements attempted at Androfert over the last years included the implementation of total air quality control within laboratories and associated facilities by construction of new cleanroom facilities with the purpose to maintain sterility and improve embryo culture conditions, incorporation of a digital recording system for assessing embryo development, introduction of a laser system for embryo biopsy, implementation of vitrification protocols for freezing oocytes and embryos, application of microsurgery to optimize sperm retrieval and facilitate laboratory sperm processing of samples extracted from men with testicular failure, and incorporation of specialized andrology testing such as sperm DNA integrity assessment [15–20]. These elements have been incorporated in the laboratory with the objective to improve different aspects of laboratory performance, and results are continuously monitored to assess the effectiveness of such methods.

Importance of Quality Management for Reproductive Laboratories

The primary forces for implementing a quality management system in reproductive laboratories are the impact on patient care and legislation requirements [6]. The latter has come from greater regulatory/accreditation oversight of reproductive laboratory

Table 10.6 Sample of quality assurance (QA) review for andrology laboratories

Phase	Standards	Results	Comments	Corrective action
Pre-analytic	Patient preparation, specimen collection, labeling, preservation, and transportation	No incidents reported	–	Not required
Pre-analytic	Laboratory test requisition requirements	No changes were made on test requisition in this period	–	Not required
Pre-analytic	Criteria used for specimen rejection	Three specimens rejected due to collection in inappropriate container or inappropriate transport conditions	–	Not required
Analytic	Analytical process	Four validation errors were found	See documented QA problems	Validation errors corrected (see documented QA problems and solutions)
Analytic	Proficiency testing	PT completed by all technicians. Results within acceptable ranges	–	Not required
Post-analytic	Timely reporting of test results	A total of 866 test requests were ordered with 14 (1.6%) requests exceeding TATs in this period	A maximum of 20% of ordered tests should exceed our defined TAT for each test	Not required
Pre-analytic	Test report form organization	No changes were made on test report in this period	–	Not required
All	Safety	No lab safety incidents reported in this period	–	Not required

Source: Andrology laboratory and reproductive tissue bank, Cleveland Clinic, with permission.
TAT turnaround time

activities, while the former is more difficult to determine since there is lack of studies demonstrating an impact of quality systems on fertility treatment outcomes and diagnosis accuracy.

Despite that, it is well accepted that results of fertilization and embryo quality provide fair evidence of quality control effectiveness in the embryology lab. The final outcome, however, is the production of an ongoing pregnancy and far ahead a live healthy offspring. As such, the process as a whole involves multiple elements that include not only laboratory issues but also patient variables. Failure to comply with QC and QA standards may prevent identification of poor performance laboratory areas that may be perceived only several weeks later when pregnancy rates fall [7]. On the other hand, adherence to strict discipline for routines and procedures minimizes such risks, and utilization and monitoring of quality indicators throughout processes allow for a faster identification of the reasons for performance decline. As a consequence, corrective actions are not delayed, and outcomes would not be irreversibly compromised [21].

The andrology laboratory poses a different problem since it has been suggested that semen analysis is now performed satisfactorily all over the world and that quality assurance in semen analysis, which is costly and labor intensive, is not essential because the results generated do not adequately predict fertility [22]. These arguments have their supporters, mainly those with responsibility for setting budgets and allocating resources, as confirmed by the fact that most IVF clinics do not have a fully equipped and certified andrology laboratory. Usually, a so-called andrology laboratory is set up to minimum or below-minimum standards despite the increased emphasis being placed on quality procedures for laboratories performing any sort of testing [21]. Such laboratories usually conduct conventional semen analysis and semen cryopreservation, while sperm processing for ART is performed by the embryology laboratory.

A careful examination of the above-cited arguments, however, raises several concerns. First, training/proficiency programs are not mandatory in most countries, and it is unknown whether all laboratory personnel engaged in performing semen analysis receive appropriate training [21]. In fact, data from surveys of laboratory practice performed in the USA and the UK indicate that semen analysis techniques are still poorly implemented [23–25]; in the aforementioned US study, 61% of participating laboratories were associated with ART programs [23]. Second, semen analysis is one of the most important elements in the evaluation of male subfertility, and its results are often taken as a surrogate measure of his ability to pregnancy fatherhood. Semen analysis results provide information on the functional status of the seminiferous tubules, epididymis, and accessory sex glands [26]. It is true that the prognostic value of semen characteristics, such as sperm concentration, percent motility, and morphology, as surrogate markers of male fertility, is limited; the fertility potential of a man is influenced by sexual activity, the function of the accessory sex glands, and other conditions, and wide biological variability exists within the same individual. In fact, results from at least two separate seminal analyses must be obtained, although a definitive conclusion on a male fertility status may not be obtained in certain occasions since routine semen analysis itself does not account

for sperm dysfunctions such as immature chromatin or DNA damage [26]. Nonetheless, semen analysis results aid in defining the severity of the male factor as well as guiding the evaluation including whether the patient may need a full endocrine evaluation, imaging studies, specialized semen tests, or genetic screening [20]. With both accuracy and precision, the clinician is able to rely upon the values provided by the andrology laboratory, thus properly directing the further work-up, diagnosis, and counseling of the subfertile male. Despite being nonspecific for identifying male factor infertility etiologies, semen analysis is often the gateway test from which multiple expensive and often invasive treatments are based. As such, the importance of a reliable andrology laboratory cannot be underestimated.

A practical example illustrating the importance of accurate and precise standardization in semen analysis comes from our own experience with regard to the assessment of azoospermia. Examination of azoospermic semen is important not only in cases of postvasectomy but also for those individuals with nonobstructive azoospermia who seek for a chance of fatherhood [20]. In the former, presence of sperm may indicate failure of vasectomy or delayed sperm washout, while in the latter, it may confirm that minimal sperm production exists, and as a result there is a chance of success with the use of such spermatozoa for ART. It is recommended that the laboratory diagnosis of azoospermia is confirmed in both uncentrifuged and centrifuges specimens, as well as in fixed-stained smears [8]. It has been our observation, however, that in some cases involving men with nonobstructive azoospermia, sperm are not obtained at the time of IVF-ICSI (in both post-ejaculation and postsurgically retrieved specimens using modern microsurgical sperm retrieval techniques [19]) despite rare sperm had been previously documented on initial investigation. In cases of nonobstructed azoospermia, the presence of sperm in a wet or stained prep and a negative one (even after surgical sperm retrieval) at the time of IVF poses a tremendous psychological and financial burden to the infertile couple who must face with the decision of aborting treatment or proceeding by using heterologous sperm for insemination [19]. We thereby identified errors that have occurred at the analytical phase by investigating such unusual occurrences (1) same air displacement pipette used during routine semen analyses, (2) same solutions used for staining fixed smears during routine semen analyses, and (3) pipette tip without filter used to dispense semen suspensions for both wet and fixed-stained examination. As such, the presence of sperm, as seen in uncentrifuged or centrifuged specimens (either wet or stained), might come from sample-to-sample cross contamination either from the pipette used to handle semen from different patients (spermatozoa may become trapped at the pipette shaft due to poor pipetting technique) or the staining solutions, or both. We therefore implemented three modifications to our analytical process when handling azoospermic specimens, as follows (1) use of a dedicated air displacement pipette, (2) use of hydrophobic polyethylene filter tips to protect pipette shaft from contamination, and (3) use of dedicated-stain solutions for azoospermic specimens.

The above-cited practical example highlights the importance of quality assurance in the andrology lab. Although it became commonplace to say that clear examples of how semen analysis QA has resulted in the correction of a methodological

problem are rare, this may be because few laboratories are sufficiently dedicated to the principles of quality [7]. In practical terms, implementation of a quality management system within the context of andrology laboratories is a mode of ensuring that semen analysis results represent an accurate and precise reading of that particular semen sample, thereby negating the need for multiple repetitive analyses and expensive complementary investigation.

For clinicians and patients, laboratory adherence to QM also provides a marker of its dedication to quality control which is often linked to a greater reputation among their peers. In Table 10.7 we provide an overview summarizing the main features of quality management that may be used for reproductive laboratories willing to implement such program.

Table 10.7 Overview of quality management for reproductive laboratories

QM indicator	Comments and relevance
Written quality management/ quality control (QM/QC) program	Documented procedures describing scope of activities; staff competencies and responsibilities; methods for patient identification and preparation; specimen collection and labeling; specimen rejection criteria or procedures for handling suboptimal specimens; specimen preservation, processing, storage, transportation, release, and discard; result reporting; biosafety norms, laboratory description, and rules of operation. These elements should be consistent with good laboratory practice and must qualify throughout the pre-analytic, analytic, and post-analytic phases of testing/procedures, and should be readily available to laboratory personnel. The program must be capable of detecting problems in the laboratory's systems and identifying opportunities for system improvement. The laboratory must be able to develop plans of corrective/ preventive action based on data from its QM system
Quality control guidelines for instrument and equipment	The laboratory must have an ongoing daily evaluation of instrument performance to detect errors and to perform corrective/preventive actions. It should also have a preventive maintenance program for instrument calibration and equipment function in place
Documented system to detect and correct, in a timely manner, clerical and analytical errors, and unusual laboratory testing results	Testing results should be reviewed by a qualified person before release, and results should be corrected in case of errors before available for clinical decision. If an unacceptable or suboptimal specimen is received and processed, there must be a mechanism to notify the requesting physician and to note the condition of the sample on the report. For suspected errors detected by the end user after reporting, corrections must be promptly made if such errors are confirmed by the laboratory
System for reporting nonconformities, preventive and corrective actions	The laboratory must have an ongoing system for reporting unusual or abnormal events to the supervisor, director, or quality manager, as well as proposed and implemented corrective and preventive actions

(continued)

Table 10.7 (continued)

QM indicator	Comments and relevance
Document review by qualified person	The laboratory must have an ongoing reviewing system for quality control of routine procedures, documentation of in use reagents and their source, and instrument function checks. Moreover, the director must ensure that the policies and technical protocols are complete, current, and have been periodically reviewed by a qualified person. Current laboratory practice must match the policy and procedure documents, and a system should be in place to document that all lab personnel are familiar with contents of the QM/QC program and the SOP relevant to their scope of activities. New policies/procedures and substantial changes to existing documents must be approved before implementation, and discontinued procedures should be maintained for consultation
Clinical outcome and clients satisfaction review by qualified person	The laboratory must have an ongoing reviewing system for reviewing clinical outcomes and clients satisfaction in relation to data collection

Adapted from the College of American Pathologists Standards for Reproductive Laboratories Accreditation, 2009.
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Part III
International Experience

Chapter 11
Singapore

P.C. Wong

The ART program in the National University Hospital (NUH) started since the hospital opened in 1985. NUH is an acute care tertiary general hospital. Patients with infertility problems are either referred by family physicians or other gynecologists, or they may be self-referred. NUH is also a training hospital with a residency program in obstetrics and gynecology.

Initially, the program was smaller, and the manpower i.e the nurses, laboratory personnel, embryologists and physicians were fewer in numbers (Fig. 11.1). When the numbers grew, it became evident that a quality management (QM) system was needed to standardize our functions and operations. If the growth of the ART program were to progress effectively, procedures need to be standardized. Any deficiency needed to be identified and dealt with early and efficiently.

This harmonization of all our procedures is in effect the drawing up of a quality manual. So in effect in so doing, we are "saying what we do and doing what we said."

Why We Needed a QM System?

As the program grew, the pressures were increasing from many quarters to produce a quality manual. All our staff members needed to be doing the same procedures over and over again with no variation by individuals or day of the work week.

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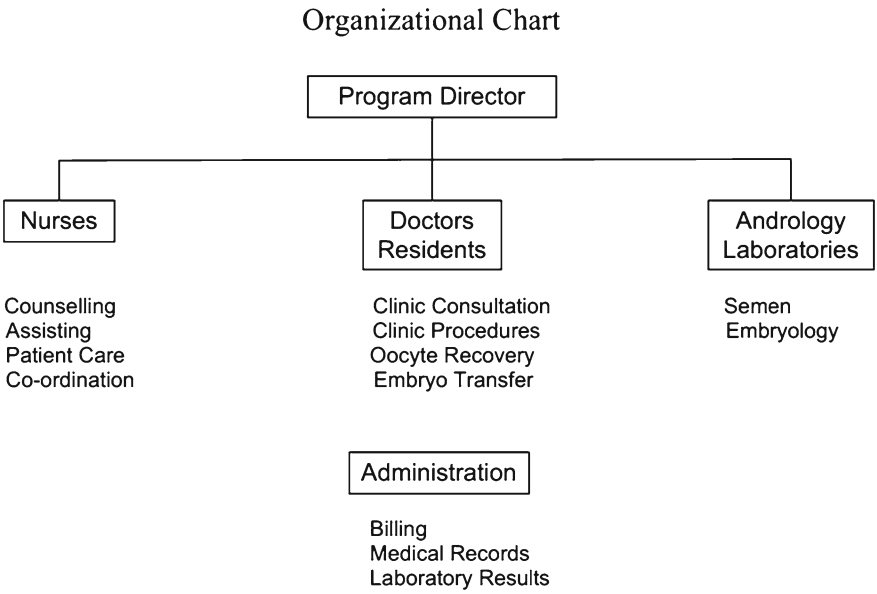

Fig. 11.1 Organizational chart in an ART center in Singapore

Physicians

As we recruited new physicians, we had to standardize many of our functions. From the beginning, we had to standardize how we investigated the patients that were referred to us. We also devised treatment algorithms to decide when patients were ready for assisted reproductive techniques. Even while doing the follicular ultrasound scan, we had to standardize how we should measure the follicle, which view to take, etc. We had to standardize at what follicular size we administer hCG. This standardization was important so that every member in the team knows beforehand how each patient will be managed.

Nurses

As we recruited new nurses, the task of training new recruits usually fell on the senior nurse. If there were no manual to follow, then the training of a nurse would be ad hoc and unsystematic. This often led to inconsistent training and resulting in variations of what was taught or omitted. With the introduction of the manual, all new nurses need to read the manual and be taken through the pages, thereby learning everything that they were expected to.

Laboratory

We found that the greatest need was in the laboratory. Without standardization, there was bound to be wide variations in what each technician or embryologist does. ART results are so dependent on the embryologist that the standardization is so crucial. The same rationale applied when we recruited and trained new embryologists. The presence of a quality manual allows easy reference and provides the framework for training the new recruit in a systematic and comprehensive way.

Residents

For the residents rotating through reproductive endocrinology and infertility, they need to understand why certain procedures were done and to facilitate their learning the written protocols and operational procedure would come in useful to complement their own reading.

What System Did We Choose?

We did not choose the certification system. Our hospital initially picked the ISO—9001 [1] for certification. But because the ART program was situated within the hospital, the accreditation process was taken as a whole. But still the certification process was similar.

What were the difficulties we faced in implementing such a system? The biggest difficulty was to write down all our protocols and operational procedures. These were painstaking. We divided the work among all our staff, and we started to put on paper what we usually did. This process was laborious and time consuming. Prior to this, some of the protocols and operational procedures already existed, but they were not centrally located, for example, nursing protocols were with nurses and laboratory protocols were with the laboratories. Furthermore, they were written in a nonstandardized way. So we had to rewrite all our existing protocols and standard operational procedures into a standardized way. In areas where we did not have prior protocols, new ones were written up. Each section did its own writing of the protocols because we believed that each section i.e nurses, physicians, and laboratory personnel know their work best. These were subsequently reviewed as a group and then approved.

Second Phase

The second phase of our QM journey was when our hospital later decided to seek certification by the Joint Commission International (JCI), the international version of the Joint Commission Accreditation of Health Care Organization (JCAHCO) [2].

The requirements of the JCI accreditation were somewhat different from the ISO, but basically there were a set of quality areas that we had to adhere to. After having gone through the ISO certification previously, we were somewhat prepared to make the necessary changes and challenges leading to our certification and subsequent recertification in 2010.

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Chapter 12
India

B.N. Chakravarty and S. Sharma

There has been a rapid expansion of assisted reproductive technology (ART) over the last two and a half decades in India. Live birth rate following ART program has steadily increased from <1% to roughly 33% in just over 30 years. The improving success rate may be attributed to the advances in ovarian stimulation protocol and improvement in quality and competence of IVF laboratory and personnel. Still many attempts lead to failure despite recent clinical advances in ovarian stimulation regimens and surgical procedures to collect gametes.

ART laboratory is the most important component of the ART program. In human in vitro fertilization (IVF), gametes and embryos require fastidious procedures, and there is considerable awareness that the environment of the laboratory itself can alter the quality of the *embryos*. So there is an increase in the use of quality management systems to guarantee high-quality patient care as well as to ensure that the laboratory is maintaining consistency, thus maximizing embryo quality and success in ART program [1, 2]. This will also help to alleviate patient's anxiety.

Anxiety starts from registration in the clinic and continues up to the period of time from embryo transfer till the result of pregnancy outcome is known. If the patient is aware that every step of the procedure is being monitored or verified, she remains more confident about the integrity of the clinic [3]. Therefore, it is mandatory for each and every ART clinic to design and apply appropriate and conscientious internal quality control (QC) procedures and external quality assurance (QA) programs for establishing and maintaining the highest level of patient care. Quality is the heart of management in any laboratory, more importantly in human ART laboratories. Quality management (QM) is not limited to initial certification/accreditation but requires continuous improvement of all aspects in an ART program. QM systems integrate quality control (QC) and quality assurance (QA).

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Definition of Quality Control and Quality Assurance

Quality Control

Quality control is the process by which all aspects of the program are monitored and confirmed as functioning within acceptable limits. The quality control should ensure that the program is operating in a consistent and reproducible fashion. Without this stability in the program, it becomes very difficult to determine whether an unusual outcome for a particular patient is due to a patient-related issue or due to a programmatic failure.

Quality Assurance

The objective of quality assurance is not only to maintain the standard (quality control) but to improve the outcome. From that point of view, quality control is a part of quality assurance. Therefore, quality assurance includes quality control assessment of personnel, procedures, and materials, which provide data for improvement of activities.

Obligation to Quality Control and Quality Assurance

Quality control and assurance are possible through legislation or through guidelines. The legislation or the guidelines will formulate quality management system that will be governed not only by the clinic authority but by a central regulatory body. In India, the Indian Council of Medical Research (ICMR) has introduced mandatory guidelines for the ART clinics [4], which will certainly upgrade the standard of ART treatment through adequate quality control to provide optimum care to the patients. These guidelines are likely to be converted into bill/legislation after approval by the parliament.

For quality control of ART clinic and laboratory, the guideline has laid down emphasis on five basic components:

1. Minimum physical requirements for an ART clinic.
2. Essential equipments, record of their proper maintenance, documentation, and auditing of daily activities.
3. Composition, essential qualification, and responsibility of the members of the ART team.
4. Training and upgrading the knowledge of existing members of the ART team and those aspiring to start an ART clinic.
5. Lastly and not the least, quality management should ensure that the code of quality practice is being maintained.

It will be the duty of the accreditation committee to ensure that every ART clinic is following and maintaining these basic principles. This will not only fulfill the criteria laid down under the definition of quality control but also achieve better success rates in ART programs, which has been defined as quality assurance.

Each component outlined in the guideline has stressed points that are directly or indirectly linked with quality management of ART centers in the country. This chapter primarily highlights:

(a) The suggestions encoded in the ICMR guideline [4] for quality management of an ART clinic in Indian environment
(b) Difficulties initially encountered and still existing for their practical applications
(c) Remedies if possible to correct and improve standard of quality management of ART clinics in Indian context

Minimal Physical Requirement of an ART Clinic

For quality management, there should be minimum physical requirement for all ART centers. A well-designed ART clinic should have non-sterile and strictly sterile areas. Some of the spaces may be combined (i.e., the same space may be used for more than one purpose) as long as such a step does not compromise the quality of service. However, the space provision for the sterile area cannot be combined with those of the non-sterile area and vice versa.

Because of inadequate resources, many small centers in the country initially insisted on running the centers with minimum physical space allotment. However, with the number of centers increasing and competition mounting, centers are becoming more disciplined and organized compared with those that existed 20 years ago. Some of the clinicians aspiring to start an infertility/ART clinic demanded that an IUI clinic need not be accredited. But in the ICMR guideline [4], IUI laboratory just like an ART laboratory will require accreditation for quality management. This issue remained controversial for a long time. In our opinion, IUI is not an ART procedure (because female gamete is not extracorporeally manipulated), and hence IUI laboratories need not require strict accreditation and may only be governed by the regulation of standard operating procedures (SOPs). However, subsequently, it was unanimously accepted that laboratory where semen (biological fluid) is to be prepared for insemination will require accreditation, though the clinic performing IUI need not require accreditation provided the doctor performing IUI in the clinic has a postgraduate degree in obstetrics and gynecology.

However, semen preparation room for IUI and IVF should be separated. IUI semen preparation room, therefore, may not be strictly in the IVF sterile area but should be at least away from the non-sterile area (which has been mentioned in Fig. 12.1 as semi-sterile area).

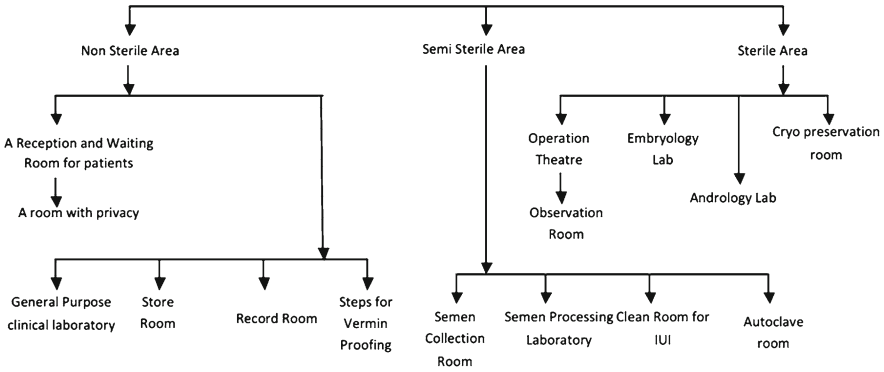

Fig. 12.1 Minimal physical requirements of an ART clinic

Availability of adequate space has significant impact on quality management of an ART clinic. At the outpatient's department, a spacious area for counseling and audiovisual presentation in a patient waiting room will have a positive impact on the anxiety stricken couple who will come to know each step of any "process" that goes on in the clinic. So also in the laboratory, sufficient capacity should exist to accommodate a sufficient number of incubators (so that doors are not opened frequently) and also for controlled-rate freezer because all the spare embryos should be frozen at the right time.

Essential Equipments and Record Maintenance for Quality Management

Many countries have implemented written regulations to upgrade ART procedures through quality management measures. This has also been indirectly introduced in India through "National Guidelines for Accreditation, Supervision and Regulation for ART Centers in India" edited by Indian Council of Medical Research (ICMR). The guideline has identified which areas should be specifically standardized for quality management of ART practice in the country [4]. Some of the relevant points are described below.

Maintenance of the Laboratories

Each laboratory should maintain in writing, standard operating manuals for the different procedures carried out in the laboratory. It should be ensured that there is no mix up of gametes or embryos. The patient's name should be clearly labeled on all the tubes, dishes, and pipettes containing the gametes or embryos. All pipettes should be immediately discarded after use.

Laminar flow hoods, laboratory tables, incubators, and other areas where sterility is required must be periodically checked for microbial contamination using standard techniques, and a record of such checks must be kept. A logbook should be maintained to record the temperature, carbon dioxide content, and humidity of the incubators, and the manometer readings of the laminar airflow. All instruments must be calibrated periodically (at least once every year) and a record of such calibration maintained.

Quality of Consumables Used in the Laboratory

All disposable plasticware materials must be purchased from reliable sources after ensuring that they are not toxic to the embryo. Culture media used for processing gametes or growing embryos in vitro should be preferably from reliable manufacturers. Each batch of culture medium needs to be tested for sterility, endotoxins, osmolarity, and pH. The embryologist should know the composition of the media that are being used. Most media are supplemented with serum; they should, therefore, be tested for antibodies to HIV 1 and 2, hepatitis B surface antigen, and hepatitis C RNA. Human serum albumin should contain embryotrophic cytokines; otherwise, it would be a major source of endotoxin contamination [1]. It has been emphasized in the ART guidelines that no product or device should be used in ART laboratory that has not been approved by appropriate regulatory authorities such as the Food and Drug Administration in the USA and Drug Control General in India.

Infection Control

Infection control in the ART laboratory is essential not only for success but also for quality control and medicolegal reasons. The two main sources of infection in the laboratory are semen and serum used for preparation of culture media. Semen and serum may infect both the gametes as well as the laboratory personnel.

Routine semen analysis on d2 of treatment cycle is mandatory. If the number of WBC is more than normal, a course of suitable antibiotic is to be given and semen to be prepared on the day of OPU by density gradient technique. During insemination, if clumping of sperm is seen, short exposure of oocytes to the sperms can avoid contamination. Half yearly fumigation of the culture room is essential to provide a sterile environment for oocyte and the embryo culture throughout the year.

In case of HIV-positive patient or hepatitis surface antigen carrier, the embryologist should be very much careful and incubate the gametes in a separate incubator. Proper screening of the patients in the investigation cycle (HIV and HBSAG) is mandatory.

Moreover, central air-conditioning, air modulator, restricted entry to the laboratory, and regular cleaning are necessary to provide a clean sterile and nontoxic environment for oocyte and embryo culture. Proper and regular disposal of the laboratory garbage is advisable to maintain a clean and healthy surrounding. The embryologist/andrologist should wear gloves all the time for self-protection.

Documentation and Record Keeping

Apart from defining the processes relevant to a quality management system, it is imperative to maintain correct documentation. For example, if an unwanted incident occurs, the incident must be documented and measures should be taken to correct and implement changes in order to prevent recurrence. The quality manual is the most important document containing the structure of the organization, a brief description of how important procedures are done. It also states the position of staff and their responsibility.

Handbook or standard operating procedure (SOP) details the process step by step and describes the materials and method used and the way each process is performed [5]. Protocol sheets should be filled in by the person who performs the respective procedure with date and signature. It should be available to all personnel involved in the process. A vital part of documentation is the outcome of procedures, which includes pregnancy rate per treatment cycle.

Audit

Audits are tools that improve and keep the system up to date with the standards. They can be internal or external, both ensuring that the quality system is working well. They help the clinician in improving the outcome.

Backup Power Supply

There should be no interruption in power supply to the incubator and to other essential services in the clinic. Given the power supply situation in India, it is, therefore, imperative that a power backup in the form of UPS system and/or a captive power generation system is available in infertility clinics offering ART services.

Composition, Essential Qualifications, and the Responsibilities of the Members of the ART Team

Essential Qualification of the ART Team

Results in an ART center are best achieved by the whole team, working effectively both as a team and as individuals [6, 7]. It is the responsibility of the director to develop staff for the ART center [8, 9]. The practice of ART requires a well-orchestrated teamwork among the gynecologist, the andrologist, and the clinical embryologist supported by a counselor and a program coordinator/director.

Gynecologist (Clinician)

Gynecologist for ART team should have a postgraduate degree in gynecology having special interest in infertility and reproductive endocrinology. The responsibilities of the gynecologist would include the following:

- Interviewing of the infertile couple initially
- History taking
- Physical examination of the female patient
- Recommendation of appropriate tests to be carried out, interpreting them, and treating medical disorders (infections, endocrine anomalies)
- Carrying out laparoscopy or sonohysterosalpingography for determining the status of the uterus and the fallopian tube
- Advising the couple on planned relationship in simple cases
- Carrying out AIH, AID, IUI, IVF, and ICSI as the case may warrant, based on diagnostic evidence
- Proper record keeping

Andrologist

Andrology is concerned with male reproduction, and 50% of infertility cases are related to male factors. In India, a urologist having an additional training in diagnosis and treatment of various types of male infertility can be appointed as an andrologist in an ART center because specific training in andrology or seminology in the country either in the universities or the national board is still not available:

- The andrologist must have knowledge of the occupational hazards, infections, and fever that can cause reversible or irreversible forms of infertility and knowledge of ultrasonographic or vasographic studies to detect partial vasal occlusion that can be surgically corrected.
- He or she must understand the principles of semen analysis and sperm function tests and should be able to interpret those.
- He or she should be familiar with surgical procedures such as PESA, MESA, TESA, and TESE for ICSI in azoospermia.

Initially and even now, it is difficult to get a specially trained andrologist to cover all the ART centers in the country. Except few centers, one andrologist usually works for 2–3 centers at a time. Most of the andrologists have been self-trained through their own interest and devotion.

Clinical Embryologist

The clinical embryologist must be knowledgeable in mammalian embryology, reproductive endocrinology, genetics, molecular biology, biochemistry, microbiology,

and in vitro culture techniques. The biologist must also be familiar with ART. He or she must be either a medical graduate or have a postgraduate degree or a doctorate in the appropriate area of life sciences.

Responsibility of the Embryologist

Due to inadequacy of training facilities, there are not many trained embryologist in India to run all ART centers in the country. It has been suggested that one full-time embryologist is essential for each 125 stimulated treatment cycles per year [2]. Most of the embryologists are trained through short-term training either from reputed center in the country or through various workshops organized within or outside the country. However, currently more than 50% of various ART centers in India have adequately trained embryologists.

Even then they are overworked and still now there are centers which run with part-time embryologist. Overwork brings down the quality of work. Embryologist must be alert in order to perform all aspects of their work accurately and reliably with the lowest possible risk of making mistake. Quality management should ensure that staffs are not working without break at their maximum capacity which invariably will reduce their qualitative efficiency.

In ART guideline of India, it has been categorically mentioned that when an embryologist is working in more than one clinic, he or she should give in writing that he or she is able to take care of the entire work of the clinic without compromising the quality of service. An embryologist must not be associated with more than two centers at a given time.

Counselors

Counselors are important adjuncts to any fertility clinic. Counseling for ART is not taught as a separate subject anywhere. A person who has at least a degree in social sciences, psychology, life sciences, or medicine and a good knowledge of the various causes of infertility and its social and gender implications and the possibilities offered by the various treatment modalities should be considered as qualified to occupy this position. The person should have a working knowledge of the psychological stress that would be experienced by potential patients and should be able to counsel them to assuage their fears and anxiety and not to have unreasonable expectations from ART. A member of the staff of an ART clinic who is not engaged in any other full-time activity in the clinic can act as a counselor.

The counselor must invariably appraise the couple of the advantages of adoption as against resorting to ART involving a donor. An individual may act as a counselor for more than one clinic, but each clinic where the counselor works must own responsibility for the counselor and ensure that the counselor is able to take care of

the entire counseling load of the clinic without compromising on the quality of the counseling services.

Program Coordinator/Director

He or she should be a senior person who has had considerable experience in all aspects of ART. The program coordinator/director should be able to coordinate the activities of the rest of the team and take care of staff administrative matters, stock keeping, finance, maintenance of patient records, statutory requirements, and public relations. He or she should ensure that the staff are keeping up with the latest developments in their subject by providing them with information from the literature, making available to them access to the latest journals, and encouraging them to participate in conferences and meetings and present their data. The program coordinator/director should have a postgraduate degree in an appropriate medical or biological science.

Training and Upgrading the Knowledge of the Existing Members of the ART Team and Those Aspiring To Start an ART Clinic

Training/Qualification of ART Personnel

Until recently, there was hardly any official program either systematic educational or short-term practical that could provide the necessary training to be a full-fledged embryologist, andrologist, or sonologist. The National Academy of Medical Science (NAMS) under the control of National Board of Examination, Ministry of Health, New Delhi, has introduced a fellowship on reproductive medicine. The board has identified some ART centers in the country where the selected students (MD or DNB in gynecology) are deputed for a period of 2 years to undertake intensive training in infertility including ART.

It is now essential for the board or other academic bodies or universities to open courses on embryology, andrology, and reproductive sonology so that those aspiring to start an ART clinic can really have the benefit of availing the services of properly trained personnel. Such type of training is possible in the existing ART centers of our country, which are functioning with reputation for more than 10 years. Till such facilities are available for general training, upgradation of knowledge will depend on information available at workshops and short-period training periodically organized by big ART centers in the country. But this will not be enough for adequate training for our future generation. It is expected that an organized and well-coordinated training of different categories of staff of an ART clinic will help to upgrade the quality of services which is expected from our ART centers.

Maintenance of Code of Practice for Quality Management of ART

To maintain the quality of an ART clinic, it is essential that the code of practice outlined in the ICMR guideline for accreditation and supervision of ART clinics in India should be strictly followed [4].

Code of Practice

The code of practice deals with all aspects of the treatment provided and the research conducted at the ART clinic. The areas that commonly affect the quality of service offered by an ART center are summarized here.

Staff

A person responsible shall take full responsibility for ensuring that the staff of the ART unit is sufficiently qualified, that proper equipment is used, and that genetic material is kept and disposed off properly. There are minimum acceptable standards of experience and knowledge and qualifications of clinical and scientific staffs, which have been detailed in ICMR guideline [4].

Facilities

These must cover the standards expected in respect of provision of clinical, laboratory, and counseling care. Proper systems for monitoring and assessing practices and procedures are required (e.g., in the form of standard operating procedures) in order to optimize the outcome of ART.

Confidentiality

Any information about clients and donors must be kept confidential. No information about the treatment of couples provided under a treatment agreement may be disclosed to anyone other than the accreditation authority or persons covered by the license, except with the consent of the person(s) to whom the information relates, or in a medical emergency concerning the patient, or a court order. It is the above person's right to decide what information will be passed on and to whom, except in the case of a court order.

Information to Patient

All relevant information must be given to the patient before a treatment is given. Thus, before starting the treatment, information should be given to the patient on the limitations and results of the proposed treatment, possible side effects, the

techniques involved, comparison with other available treatment, the availability of counseling, the cost of the treatment, the rights of the child born through ART, and the need for the clinic to keep a register of the outcome of a treatment.

Consent

No treatment should be given without the written consent of the couple of all the possible stages of that treatment, including the possible freezing of supernumerary embryos. A standard consent form recommended by the accreditation authority should be used by all ART clinics. Specific consent must be obtained from couples who have their gametes or embryos frozen, in regard to what should be done with them if he or she dies, or becomes incapable of varying or revoking his or her consent.

Counseling

People seeking licensed treatment must be given a suitable opportunity to receive proper counseling about the various implications of the treatment. No one is obliged to accept counseling, but it is generally recognized as being beneficial, and the couple should be encouraged to go through it. The provision of facilities for counseling in an ART clinic is, therefore, mandatory. Couples should be referred for support or therapeutic counseling as appropriate.

Use of Gametes and Embryos

Not more than three embryos may be placed in a woman in any one cycle, regardless of the procedure/s used, excepting under exceptional circumstances (such as elderly women, poor implantation, adenomyosis, or poor embryo quality) which should be recorded. No woman should be treated with gametes or with embryos derived from the gametes of more than one man or woman during any one-treatment cycle.

Storage and Handling of Gametes and Embryos

The highest possible standards in the storage and handling of gametes and embryos in respect of their security and in regard to their recording and identification and verification should be followed.

Research

The accreditation authority must approve all research that involves embryos created in vitro. A separate license should be issued for each research project involving human embryos. The accreditation authority must not give a license unless it is satisfied that the use of human embryos is essential for the purposes of the proposed research and the research is in public interest.

Complaints

All ART clinics are required to have procedures for acknowledging and investigating complaints, and to have a nominated person to deal properly with such complaints. The accreditation authority must be informed of the number of complaints made in any year and those that are outstanding. The entire procedure of quality management of ART clinic can be summarized in the flow diagram shown in Fig. 12.2.

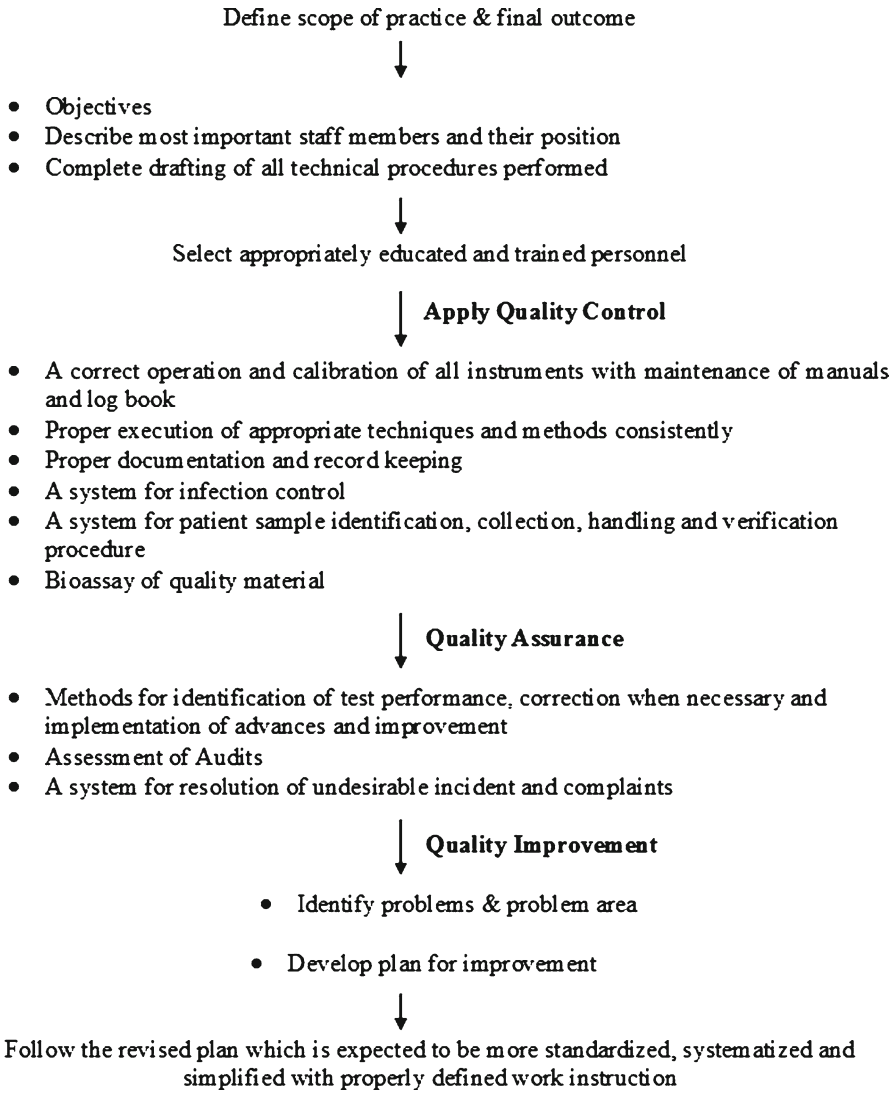

Fig. 12.2 Flow diagram summarizing the entire procedure of quality management of an ART clinic

Some of the Problems Encountered in the Implementation of Quality Management in India

- Inadequate resources: Small centers use minimum resources to perform ART at minimum cost. The equipments and drugs used for the procedure are kept at minimum compromising on the standard of care. Unless the ART bill is passed and strictly implemented, this problem of uniform quality management in all the centers in India will be difficult to eradicate.
- Equipment: Disposables/equipment used in ART centers are highly specialized, sensitive, and sophisticated. They are usually imported from other parts of the world. This makes them vulnerable to breakage and damage. Repair and replacement takes a long period interfering with the treatment procedure.
- Power supply and voltage problems: Continuity of electrical power supply to critical equipment should be ensured because equipments used in ART laboratory are all very sensitive to power fluctuations.
- Weather change/environment: High humidity in the atmosphere may cause leakage of current and can also be a source of infection within the sterile—demanding extra care. Dehumidifying air conditioner may be helpful which again adds to the cost.
- Lack of competent and effective management: In 2002, Indian Council of Medical Research (ICMR) started thinking of accreditation, supervision, and regulation of ART centers in India and formulated an expert committee to frame a guideline in order to improve the quality of management of ART treatment in India.
- But still in many of the centers in the country, the management is ignorant of or too casual in following the instructions documented in the guideline. Consequently, the management cannot allot proper duties to the proper personnel to generate efficient work atmosphere.
- However, after the bill is passed and enforced in practice, the quality management scenario in India is expected to improve significantly because labor is relatively inexpensive. Generally, doctors aspiring to start ART clinics are very intelligent and enthusiastic. With proper training and backed up by efficient and organized team effort, it will not be difficult to implement effective QMS in the country. They can work 6 days a week ungrudgingly with better efficiency and productivity.

With Existing Resources, How Can Quality Management in the Country Be Improved?

The medical director should have a clear concept of the meaning of quality management. And then he or she can implement the philosophy of the procedure to every team member of the clinic. After this has been done, the director may delegate

responsibilities to individual team members. Although responsibilities have been distributed, the director remains ultimately responsible for all good and bad outcomes of the clinic. But there should be no ambiguity about which person is responsible for which action. The director however has the power to implement changes.

Although these points have been mentioned in the National Guideline, their implementation over the years has been very slow. Because besides written documents, like this quality management book or quality management guidelines, success of quality management will depend on commitment, devotion, time, and money.

Summary

Quality management data and its regular supervision will ensure that all aspects of the program are operating satisfactorily. This will help to achieve a stable and repeatable result for the patients. Each item of quality management parameter should be recorded so that these data can be analyzed when unexpected events occur in the clinic or in the laboratory. Quality management is the yardstick by which improvement of the result of ART in future may be expected. Therefore, the practice of quality management should be continued until we can reasonably ensure viable pregnancies to all the patients who will undergo ART treatment. Unfortunately, except in very big and reputed centers, this is strictly not being followed. But it is hopefully expected that after ART bill is passed by the Parliament, the situation is likely to improve.

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Chapter 13
South Africa: A Laboratory Perspective on Quality Control

Marie-Lena Windt de Beer and Gregory Michael Tinney

Background

In the 1980s, the early years of assisted reproductive technology (ART) in South Africa, guidelines for quality management were in many regards lacking, and pioneers in the field visited well-established clinics elsewhere in the world (Jones Institute, Norfolk, Virginia and Melbourne, Australia) to obtain guidelines for good practice in ART. Prof. Theunis F Kruger, head and founder of the Aevitas/Tygerberg Fertility Centre, was one of the most important individuals during this period.

Currently, there is no official, binding accreditation system in place, but very recently, the Southern African Society of Reproductive Medicine and Gynaecological Endoscopy (SASREG) [http://www.fertilitysa.org.za] initiated serious efforts to put into place standard guidelines for good practice in ART and for accreditation with SASREG. These guidelines are modelled on the "HFEA. *Code of Practice*. 6th Edition" and the "American Society of Reproductive Medicine's Guidelines and Protocols" and has been adapted for the South African situation. Currently, governmental legislation for ART in South Africa falls under the National Health Act (No. 61 of 2003 Chaps. 1–3), the Human Tissue Act (No. 65 of 1983) and, for surrogacy, the Children's Act (No. 38 of 2005).

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The following issues are addressed in the SASREG guidelines for accreditation: personnel, specialised training and experience, quality assurance, laboratory facilities, equipment and maintenance, embryo and gamete cryopreservation, safety, record keeping, informed consent and ethical guidelines. However, in the document it is stated that it is "not designed to cover all clinical situations or practices, but rather should be reviewed by an ART programme and laboratory directors to be certain that their programme's practice reflects current recommendations. It includes sections on ethical and experimental procedures, record keeping, and informed consent, all of which are areas of increased importance in contemporary ART practice. The document is intended to enhance the already high standards practised by ART programmes".

Quality Management: Aevitas/Tygerberg Fertility Centre, Cape Town, South Africa

Quality management is extremely important in the successful running of our in vitro fertilisation (IVF) clinic. It ensures the most efficient operation, with the highest safety measures and greatest success rates for our patients. We strive to comply with worldwide IVF standards by following international regulations and trends, as is proposed by SASREG. We try to make sure that there is a correlation of technological and quality standards among our clinic and other clinics, both nationally and internationally. We endeavour to ensure that we enforce the highest quality standards to ensure the highest success rates and minimal risks.

It is the responsibility of our laboratory to ensure cleanliness and sterility in the laboratory where necessary and ensure that we have standard measurements for our equipment (e.g. incubators, refrigerators). We try to make sure that we have sufficient staff in the laboratory to cover all duties without risk of making errors due to too high a workload. We also prefer a low turnover rate of laboratory staff to ensure consistency in our work environment.

Personnel

In line with minimum standards for accreditation as an ART programme, personnel with the necessary expertise are employed at our unit. More than the minimum of two full-time qualified and experienced specialist gynaecologists and embryologists are employed. The medical director is a registered specialist gynaecologist, and the embryology laboratory director has experience in the organisation and maintenance of a basic and clinical embryology laboratory as well as in tissue culture techniques. All the clinicians employed are individuals with training and experience in reproductive endocrinology, the use of ovulation-inducing agents and hormonal control

of the menstrual cycle. Employed clinicians are also individuals with expertise in pelvic reparative (infertility) surgery and laparoscopic and ultrasound-guided oocyte retrieval techniques.

Laboratory personnel also include individuals experienced in male reproduction (andrology) with special competence in semenology, and a consultant urologist with expertise in reproductive surgery is also available to the laboratory. All employed embryologists are individuals with specialised training and experience in gamete and embryo cryopreservation techniques as well as experience in micromanipulation techniques.

The nursing sisters employed at the unit are specialised fertility sisters trained to work with all facets of caring for the infertile patient. A qualified and motivated secretarial and administrative team complete the personnel component of the unit. We have a backup system in place for all personnel essential to our clinic's functioning. Our laboratory is situated in a hospital complex, and rapid assays of all the necessary reproductive hormones (including estradiol, LH and progesterone) are readily available from a laboratory that demonstrates adequate competence, quality control and service.

Specialised Training and Experience

Clinicians

In our unit (as in all accredited ART units in South Africa), gynaecologists must have fertility specialist training, experience and accreditation (Health Professional Council of South Africa—HPCSA) in reproductive endocrinology and infertility. These specialists direct the follicular recruitment phase of the ART cycle—including oocyte retrieval and ultrasound monitoring of follicular development. Fertility specialists have more than adequate experience since the unit performs substantially more than the required minimum of 30 aspirations and transfers per year. Our unit performs ±750 cycles per year.

Embryo Laboratory Scientists/Technologists

All employed embryologists have either a Bachelor of Science degree and 2-year full-time training or a BTech diploma in Clinical Technology (Reproductive Biology) from an accredited institution. We are also one of the accredited (HPCSA) training laboratories, and a 2-year full-time training period ensures that the embryologists completing the training are adequately skilled in all IVF procedures and are of a high standard. All trainee scientists are registered with the HPCSA during training, and student interns work under continuous supervision of the laboratory director and trained, qualified supervisors.

Among our embryology laboratory staff, there are several people with knowledge and experience in preimplantation embryology techniques (including preimplantation genetic diagnosis: PGD), andrology, micromanipulation and pre- and post-fertilisation events.

The laboratory director is an individual with a demonstrated knowledge of all laboratory aspects of ART and fulfils the following requirements as specified by SASREG accreditation guidelines:

- Holds an earned doctorate degree (Ph.D.) from an accredited institution in medical sciences (Reproductive Biology)
- Is responsible for formulating laboratory policies and protocols
- Has more than 5 years of documented pertinent experience in a programme performing IVF-related procedures, familiarity with the laboratory quality control, inspection and accreditation procedures
- Has detailed knowledge of cell culture, ART and andrology procedures performed

Quality Assurance

The SASREG guidelines for accreditation document state (http://www.fertilitysa.org.za/): "The quality of the embryo laboratory is recognised as one of the most important components of a successful ART program. However there are inherent difficulties involved in evaluating the 'quality' of any laboratory system. It is therefore necessary to allow flexibility in the interpretation of any standards of the quality to accommodate different methods of maintaining laboratory quality. Each laboratory should design its individual quality control procedures and protocols about these quality control procedures should be available for accreditation purposes".

In our unit, we have the following protocols and policies regarding quality assurance.

Sterility

To prevent any contamination in the IVF clinic, a high level of sterility is absolutely vital in the laboratory. This is accomplished in a number of ways depending on the need. It is very important not to use any cleaning chemicals that are volatile with high VOC levels (e.g. ethanol, ammonia). When we sterilise the surfaces of the laminar flow cabinets or bench tops in the IVF lab, we therefore utilise an IVF-laboratory-approved disinfectant (Fertisafe, Research Instruments). This solution is constituted as per the regulations for toxic compounds (67/548/EWG) and is classified as non-dangerous (88/279/EWG). When the floors of the laboratory are

cleaned, we usually use water and a small amount of non-toxic disinfectant (Oosafe, IC Products).

The shelves and side panels of our large CO_2 incubators (Forma Scientific) are removed and autoclaved annually, while the water tray in the bottom of each incubator is emptied and autoclaved every 2 weeks when the sterile water in the tray is replaced. The insides of our MINC incubators are wiped with a sterile, wet, lint-free cloth whenever necessary.

All plastic ware, aspiration needles and embryo transfer catheters are purchased commercially in a sterile condition. All glass pipettes that are used for ovum pick-up and that are drawn for embryo manipulations are rinsed with sterile water and sterilised in a dry heat oven (160 °C for 3 h). The containers used for semen collection are sterilised by gamma radiation (it is important not to gas sterilise with ethylene oxide as this can affect the semen sample).

To ensure a maximum sterility in the IVF laboratory, we have the following in place: sterile filtration of the air entering the laboratory using a HEPA filter. A positive air pressure in the laboratory ensures that non-sterile air does not enter the laboratory. HEPA filters in our laminar flow cabinets ensure that the working surface remains sterile. All these filters are checked annually to ensure that they are functioning correctly with the correct degree of particle filtering. We also utilise Coda inline filters in our CO_2 incubators (Forma Scientific), and these are replaced every 6 months. All our incubators are serviced annually. All people entering the IVF laboratory are compelled to wear clean theatre clothes, cap/hairnet and clean overshoes. Everyone working with gametes/embryos washes their hands frequently with non-toxic soap.

Laboratory Facilities

Our IVF laboratory has the standard features of a "clean room": laboratory temperature and humidity is controlled, and filtered air enters the lab with an appropriate number of air changes per hour; walls and floors are composed of materials easy to wash and disinfect; no substances producing toxic VOC substances are used for cleaning and disinfections. The IVF laboratory is adjacent to the oocyte collection/procedure room.

Equipment and Maintenance

The IVF laboratory is equipped with all the necessary and essential equipment. These include a laminar flow cabinet, dissection microscope with a heated stage, CO_2 incubators (Forma Scientific and MINC), light microscope, inverted microscope (Nikon) equipped with Narishige micromanipulators (with heated stage and the facility to do IMSI), a microscope (Zeiss) with laser facilities and a fridge for media.

All major equipment items are maintained adequately and laboratory items (e.g. laminar flow hoods) are certified by on-site inspection on a regular (6–12 months) basis. Equipment such as balances, pipettes, thermometers, pH metres, centrifuges and refrigerators are calibrated when necessary with appropriate record keeping.

Routine quality assurance of equipment is important and should include scheduled checkups. In our laboratory, checks are performed daily or weekly where applicable. The temperatures of our large CO_2 incubators are checked daily by means of thermometers inside each one. We are currently investigating the use of a locally made temperature probe for measuring the temperature within drops of medium within the incubator (both Forma and MINC). Fridge temperature is also checked and recorded daily.

We test the pH of our media in all our incubators weekly by placing medium overnight in blood-gas syringes and then performing pH testing the next morning using a blood-gas machine. In the Forma Scientific incubators, CO_2 concentration is adjusted to obtain the correct pH, and in MINCS, we make sure that the gas mixture is correct to produce the correct pH. Records of these checks are documented. When any medium is divided, tubes and containers with the aliquots are labelled clearly with the name of the medium and any supplements added, as well as with the expiry date. We make sure that no expired media are used for culture of oocytes or embryos. The levels of the gas cylinders and the liquid nitrogen storage tank are checked daily, and the levels of the liquid nitrogen storage containers are checked weekly. Backup systems for the gas supply to incubators are available. Regular preventative maintenance schedules are in place for cleaning and decontamination of incubators, laminar flow hoods and related items, and a power backup (both the hospital's emergency power and our own petrol generator) is available for the laboratory.

Safety

An IVF laboratory is one place where mistakes or mix-ups are not permissible. Any error could result in severe repercussions, loss of jobs and even the closing of the clinic. It is therefore very important to try and implement systems where one scientist will double-check another.

This can be done in almost all procedures in an IVF clinic. For example, when inseminating oocytes, it is necessary for the name on the labelled tube of sperm to be checked to determine if the correct sperm is being used. In our laboratory, tubes with sperm samples are labelled with both the initials and surname(s) of both partners. Also, during semen preparation, it is important to keep check of all tubes to make sure that one is dealing with the same patient. This is of particular relevance when more than one patient's semen is being prepared at one time. In order to help with this matter, in our laboratory, we put the stickers of the same colour onto each tube for a single patient, varying colours between patients. This is a quick method of seeing that one is handling the same patient throughout. One should also label each tube with the patient's name and not only rely on the coloured sticker system

but also check the name on the tubes. Procedures for double-checking are also in place for transfer of embryos into new medium drops, embryo transfer and embryo and gamete cryopreservation. Whenever possible, semen samples are not processed in the IVF laboratory, but in the andrology laboratory.

Prior to each aspiration/transfer, patients are identified by asking them to say their name and surname out loud and double checked on their identification bracelet. Incubator doors/lids are also labelled clearly with patient's surnames to make quick identification and location of specimens possible. Whenever pregnancy or other outcomes (survival after thawing) are below expected, we perform problem shooting and change one thing at a time to find the problem.

Embryo and Gamete Cryopreservation

Special care is taken with the safety controls and storage of cryopreservation of gametes and embryos. At all times, double-checking takes place when gametes/embryos are cryopreserved and prepared for storage and removed from storage for thawing and also when samples are prepared for transport to another facility or received from another laboratory. Detailed records are written down on specially designed forms, and everyone involved signs in the appropriate place on the forms. We do treat HIV-positive patients, and samples from these patients are also stored separately.

Record Keeping

Documentation with proper identification, outcome and details of all gametes and embryos are kept and updated daily on individual patient forms. Documentation identifies all clinic and laboratory personnel who have handled gametes and embryos during each procedure. Each patient has an individual file, and all documentation regarding the patient's treatment cycle is kept in this file. All additional comments and discussions with the patients or between embryologists/clinicians are written in detail in the patient's file. Documentation includes details of operation reports and photos, various consent forms, semen analysis, hormone tests, ovarian stimulation record, oocyte aspiration, sperm preparation, fertilisation procedure, embryo culture, embryo transfer, cryopreservation and pregnancy/birth outcome. For cryopreservation, the developmental stage at which the embryos were frozen, the freezing protocol used, the recommended thawing procedures and the physical location of each embryo/gamete within a storage container are documented. Containers with embryos/gametes are labelled with the patient's initials and surname, the identification number [date of birth] and the date of cryopreservation. The majority of this information is also stored electronically on an access database for calculation of monthly and annual statistical outcomes.

Informed Consent

All prospective patients sign informed consent for all procedures performed on themselves as well as on their embryos/gametes. Consent forms are written in a language known the patients. Alternatively, an interpreter fluent in both English and the patient's mother tongue is available to convey all information.

Specific consent forms for all procedures are available. These include hormone treatment procedures, oocyte aspiration, all surgical procedures, fertilisation procedures, laser-assisted hatching, cryopreservation and storage of gametes and embryos (and the thawing thereof for use, donation or discarding) and blastomere biopsy for PGD. Information about all the procedures offered by the clinic is available either in a written format or on an informative DVD. Fertility sisters, clinicians and embryologists are also always available to explain procedures and consent forms. Consent forms are frequently updated to allow for new information and options.

Couples are provided with all the information concerning alternative procedures available to circumvent their specific infertility problem, including procedures that are not performed at our clinic and nonmedical options such as adoption.

Ethical Guidelines

The ethical guidelines of (SASREG) are applied in our clinic. These are structured to adhere to the laws of the country applicable to ART [the National Health Act (No. 61 of 2003 Chaps. 1–3), the Human Tissue Act (No. 65 of 1983) and, for surrogacy, the Children's Act (No. 38 of 2005)]. All research projects that are conducted at the clinic are approved by the Ethical Committee of The University of Stellenbosch (Faculty of Health), Tygerberg Campus, Tygerberg, South Africa [http://www.sun.ac.za].

Problems Implementing Quality Management

In a country that has previously had limited regulations and standards for IVF clinics and that now has new guidelines, it has been difficult to organise clinics to follow similar standards and policies. At present, new guidelines and systems are being put into place that will bring about a standardisation within clinics nationally.

When starting any new quality control practice in the laboratory, for example, SASREG accreditation, it has proven to be very time consuming and initially disruptive to the daily routine. However, once the staff has become accustomed to the new methods and controls, it becomes routine.

A big problem with quality control is the large amount of paperwork that our clinic faces. The double checking and record keeping is time consuming and

somewhat frustrating. In our laboratory situation, the main problems we encounter in quality management and the implementation thereof are.

Introduction of Alarm Systems (Accessible After Hours Outside of the Laboratory)

This is lacking in our quality management setup mainly due to the fact that we are situated inside a hospital and thus have access to emergency power for all critical electric and electronic equipment. Liquid nitrogen levels are checked daily (we never close down and there is always someone to check), and we do not feel the need for alarm systems in this situation.

HIV-Positive Patients

Compulsory testing for HIV and hepatitis in patients partaking in ART procedures is lacking in our clinic (although recommended by SASREG). All participants in any donor cycle ART and surrogacy cycles are however all tested. Reasons for the lack of testing in other patients are directly linked to the patient's human right (by law) to refuse testing or not to make their status known. In cases where HIV status is known, special precautions are taken to minimise risk (frozen sperm and embryos stored separately, sperm processed with a special double gradient and swim-up method). In general, all sperm samples are regarded as material with potential risk and handled as such.

Newest/Latest Equipment

We try to acquire the best and latest equipment. Recently, we introduced two MINC incubators (Cook Australia) into the laboratory and also started using new IMSI equipment since 2011. Lack of "the best and latest" equipment is mainly due to financial restraints.

Incubator Cleaning

Our laboratory never closes down to allow for a cleaning period of equipment and incubators. We therefore do this throughout the year and sacrifice, for instance, one incubator for 1 week in order to clean and sterilise it. Other equipment are cleaned as time allows and usually on quiet days.

Temperature in Culture Droplets/MINC Incubators

We find that, at present, it is difficult to accurately check the temperatures of our MINC incubators. We would like to check the temperature within drops of medium within the incubator, and presently, there is no probe that can go into the MINC in drops of medium. We are currently investigating a custom-made probe for this purpose.

Concluding Remarks

Although ART laboratories in South Africa (including the Aevitas/Tygerberg Fertility Centre) do not follow a specific national quality management system model, guidelines from SASREG are available and give adequate information to put into place a system that works well in our laboratory. It is therefore possible to apply a laboratory-specific quality management system regarding personnel, specialised training and experience, quality assurance, laboratory facilities, equipment and maintenance, embryo and gamete cryopreservation, safety, record keeping, informed consent and ethical guidelines.

We tried to show in a practical way how we implement what we believe to be important in quality management. We are fortunate that we are situated inside a hospital complex and can use many of their facilities to assist us with some aspects of quality management. We are also affiliated with and have access to the University of Stellenbosch (Faculty of Medicine—Department of Obstetrics and Gynaecology), giving us the ability to keep updating our knowledge regarding the latest and newest in ART. The ultimate goal of a working quality management system is of course a good pregnancy and baby take-home rate, and with a consistent ongoing pregnancy rate of >35% over all female age groups and infertility diagnosis, we are confident that the system we follow is a working one.

Chapter 14
Nigeria: Experience with Quality Management and IVF in a Developing Country

Richard Ajayi

In vitro fertilization has evolved rapidly from the experiment that lead to the birth of Louise Brown in 1978 [1] to the established treatment of infertility [2]. This evolution has been accompanied by an explosion in the number of clinics providing IVF treatment around the world as well as an increase in the number of grim stories of IVF disasters in the press. The public concern generated by these stories has led to the implementation of regulatory structures for IVF clinics in many countries around the world. While these external legal requirements are important, they are country specific, and more importantly, many countries still do not have regulatory structures for IVF clinics. There has been an increasing awareness within the IVF industry of the need for a system that can ensure that these risks are minimized without reference to regulatory structures. The International Standards Organization—ISO—has defined quality standards that have been adopted from the product industry to the service industry and (ISO 9000) was introduced as a system for IVF clinics in 2002 [3]. This call was heeded, and a lot of clinics went through the ISO certification system purely on a voluntary basis and increasing driven by statute (at least in Europe) with the introduction of the European Tissues and Cells Directive of 2004.

The developing world has also been part of this explosion in IVF technology. The absence of regulation, poor infrastructure, lower level of education, lower experience with IVF technology, higher social consequences of infertility leading to high demand for services and an economically driven generally more utilitarian perspective to very difficult ethical issues suggests that quality management systems must be important for clinics operating in developing countries. The Bridge Clinic was certified according to the ISO 9001:2000 standards in 2004 ahead of most clinics in the UK. The purpose of this chapter is to outline our experience with quality management in a developing country.

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This chapter describes quality and quality management and our experience with the implementation of quality management across the following operational areas of the organization, governance, human resources, information systems and information technology, and environmental, clinical and laboratory services. This chapter concludes with our overall impression of the quality management system in a developing country.

The term *quality* is used very widely, and we all know what it means when we say something is "of quality", but the concept of quality gets difficult to breakdown when we describe a service such as IVF. Quality can be defined as fit for use with the focus being orientated towards the customers' perceptions and opinions. This can also be termed conformance to customer requirements. One of the early teachers of quality management, W. Edwards Deming, made an important statement about quality and its modern application: "Good quality does not necessarily means high quality". It means a predictable degree of uniformity and dependability with a quality suited to the market. In medicine, quality can also be defined as duty of care, and this means the achievement of best practice. Thus, we can define the concept of quality in IVF as effective, efficient and safe services that protect the rights and dignity of all parties involved, including the welfare of the unborn child.

The objective of a quality-focused IVF clinic must be to provide the couple with safe treatment that provides a high chance of achieving a pregnancy in a pleasant environment where they receive excellent service. This means that the staff must be well trained and professional, the stimulation protocols must be safe and patient friendly and must yield the best oocytes, the egg collection procedure must be acceptable to the patients, the laboratory systems must deliver high fertilization rates and a high proportion of high-grade embryos leading to high implantation and high pregnancy rates and the cryopreservation systems must deliver top-grade embryos. The environment must be pleasant; there must be an easy and quick access to the clinic; waiting times should be short; the staff must be committed, honest and empathetic and the overall service delivery must be professional. There must be systems in place to measure outcomes focusing on leading indicators such as fertilization rates, and there must be effective customer feedback mechanisms that inform on their perception of service quality. All these systems form the quality management system which drives continuous improvement in customer satisfaction levels.

Governance

Leadership is one of the key principles of quality management. A good IVF clinic must be driven by appropriate managers looking after the different areas of the business, the scientific director, the clinical director, the general manager of administration and finance and the nursing director. The IVF market in Nigeria is in its infancy, and unfortunately, the concerns of many clinics are more commercial than academic, with a consequent shallow skill set in the local market. This will make it

difficult to set up the right governance structure, and it may be necessary to depend on the international market to solve this very important issue. It will be difficult to drive the implementation of an effective quality management system without the right team of managers, even if the chief executive is committed to the process.

People Involvement

The Nigerian government spends a small fraction of the budget on education when compared to defense spending [4]. Consequently, although Nigeria is potentially endowed with human capital, the quality of education is very poor, and this translates to poor skill sets in the local market. Furthermore, years of military rule with brief spells of nonideologically driven democratic government has led to a country where most of the people available for employment are poorly educated and driven by a generally materialist value system. It is absolutely essential that the recruitment processes be robust enough to identify staff that have the right education and values and fit with the organization. There must also be systems in place to induct and orient them towards the vision, values and culture of the organization. It is very difficult for staff to be quality oriented when they live in a country where nothing works, and the orientation process must be deep enough to affect the required paradigm shift. There must be clear and strategically defined training plans with strict competency certification systems. There must be incentive and retention systems driven by an effective performance management system. In addition to developing these systems, it is important to have the right managers in the organization to drive the implementation of these systems.

Information Systems and Information Technology

One of the requirements of our quality management certification was that we had an effective system for document management and communication within the organization as well as a confidential system of archiving patient records. The best way to achieve all of this is with an electronic system, and although there are quite a few proprietary software systems available internationally, it was very difficult to find the right skill sets locally to assist with the implementation and maintenance of such a system. The few that were available serviced the highly lucrative oil and gas industry and were economically out of our reach. We have persevered with this strategy, and we have now moved to a paperless work environment, with our three clinics connected on a wide area network. Our IT journey has included setting up our own IT company Sierra Systems to defray the cost of the IT expert we had to bring in from the United Kingdom to our current system, which is a shared service platform looking after a few client companies and managed by an experienced manager from another country.

Quality Management Documentation System

An important part of any quality management system is process definition. All our processes at The Bridge Clinic are studied, documented and developed, and we have systems in place to ensure that these processes are being constantly reviewed (Fig. 14.1). All processes are linked and there is interplay with all processes. It is important to make a distinction between process owners such as the client coordinators who manage the interplay with the client through all our processes and functional process owners such as the laboratory manager who manages the laboratory. It is important to define all the responsibilities of the process owner even beyond the functional areas. The process owners should be technically competent, have the right social interplay and be highly interested in a satisfactory outcome. The main task of the process owner is the overall responsibility for the improvement of the process. Process definition and training is a never-ending task, and it is important to communicate the strategic objective of the process to drive its effective implementation. The process definition leads to the development of standard operating procedures (SOPs), and all staff are supposed to carry out their activities according to these SOPs. We have to continually train as well as communicate the strategy behind the SOPs to ensure compliance, and in addition, we have a compliance department that carries out regular internal audits to ensure that all staff are complying with the processes as defined.

Infrastructure and Utilities

The electricity supply from the national grid is not reliable, and we spend 80% of the day without reliable power supply. We support each clinic with three power-generating sets, two to run 12-h shifts with the third generator in standby.

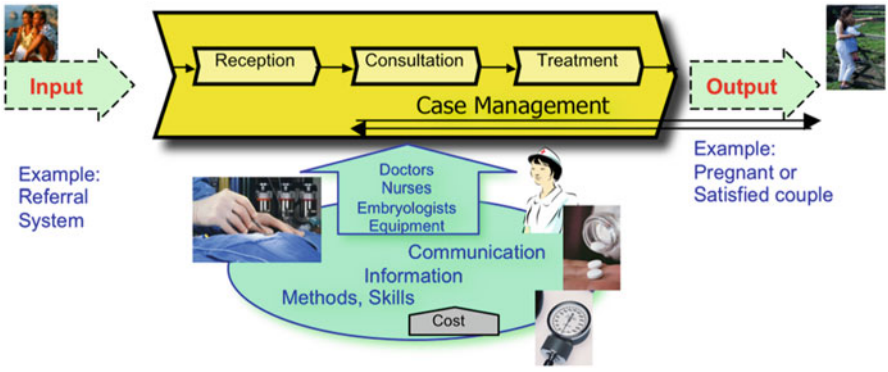

Fig. 14.1 The *top of the figure* shows a theoretical model, and *below* this theoretical model was converted to represent our workflow at The Bridge Clinic

Furthermore, all the critical equipment such as the incubators and the information technology systems (computers and server) are on a deep cell battery-driven power inverter system that will provide an additional 8 h of uninterrupted power if all generators fail. Furthermore, the inverters we have deployed produce an alternating current as a modified sine way, and we further pass the current through uninterrupted power systems (UPS) to assure the delivery of good current into the very sensitive equipment. The challenges that I have described with securing power to our equipment extend to providing adequate water to serve our toilet facilities. The water supply from the government systems is practically nonexistent, and in addition to installing powerful pumps that we use to prospect for water in the early hours of the morning when water of very low perfusion pressure may be supplied, we have had to sink a bore hole with a water treatment plant to assure the supply of water.

Our ISO certification system requires us to manage the total chain of the disposal of sharps, and although there is now a government-driven waste disposal system that provides us with sharps bins and disposes of the bins, we had to burn the sharps bins then remove them from our premises for we had to incinerate the sharps bins ourselves in a drum at the back of the clinic and take photographs of the process for our records as there were no certificates to confirm that proper disposal had taken place.

Laboratory Systems

There are many elements to consider in optimizing the IVF laboratory to deliver excellent quality embryos with implantation potential. This starts with having the right staff in the laboratory. We have evolved from the purely technical focus of our earlier recruitments where we employed graduates of human science degrees without reference to their potential, which delivers a technically competent though not necessarily aligned individual. The up-scaling of the embryologist skills was managed by extending their training to include a master's program in a United Kingdom (UK) university. We have to import IVF media from abroad, and it is important to manage the cold chain to prevent degradation of the quality of the media. This means educating the courier companies on the nature of the cargo, and we have been able to set up the required systems to achieve this with confirmation of the temperature at receipt as well as validation of the integrity of the material before use. Furthermore, we have always had challenges with the maintenance of the rather sensitive equipment required for IVF. Our pioneer status meant there was no local support, and we had to fly incubators to Europe for the required maintenance in the early days. We have since supported the development of an equipment maintenance company that is capable of providing the required support for our equipment. The risk of gamete mix-up in the IVF laboratory has always been a cause of concern, and we implemented a witnessing system as early as 2002. All our staff has received training on this, and it has become part of the culture of the organization to perform witnessing during every procedure including venepuncture.

Clinical Systems

The clinical system must be in place to support the laboratory systems to deliver high pregnancy rates. We focus on training the doctors both on the technical as well as the emotional aspects of IVF practice and focus on the special requirements of the IVF patient. It may sometimes be necessary to train doctors in communication skills to allow us to deliver the required level of professionalism. We have a strict training program to guide the development of technical competence with emphasis on protecting our patient's right to receiving high-quality treatment as well as safety. During our last ISO audit, there was some concern with our sterilization systems as we could not reproduce European standard hygiene and disinfection systems because of lack of access to the right consumables. The problem was solved by making a decision to use single-use materials for most of our procedures.

The Bridge Clinic has had a quality management system since 2004, and we still have to communicate the essence of the quality management system on a daily basis. I sometimes joke that it is easier to get a quality management certificate than get a quality management system because the process of acquiring a certificate can be driven by the leadership of the organization with the support of some management consultants, but the process of turning the organization into a quality management organization involves changing the minds of the people. This is not an easy task in a developing country such as Nigeria where most of the public infrastructure and utilities are non-functional. Most of the staff does not understand what you are trying to achieve. Their perspective is that things do not work and your quest for quality is seen as idealistic. They have not seen anything work, and the concept of quality is beyond most of the staff. An essential part of implementing a quality management system will be the exposure of key staff to facilities abroad where they start to see the system in action and understand that it is within their capabilities to drive the development of a quality management system.

The other major consideration is the cost of implementing the quality management system in a country where quality is not considered important and healthcare is considered a commodity. The challenge therefore is the effect of the quality management system on the cost of service delivery, and this must be managed by effective communication to drive the essence of the organization.

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Chapter 15
Gulf Countries

Mohamed Elkalyoubi

With the number of people living in Gulf countries exceeding 38 million (Table 15.1), they are witnessing an increase in the number of IVF centers at a time when, paradoxically, competition is high. There are well-established governmental regulatory bodies, i.e., Ministries of Health, licensing departments, etc.; however, there exist no IVF laws or directives in most of these countries. One of the main aims of the legislations for IVF centers is to set standards, particularly for andrology and IVF laboratories [2]. While IVF laws, directives, and regulations vary widely between countries [3], most aim at protecting the rights of all involved. They also lead to a decrease in some complications during IVF treatment. An obvious example is defining the number of embryos to be transferred, which successfully reduces the incidence of multiple pregnancy [4]. Some IVF experts, however, feel that less forceful regulation and more scientific freedom would allow faster development [5, 6].

Many authorities in the field of assisted reproductive technology (ART) as well as leading IVF centers all over the globe have confirmed the importance of implementing a quality management system (QMS) in IVF centers [2, 7–9], which systematically measures the outcome of all of the center's processes. Decisions to introduce change to a process must be based on facts that do not ignore the dynamics and interactions between this and other processes.

Gulf countries have the opportunity to introduce IVF laws that balance between protection and ART development. One of the tools is obligatory implementation of QMS in IVF centers especially since recent data support using a QMS as a means of improving pregnancy rates [10].

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Table 15.1 Estimated Gulf countries' population (national and nonnational)

Country	Population [1]	Approximate number of IVF centers in Gulf countries
Saudi Arabia	26,131,703	12
United Arab Emirates	5,148,664	9
Oman	3,027,293	2
Kuwait	2,595,628	11
Bahrain	1,214,705	4
Qatar	848,016	2
Total	38,966,009	40

IVF Centers in Gulf Countries

The lack of directives in assisted reproductive technology (ART) in Gulf countries has allowed many private as well as governmental bodies to build IVF centers with in-house-prepared guidelines, protocols, and regulations. Even GPs and gynecologists, in addition to the infertility specialists, treat infertile patients and can prescribe ovulation induction medications, including gonadotrophins' injections, as well as offer intrauterine insemination services while using the equipment of a general medical laboratory. All come, however, under the general regulations of running a medical facility, which is not necessarily the same as running an IVF center, particularly in the case of andrology and IVF laboratories. It is not an exaggeration to claim that a good number of these IVF centers do not implement any type of integrated QMS. They do, on the other hand, monitor some of their activities, mainly the IVF laboratories and their success rate, i.e., pregnancy rate, which does not necessarily include miscarriages; multiple pregnancy; or live birth rates.

The majority of the IVF centers in the Gulf are staffed by expatriates with different cultural, social, and religious backgrounds, who are trained in different countries with different laws and directives. They are used to working efficiently with any given established quality management system and do not feel threatened by the system; rather, they perceive it as a tool for improvement. When they move to the Gulf, to a center without a QMS (sometimes even without a proper orientation of the center's structure, policies, procedures manuals, and strategic plans), they quickly realize that keeping the job is not about performance, and their overall quality drops. As such, there is an urgent need for IVF laws that not only define the process of licensing centers but also enforce the use of a QMS.

Moreover, in the UAE, which recently introduced an IVF law, some of the already functioning IVF centers face the possibility of permanent suspension of their activities because of failure to meet the required standards. This is a clear indication that there are some IVF centers in Gulf countries that are working below reasonably acceptable standards.

Some Common Reservations About QMS

In a simple questionnaire sent to leading IVF centers in Gulf countries, only one third reported using a QMS which in the majority of cases are in-house prepared. The questionnaire, as well as personal communication, highlighted the main reasons for not using any QMS, which can be summarized into the following issues.

Fear of Starting from Scratch

All IVF centers in Gulf countries have clinical and laboratory protocols, policies, and procedures. Some of them have computerized, online file keeping, and services. Obviously, in such case, there is no need to start from point zero. It is not a must to use the most sophisticated and highly expensive system, but to implement a system that aids the center in achieving the best possible performance. Examples of IVF laboratory standards in use around the world can be found on the website of the American Society for Reproductive Medicine, the European Society of Human Reproduction and Embryology (ESHRE), the US Department of Health and Human Services, the International Organization for Standardization, and the Australian Council of Healthcare Standards.

Too Complicated to Use

This was one of the most commonly mentioned reservations. The majority reported difficulty in fully understanding the meaning of a QMS and its structure. It was often mentioned that a QMS is usually presented in abstract terms that is not specific to IVF centers. The fact is that IVF centers all over the globe may serve the same purpose; however, in reality, they differ significantly in many aspects, i.e., type of patients, staff, equipment, suppliers, and law. A QMS in abstract form allows the main elements of any QMS, namely, quality planning, quality control, quality assurance, and quality management [11], to interact in a way that is required by the staff to suit their circumstances while maintaining high performance.

No One Is Using It and Those Who Are Have Not Found It Useful

Although the use of a QMS in a small IVF center may take a long time to produce meaningful data, short-term quality control (weekly to monthly) can be used until more data are collected. Some IVF centers do not differentiate between a QMS and staff management [12], while others have highly sophisticated equipment without

real quality service. For example, one IVF center purchased a 4D ultrasound machine, and the owner of the center managed a good price with a package of a fully paid 4-day training period for one medical staff member. One of the senior doctors attended, but no further steps were taken, including sharing of the knowledge with colleagues, who were left with the manuals to understand how the machine works, let alone how to get the best out of it for patients. The end result was that a highly sophisticated and expensive machine is being used mainly by nontrained personnel with expectedly lower than it should outcome. Astonishingly, the center is advertising that it has a high-quality 4D ultrasound service.

QMS and Semen Analysis

Some quality management systems were relatively well developed from the beginning of the late 1970s [13, 14]; however, their application in the IVF centers' laboratories has only recently gained momentum. Earlier WHO laboratory manuals for the examination of human sperm–cervical mucus interaction had no clear reference to quality management as a part of semen assessment [15–17]. Some experts [18, 19] observed a high degree of disagreement between laboratories when assessing the sperm. This highlights the importance of quality management systems for standardization. The WHO 5th edition manual [20] addresses this issue and offers guidelines for quality control and assurance of semen analysis.

Scientists and clinicians alike in most IVF centers in Gulf countries feel that their semen analysis is carried out satisfactory and that the extra work of monitoring the process is a waste of time, a view that was also expressed by others [21]. However, many international IVF centers and authorities [2, 7–9] reported the importance and the need of a QMS. Hence, the application of a QMS in IVF laboratories was acknowledged in the 2008 revised ESHRE guidelines [22], embedded in the ISO-based quality system [23] and is required by some national legislation bodies [24].

Reasons for QMS Failure

Without true commitment and real measurements of the achievements, any QMS will fail to achieve any improvement. IVF centers in Gulf countries may have committed their vision, quality service, and patient rights to papers, but unfortunately its use is limited to a framed decoration in the reception area. Quality must be real. Although most IVF centers in Gulf countries reported no problems with the QMS currently in use, some staff members, through personal communication, expressed the following concerns.

Improper Use of the System

One of the main reasons for discontinuing the use of a QMS is failure to properly use it. Not infrequently, senior staff stops completing the necessary forms, or, even worse, he or she assigns documentation to a mere junior staff. A working environment where QMS documentation is not deemed just as necessary as medical work is detrimental. It slacks the whole system and eventfully leads to its failure.

Lack of Proper Hierarchy of Authority

The IVF center's manager is the most vital contributor to the success of any QMS. Most staff starts off competent; then, he/she rises through promotion to a position that challenges his/her competence. Competent managers should share the decision-making with their staff, explain personal decisions, objectively communicate criticism and praise, and create an atmosphere of dialog and not debate.

IVF centers, like any health-care-providing facilities, have a hierarchy of authority and organizational structure that comes under the term organization chart. Full understanding of each position's job description, responsibilities, and line of communications is of utmost importance to implementing any QMS.

Lack of Communication with Patients and Insensitivity to Their Local Traditions, Culture, and Religion

The best-structured center, equipped with up-to-date facilities and managed by highly qualified experts in the field of ART, will fail to provide quality service without proper communication with its patients, community, peers, and other medical facilities. Most infertile couples find infertility treatment emotional and stressful [25]. Failure to address the emotional needs of infertile couples decreases their chance of pregnancy [26]. Proper communication is vital, and patient expectations and satisfaction must not be underestimated. Decreased performance is to be anticipated from a highly qualified expert in ART who does not speak the language native to Gulf countries (Arabic), even with the availability of a translator. Sadly, couples who fail to achieve their target or lose the pregnancy due to a miscarriage are left alone with no emotional support or proper counseling blaming themselves. What can be more damaging is the lack of sensitivity and understanding of local traditions, culture, and religious beliefs. Regretfully, a good number of IVF centers overlook these important points or only take it into consideration as a way of increasing income.

Using It Only to Obtain an Accreditation or Being Limited to One Individual's Interest

The use of a QMS to only obtain an accreditation will not lead to significant improvement in the performance. In addition, attaching a QMS to a person or a group makes it vulnerable to discontinuation should that person or group leave the center. A QMS must be considered as an integral part of any IVF center's daily work. At regular intervals, managers should make sure that the system is functioning without interruption or delay.

It Is Costly

Implementing a QMS, personnel training, and maintenance cost money that may defer higher management from using it. However, studies have shown that implementing a QMS is actually cost effective [27–29].

Summary

Introducing and encouraging the implementation of a QMS in IVF centers in Gulf countries has the potential to achieve and maintain effective, efficient, and safe service that respects the rights and dignity of the patients, children to be born, as well as the staff and to reduce cost as well as increase income. Its implementation is simple; however, its success depends on true commitment to its real achievement. A QMS will survive when staff understands its importance, how it works, and what it serves. QMS implementation can boost IVF centers' success and development. Making QMS an integral part of IVF centers will ensure that any drop in quality below the set standards would be quickly picked up and automatically followed by proper action.

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Chapter 16
United States of America

Doris J. Baker

Trained as a medical technologist (a.k.a. a clinical laboratory scientist/medical laboratory scientist) and subsequently having experience as an educator, consultant, and inspector in the field of reproductive laboratory technology, I have observed and assisted with quality management system (QMS) implementation and ongoing monitoring in laboratories, including embryology and associated laboratories in assisted reproductive technology (ART) facilities. I am familiar with quality management systems that work well, meeting the goals of improving the overall quality of a laboratory's performance, and those that are grudgingly in place to meet regulatory and/or laboratory accreditation requirements. Even in ART laboratories that have implemented a successful quality management program, the value of the practice tends to be appreciated later rather than earlier. The following discussion is a summary of experiences from ART laboratories that differ in size, complexity, location, and accrediting body.

Quality Management System

A successful quality management system is based on written and approved policies that address all areas of the ART laboratory [1, 2]. The system is implemented from defined goals, objectives, quality indicators, and performance measures designed to develop initiatives for quality improvement and are documented in the Quality Manual. Data collection begins when a system component is put into practice with continuous monitoring and evaluation sustaining the QMS. Documented review of the QMS with appropriate follow-up ensures continuing suitability of policies and

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Table 16.1 Quality definitions

QC acceptability criteria—CLIA (Clinical Laboratory Improvement Amendments) decision criteria for monitoring test performance in the clinical laboratory [3–5]
Quality assessment—CLIA's term for the overall system for assuring the quality of laboratory test results. Includes the monitoring and assessment of general laboratory systems, as well as preanalytic, analytic, and postanalytic systems, with the objective of identifying problems, making corrections, and improving the quality of testing services [5]
Quality assurance—written plan for the systematic monitoring and evaluation of all phases of laboratory testing, including preanalytic, analytic, and postanalytic phases to ensure that standards of quality are being met [6–8]
QC (quality control)—includes all processes that are in place to detect and decrease analytical errors. Written policies provide for monitoring and evaluating all analytic testing to ensure accuracy and reproducibility of patient results and reports, including testing samples of known value in conjunction with patient samples. QC is an integral part of quality assurance [6–8]
Quality management—written objectives based on goals that can be measured with resulting quality initiatives. A quality management addresses quality planning, quality processes, quality control, quality assessment, quality improvement, and quality process system [1, 2, 4, 7]
Quality plan—management focused on setting objectives and specifying processes and related resources to fulfill quality objectives. Quality planning is part of quality management [4, 9]
Quality system—all resources needed to develop and implement a quality management including policies, procedures, resources, and responsibilities, along with infrastructure required to develop and implement a quality management plan [4, 9]

procedures and effectiveness of corrective action. For each phase of the QMS, there are components that are relatively easy to address as well as many challenges and setbacks that must be countered and overcome.

Implementing the Quality Management System: Initial Concerns and Undertakings

Terminology

Regardless of the size or complexity of an assisted reproductive technology laboratory, implementing the QMS is problematic and associated with many difficulties, the first of which is defining the actual QMS. This is understandable in the field of reproductive laboratory science, since the majority of laboratory personnel have not been formally trained in clinical laboratory medicine or experienced in clinical laboratory operations where QMS is the standard of practice, and they therefore may find the concept to be novel. Not only is the concept new, for those not familiar with the model, it is akin to learning a new language. The terminology may not be familiar, and the use of terms that are similar, site specific, or use the same word as part of several, related definitions add to the confusion. For example, several *quality* items are associated with a quality management system (Table 16.1). The key word in QMS is, of course, quality. The Clinical and Laboratory Standards Institute

(CLSI) [3], an international standards developing organization that promotes the development and use of voluntary consensus standards and guidelines within the health-care community, defines quality as "the totality of characteristics of an entity that bear on its ability to satisfy stated and implied needs." Both CLSI and the International Organization for Standardization (ISO) [4], which develop global standards to serve as a common technological language to facilitate transfer of technology, define QMS as "…all activities of the overall management function that determine quality policy objectives and responsibilities; and implement them by means such as quality planning, quality processes, quality control, quality assessment, and quality improvement within the quality system" [3, 4]. The word *overall* is key to defining QMS since the description includes the word "quality" six times (1) quality planning, (2) quality processes, (3) quality control, (4) quality assessment, (5) quality improvement, and (6) quality system. Other "quality" terms that surface when addressing QMS are quality assurance, quality control planning process, quality control design, quality planning process, quality management, and quality planning model [Table 16.1]. Terms other than *quality* have created confusion as well, such as how policies differ from procedures in the laboratory setting, or how a strategic plan is different from, but fits with, the QMS. ART laboratory administrators have found that when implementing QMS, it is useful to define these terms and post key definitions, especially the ones used in their QMS model, to ensure that all personnel are referring to the same processes and for effective communication with inspecting and accrediting representatives who may use different terms to refer to the same practice.

Personnel and Fiscal Concerns

Once the definitions are agreed upon for a given facility, other initial implementation problems arise and are primarily associated with personnel and/or fiscal issues. Common problems are related to the beliefs and attitudes of personnel in the overall ART setting. Many ART laboratory technologists, supervisors, and directors do not consider QMS to be important, not accepting that the system improves laboratory quality. Since implementation of the QMS entails participation from individuals in the ART setting outside the laboratory, including the clinical and clerical staff, these team members also must commit to the concept and provide necessary input and data. Laboratory technologists have complained that they are too busy for this added effort, while other ART team members have protested to being expected to expend efforts for a laboratory project. Implementing a QMS is time intensive, and personnel may object to implementing the concept because they are already very busy or possibly overextended. In order for a QMS to be successful, a quality management officer, responsible for the various details required for the overall quality management program, must be appointed at the time the QMS is being implemented. Identifying the best suited employee to serve in this role has been problematic for several ART laboratories, often based on workload. In cases where it was determined that additional personnel, or perhaps a consultant, were justified for QMS

implementation and continuation, covering the added expenditure represented another challenge. Many laboratory directors and supervisors have discovered that defining the interrelationships of all personnel in the early stages makes it easier to identify the QMS Officer, as well as roles to be assigned to other individuals.

Delegating Responsibilities

Developing position descriptions that entail QMS duties and appointing individuals to specific positions has been found to be an excellent way to have members involved early on for development of policies, objectives, and quality indicators. Data collection can begin almost immediately. The QMS officer is essential to the plan, overseeing all aspects of the model from the beginning, including identifying issues to be addressed in the QMS and developing methods to generate data for quality assessment such as surveys. Assigning a safety officer, an individual to oversee inventory control, and an individual responsible for developing an effective document control system also have made implementing the QMS more efficient.

QMS Policies: Requirements and Provisions

Initial steps in developing the QMS, especially identifying appropriate data and initiating data collection, are very time consuming. Laboratory directors and managers who write a mission statement, determine the scope of the QMS plan, and develop QMS policies as first steps have found the process easier to execute. Policies must be developed for each area and every component in the system. Comprehensive QMS policies developed in the initial stages of implementation have helped to ensure that all requirements are met. It is helpful to begin with a review of major areas including resources (both personnel and general laboratory), facilities, standard operating procedures (SOPs), and quality assessment. Specific components of policies are then derived from the larger groupings (1) human resources—education, training, competency, and evaluation; (2) document control; (3) complaint investigation; (4) procedural quality control; (5) proficiency testing; (6) QA definitions; (7) QA monitoring; (8) error detection; (9) data collection; (10) random review; (11) laboratory and external detection of errors; (12) classification and reporting of errors; (13) internal and external audits; and (14) customer service (patients, clinical staff, others).

Goals, Objectives, and Quality Indicators

Each policy must have associated goals, objectives, and quality indicators for developing quality improvement initiatives. Objectives must match goals, and quality indicators must be measurable. For example, an overall goal “to provide quality training that ensures that all laboratory personnel are competent to perform testing

outlined in the position description, accurately, safely, and in a timely manner, and to subsequently evaluate training effectiveness" might have objectives that include on-site training and retraining, requirements for continuing education, and competency evaluations. Performance measures might include satisfactory completion of a checklist designed to assess knowledge and skills in ART laboratory procedures during the first year of employment and subsequent annual performance evaluations. A quality initiative could be to develop a training manual to include objectives, procedures, test materials, and measures of effectiveness and/or to develop written examinations with a known passing score to be used for competency evaluations along with assessment of technical skills.

A common problem is setting too many goals. While the QMS is designed for continuous improvement of laboratory services to meet patient care and that of personnel delivering the care, it is not possible to constantly track and assess all aspects of these services. Ideally, a few goals are selected each assessment period to address a specific problem or for an area where needed improvements have been identified. Managers and directors who have attempted to comprehensively appraise many (or all) areas over a short time period have been unsuccessful. Those addressing all sections in general but focusing on 3–4 areas of concern for annual evaluation and review have accomplished the most. However, not all laboratory managers and directors are overly zealous in setting goals. In some cases, goals, objectives, indicators of quality, and performance measures are selected for ease of implementation and evaluation to meet regulatory and/or accreditation requirements instead of for the collection of valuable data to be analyzed and reviewed for improvement of quality in their laboratories. Setting major goals without associated objectives or with objectives that cannot be measured is commonplace.

Resources

Fortunately, many find that some aspects of implementing QMS are straightforward. Directors have discovered that an initial overview of operations in the laboratory, the ART facility, and any tangential entity such as a sponsoring hospital provides a good starting point and that many resources for writing and complying with policies and data collection are already available. Laboratory directors and QMS officers at sites associated with a hospital or medical center have the advantage of many resources. Various documents are available to serve as models for laboratory-specific policies. Examples of policies designed to meet federal requirements are readily available (i.e., HIPAA) as well as employee training modules (i.e., discrimination, sexual harassment, and employee rights). Templates for human resource documents (including examples of position descriptions and employee evaluations), references from safety manuals, and examples of document control also are available. These external resources are not always used effectively, however. Materials from hospitals or other sources not applicable to the ART laboratory have been "cut and pasted" into the laboratory's QMS. As well, materials that could be applicable with modifications have been incorporated without appropriate revisions.

For an established site, many needed documents are already available. For example, human resource requirements, including position descriptions, evaluations, and copies of employee licensure and/or certification, are typically already on file in the personnel records. Other data at hand include procedure and equipment manuals, records of proficiency testing, and results of past regulatory (i.e., Food and Drug Administration) and accreditation (i.e., College of American Pathologists Reproductive Laboratory Accreditation) inspections. Professional guidelines, such as those published by the American Society for Reproductive Medicine (ASRM), provide minimum standards and guiding principles for developing ART laboratory policies. Incorporating federal, state, and local regulations applicable to ART laboratories into the quality management system is straightforward because of ongoing compliance with the laws and rules. Integration of laboratory certification requirements also fits within the plan. Although QMS is a specific requirement (or standard) for organizations certifying ART laboratories in the USA, the laboratory's past compliance with the overall requisites for accreditation meets many QMS requirements, easing execution of the plan. For example, the College of American Pathologists (CAP) requires a self-inspection every 2 years; such internal audits are one method for assessing the quality management system. As well, accrediting bodies have been acknowledged as a valuable resource for information and tools needed to meet QMS criteria. CAP offers instrumentation validation programs, publishes the Quality Management Tools Catalog, and has tools to evaluate quality improvement, such as Q-Probes and Q-Tracks. The New York State Department of Health Clinical Laboratory Standards of Practice provides detailed information for establishing written requirements for defined quality system elements. Laboratory managers in ART facilities that have a strategic plan in place or are included in the plan of a larger organization (e.g., hospital) have utilized the document as a model for their laboratory quality management system.

Quality Manual

The *Quality Manual* has been documented to be a valuable reference for QMS organization and planning. A manual that includes all aspects of the QMS from policies through assessment and development of new quality initiatives economizes time. Indexing and adding materials to the manual should begin with the approved minutes from the first meeting that discussed QMS. All QMS reviews and reports should be added at the time of completion.

Data: Collection, Analysis, and Monitoring

A successful QMS is an ongoing process and one that requires monitoring from the time of initiation through data gathering and following assessments. To be effective,

the quality system's monitoring plan must comprehensively include all phases of laboratory operations. For example, laboratory testing would include testing personnel, required facilities and equipment, safety, and security, as well as preexamination, examination, and postexamination of specimens. Useful data are derived from performance measurements (i.e., the number of technologists scoring at or above the passing score on an annual written examination). Many problems have been noted regarding data collection and analysis including (1) relying on indicators that do not effectively correlate with objectives, (2) indicators that are not measurable, (3) changing indicators after data collection has begun, and (4) analysis using inappropriate statistics. As noted earlier, a competent and reliable QMS officer is crucial to success, especially for this aspect of the QMS. Identifying problems during data collection is helpful as is timely corrective action when indicated. Interestingly, some laboratory personnel feel that "nonconformance" has a negative connotation and are therefore hesitant to address processes, including data collection, that require correction.

Timelines for data collection and analysis help ensure meeting deadlines for scheduled audits. Scheduling routine meetings is essential in order to keep everyone apprised of developments and to ensure that the process continues to move forward.

Audits

Successful audits and other types of evaluations are designed by qualified personnel to interpret the collective data and provide more opportunities for improvement and responses to nonconformance. Although it is often difficult in ART laboratories due to a limited number of personnel, when possible, personnel should not audit their own work. The policy for audits includes methodologies, frequency, timelines for corrective action noted on nonconformance, and documentation. Audits not detailing methods or those without a timeline are not effective.

Laboratory directors have found that coordinating QMS audits with regulatory self-inspections and preinspection preparations saves time and decreases the chance of overlooking critical items. It also has been noted, however, that the "relief of the inspection being over" has resulted in scanty documentation of audit findings and even "dropping" portions of the QMS for a period of time. This action may result in the omission of critical data.

Management Review

Management review is a fundamental component of the quality management system that sets the tone for the process. The review should include (1) report of follow-up on any previous reviews, including corrective actions taken; (2) results of

most recent audits, including noted nonconformities; (3) feedback from personnel, clinical staff, patients, and others when applicable; and (4) changes (e.g., workload, new regulations, and key personnel) since the last review.

Failure of management to evaluate all analyzed data that is available during review is not uncommon. As well, omission of follow-up activities generated from earlier reports is not always addressed. The reluctance to report negative findings appears, in some cases, to be due to a hesitancy to report problems to higher administration or the fact the auditor(s) does not feel that the issue should be addressed based on level of importance or reliability. For example, negative data from survey of support staff may not be deemed reliable. Attitude toward value of feedback, especially complaints, results in important information not being included. Consideration of changes since the last report may or may not be included even when the alteration may have significantly contributed to a current finding such as a hiring freeze resulting in reduced staff. Failure to predict effect of future changes that will affect laboratory operations and perhaps patient interactions (i.e., requirement to meet new federal regulation or new accreditation criteria) may not be considered. Managers often do not recognize this as the ideal time to evaluate key QMS personnel and make recommendations for ongoing or future employee assignments.

Outcomes of Review

Reviews should be shared with all affected personnel and decisions made based on the report. Failure to share reviews is not unusual. Action items from reviews are not always addressed, and timelines for change or correction are often not enforced. Unfortunately, there are cases where acceptable performance measures have provided reliable data that has not then been used for the development of new initiatives for quality improvement.

One product of the review, which is the development of new goals, objectives, and quality measurements that would lead to quality initiatives based on findings, may not be established. Another shortcoming is failure to define major areas to be addressed and have these areas ranked in order of priority.

Ongoing Monitoring and Continuous Review

Ongoing monitoring is nebulous, making it difficult to keep on track initially and resulting in several different types of difficulties. A common problem when implementing a new quality management system is that once the plan has been put into practice, there is a tendency to "think you are finished." This is due to a lack of understanding about QMS or a continued resistance to the concept. Having QMS functions included in position descriptions and as part of the new orientation process explains the system for new personnel. It also apprises them of expectations, so

they do not see maintenance of QMS as added duties. Having QMS as part of the checklist for annual evaluation enforces its importance.

Mismanagement, significant and unexpected increases in workload, and/or financial issues have been cited as reasons why monitoring was not continuous, making review possibly meaningless. Having a QMS calendar with timelines for processes and scheduling routine laboratory meetings with QMS on the agenda with mandatory attendance promote compliance. Frequent meetings between laboratory management personnel and the QMS officer are essential to keep everyone abreast of progress as well as problems. Once they are established, QMS processes become routine. The QMS policy manual and records of audits and reviews become a valuable resource for other laboratory compliance programs, including accreditation.

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Chapter 17
Chile

Fernando Zegers-Hochschild and Javier A. Crosby

In Chile, as in the majority of countries in Latin America, there are no laws regulating the practice of assisted reproductive technology (ART), and therefore, no official guidelines are available regulating the establishment of new centers, criteria for registering and reporting their data, and, in general, for the provision of this form of medical care.

Quality control (QC) protocols for clinical and laboratory interventions are therefore nonexistent as part of governmental policies. The only guidelines and regulations are those imposed by the Latin American Network of Assisted Reproduction (REDLARA) to centers who are part or wish to be part of the Latin American registry of ART (RLA). In Chile, as in many other countries in the region, the vast majority of centers performing ART are part of REDLARA; thus, they are all subjected to the same regulations and QC procedures.

While in Latin America today, 140 centers report approximately 35,500 initiated cycles per year, in Chile, 7 out of 8 ART centers report approximately 1,500 procedures per year. Seven institutions have been accredited by REDLARA and are subjected to a fixed certification procedure. Furthermore, an agreement was reached among these centers, whereby consent forms have the same basic structure in every institution. In this chapter, we refer to the accreditation guidelines established by REDLARA as an example of what takes place in Chile, which can be extrapolated to other countries in the region.

The Latin American Network of Assisted Reproduction (REDLARA) is a nonprofit scientific and educational organization that brings together the vast majority of fertility centers providing ART treatments in the region. The REDLARA was constituted in 1995 with 50 founding centers from 11 countries. These institutions

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were already participating in the Latin American Registry of Assisted Reproduction (RLA) for the previous 4 years. Today, 141 centers in 12 countries are either certified by or affiliated to REDLARA.

The main objectives of REDLARA are:

- Generate and publish annually the Latin American registry (RLA).
- Assess different types of ART interventions and their outcome.
- Monitor trends on safety and efficacy among centers, countries, and regions.
- Train and educate members of affiliated institutions through regional workshops and a program of continuing education.
- Maintain a continuous program of quality control and accreditation for all centers.
- Coordinate and facilitate multicenter research projects.

In this last 15 years, many of the original goals have been achieved as part of our education program, 173 clinicians and 152 embryologists have graduated in our PEC online educational program, and the RLA remains the first multinational/regional registry in assisted reproduction with uninterrupted annual publications for the last 19 years. Furthermore, REDLARA provides accreditation processes to new centers and reaccreditation every 5 years.

The accreditation program started in 1996, but it was only in 2004 that a professionalized accreditation committee was created in order to:

- Elaborate the accreditation and reaccreditation procedures.
- Unify criteria between evaluators with courses and workshops.
- Check accreditation and reaccreditation results given by the evaluators and provide results to the board of directors for the final decision.
- Recommend corrective actions or even sanctions to centers reporting unreal results or the lack of rigor in reporting their data. The absence of appropriate consent forms, duly signed by couples, is considered a serious fault.
- Promote the improvement of quality service given by the associated institutions.
- Install the accreditation process of RED as a symbol of regional recognition.

Process of Accreditation

Very few countries in Latin America have established their own accreditation processes for quality control assessment of clinical and laboratory activities. For this reason, ART centers in Chile as well as other countries in the region are subjected to the accreditation protocol established by REDLARA to regulate the practice of ART in their countries.

The accreditation process is initiated with a visit to the center by a clinician and an embryologist that act as evaluators. The evaluators are members of already-accredited centers of renowned formation and working experience of at least 5 years.

Evaluators must belong to a different country they are visiting and must sign for nondisclosure of the data concerning a particular center. They must also acknowledge absence of conflict of interest.

Accreditation

It is mandatory that during the accreditation visit, the clinical and laboratory directors be present and available for questions and a final discussion. The visit includes:

- A tour of the facilities to see the working areas and equipments
- Review of the clinical and laboratory procedures/protocols and manuals
- Review of the quality control procedures of the laboratory
- Verification of accuracy in the data reported to the Latin American registry (RLA)
- Review of the informed consents signed by all patients

Requirements for Accreditation

Personnel

1. Clinical director: with an MD degree, board certification in obstetrics and gynecology, and preferably training in reproductive medicine. He/she is responsible for developing manuals for clinical procedures such as:
    - Patient selection including a checklist of laboratory and clinical procedures to be performed
    - Protocols for controlled ovarian stimulation (COS)
    - Patient monitoring throughout COS
    - Protocols for follicular aspiration and embryo transfer
    - Description of procedures to be performed and accepted in consent forms
2. Clinician trained in infertility and reproductive endocrinology, particularly trained in the use of drugs for COS.
3. Clinician trained in gynecological ultrasound: the professional responsible for oocyte pickups must have had at least 20 procedures supervised in a recognized institution.
4. Laboratory director: must have a degree related to biology, biochemistry, or biological/health science and must have experience and knowledge in the organization, preparation, and management of gametes and embryos. It is his/her responsibility that every member of the laboratory has a detailed description of their duties and obligations and is aware and follows the chain of command of the personnel. He/she is also responsible to offer continuous education to the members of the laboratory.

Other Optional Personnel

- Clinician trained in gynecological surgery and laparoscopy
- Clinician trained in andrology
- Laboratory supervisor: is the head of the laboratory when the clinical director acts as laboratory director or when the laboratory director works in more than one center
- Personnel trained in cell micromanipulation
- Personnel trained in cryopreservation of gametes and embryos
- Personnel trained in psychological support for couples
- Nurses or midwifes

Clinical Facilities

The clinical facilities must be in compliance with local laws when available. The center must have all the medical equipments and facilities for the monitoring of COS, transvaginal oocyte pickup, and embryo transfers. There must be a plan to solve emergencies and complications (heart attack, anaphylactic shocks, hypovolemic shocks, etc.).

Embryology Laboratory

The laboratory facilities must be in compliance with local laws when available and work according to guidelines provided by the "Manual of Laboratory Procedures" published by REDLARA.

Infrastructure

The laboratory must have space and facilities in compliance with the number of cases reported or expected. The physical space has to be isolated from other activities and must contain separated space for semen manipulation, media preparation, and storage. The architecture must facilitate cleaning and controlled temperature and air purification system.

Operational Procedures

The laboratory director must prepare and have available to all staff a manual of procedures with a detailed description of all techniques and procedures used in the laboratory.

The laboratory must have a biological quality control (QC) assay to analyze all materials and culture media used with embryos. There must be written documentation of media lots, dates of preparation, biological controls, and expiration dates, as well as a routinely microbiological control for all equipments and spaces. Protocols and requirements for QC assessment of equipments, supplies, culture media, procedures, etc., can be found in http://www.redlara.com.

Chapter 18
Brazil

Fabiola Bento and Sandro Esteves

In 2006, Brazilian's regulatory agency (ANVISA) issued a new regulation for reproductive cells and tissues banks, which included assisted reproductive technology (ART) centers [1]. The new regulation was later reviewed, in 2011, and included more details and explanations of aspects not very clear in the first resolution [2]. The new set of regulations demanded, besides many technical requirements for operation, the establishment of a documented quality management system (QMS), which should be known by all personnel, administrative, technical, and scientific, should be established in a 1-year time period, and should include:

1. Elaboration and periodic review of standard operating procedures (SOP)
2. Periodic personnel training
3. Periodic internal audits, to verify compliance with technical regulations
4. Procedures for detection, registration, correction, and prevention of errors and nonconformities
5. Compliance with biosafety regulations
6. A system to evaluate and control equipment and materials used

Many other demands also related to a quality management system were included in this new regulation, such as:

1. Having a technical manual with:
   (a) Administrative and technical organization
   (b) Qualification and responsibilities of all professionals involved
   (c) Conduct in case of nonconformities
   (d) Biosafety norms
   (e) Annual review
2. Proper sample identification

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3. Keeping at least two copies of all data, in other words, a backup system and guarantee that data cannot be altered at any time
4. Having a maintenance plan for all equipment

Besides all the quality management demands, the new regulation included technical and operational rules, to standardize and level all centers in our country. It had a huge impact, especially in smaller centers, which did not have the structure and could not, for various reasons, adapt themselves to comply with the new regulation. In our center, many of the demands were already part of our daily routine. The difficulty was to formalize everything we did so as to have a solid QMS. Moreover, we did not have standardized procedures for our administrative activities, and even though we already had a system to deal with nonconformities and correct deviations, we did not have a proper registration system. Much of what was done was not recorded at all.

Quality Management System

After making an extensive research, we decided to follow the International Organization for Standardization (ISO) 9001 quality management model [3], first because it included all basic aspects of the new regulation and also because the ISO was being suggested by the European Community. In our view, it was the most complete model available at that time and was also known, accepted, and respected worldwide.

We started very simple. The first thing we did was create our "nonconformity and corrective action registration procedure" (see Chap. 3). The concept was that anyone from any area could record nonconformities, even if the nonconformity was not from this person's area. We had a specific training about the model we were going to follow, teaching our personnel how to fill in the nonconformity form and respond appropriately. Registering nonconformities was rather easy; however, responding to nonconformities was the greatest problem. That is because our staff tended to think only in immediate actions to solve whatever problem had happened or would think of solutions that did not address what had caused the nonconformity in the first place. Analyzing the cause of the nonconformity was our main challenge. Registers would come and go countless times until proper analyses had been made and a proper solution had been suggested. This process was not easy and demanded a great amount of time and training.

Training

At the same time, we started a lengthy training program, which included all personnel and focused on ethics, moral values, organizational values, and many other

aspects, to emphasize the importance and responsibility of each one in the process of offering a quality service. This was of extreme importance, for many times the laboratory work and staff was "overvalued," and the support staff was kind of left aside, as if talking to patients in a warm and receptive way, managing the daily schedule and appointments, and even cleaning was not "as important."

The creation of the concept of "team work" was our primary goal. If people did not see each other as equals, it would be impossible to follow the model we were establishing. Until today, we need to reinforce this concept, both to "remind" our staff and also to train new collaborators. Creating this environment helped us help each other, for many times someone who does not work directly in an area is able to see more clearly and suggest changes, while someone who is too involved tends to follow the same routines without really seeing what can be improved and how his work affects that of others.

Another concept that had to be established and fully accepted was that of "continuous improvement" and "commitment" to this concept. It is not easy to be criticized if it is seen negatively. Therefore, it was important to all staff to learn to accept this criticism and mainly to see it positively, as a means to achieve our ultimate goal, which is offering a high-quality service. To avoid competition among colleagues and make people focus on our common goal, nonconformities were registered with the name of the area in which it had occurred rather than with the name of the person involved. In other words, we avoided the direct criticism of any individual team member and worked on the idea of teamwork directly. We did not have a nonconformity issued for "Embryologist A," but to the IVF laboratory, which included all embryologists. They had to respond to the nonconformity as a team. This teamwork led them to develop a closer bond with each other and also taught them that they depended on each other to have a good performance. It was not a matter of doing one's job anymore. Performance was not seen individually; therefore, it required some time for people to adapt to that, share responsibilities, distribute tasks, and really work together instead of simply sharing the same work space. From then on, everyone was responsible for everything in their areas, and answers like "I thought he/she had done it," or "I didn't know about that," or "It was not my responsibility" were not accepted any longer. A deep change occurred.

After this basic training and after everybody got used to recording nonconformities and corrective actions, we moved on to the ISO itself. We had trainings introducing the model, its demands, and what had to be developed to comply with the ISO, once many aspects were already part of our routines. In our laboratories, all procedures were already described and reviewed periodically. Besides that, we already controlled all equipment and had a maintenance plan in place. However, maintenance actions were not appropriately registered, and we had to describe what was included in the preventive maintenance of each and all equipment used and also record all maintenance performed in any equipment, regardless of being preventive or corrective. The maintenance periodicity was also established and differentiated according to the use of the equipment.

Procedure Descriptions

Regarding our clinical activities, almost all procedures were described too. We already had a description of most procedures performed by nurses and doctors. All those not described were then formalized and documented to guarantee uniformity. Besides, the nonconformities that were registered showed us the procedures that were lacking and the ones that were incomplete or insufficient to guarantee uniformity and quality. We then worked on the specific problems that were detected that way as well.

Our administrative procedures had no descriptions at all. To start with, we decided to create different flowcharts showing the moment a patient calls to schedule appointments and tests, the moment a patient comes into our center for any procedure, and so on (see Chap. 4). From those, we were able to determine the activities performed by our administrative staff and describe them. We identified and formalized all procedures performed within the center, trained all staff, and therefore were able to monitor whether or not they were being done correctly.

These flowcharts were so helpful that we decided to use them in all areas. Many flaws were found through the flowcharts. For example, looking at the "Clinical Evaluation of the Infertile Couple SOP," we detected that some simple procedures were not described and then created the minimum standards to be followed by all doctors. Surgeries and procedures that were very rare had no description and were developed as well.

While developing and describing SOPs, we started establishing our mission statement. This was not difficult since our staff was already prepared and directly involved in this process. From our mission statement, we came up with our quality policy, and later with our policy objectives, which determine what aspects of our quality system are evaluated and monitored (see Chap. 3). For example, our quality policy talks about satisfying our clients, so we had to monitor their satisfaction over time to verify if we were achieving our goal. To monitor that, we use "satisfaction questionnaires" (see Chap. 3) and determine objectives such as 80% of "satisfactory" in a specific aspect. Our satisfaction questionnaires ask about our patients' satisfaction with the assistance they receive over the phone, at our clinic, from our secretaries, from our nurses, from our administrative staff, from the doctors and laboratory personnel, etc. The idea is to have as much information as possible in a very practical and quick way.

Our patients answer this questionnaire at the end of their treatment cycle, more specifically on the day of their embryo transfer. We found out this is the perfect time to obtain good information, because by then patients will have already used all services and will not be under the influence of a positive or negative result. However, they may fill in a questionnaire at any time during their treatments if they want to, as questionnaires are available at our reception area. We have always used this tool, since the beginning of our activities, and it has helped us understand our patients' needs and develop new services to better assist them. For example, from those questionnaires we have been able to detect problems with our telephone system, identify

the best hours to schedule appointments, detect a demand for psychological support, etc. Besides being a way our clients can communicate with us, it is also a way to monitor quality. It is important to stress that our satisfaction questionnaires are reviewed over time. Depending on the information we get or want to get, we add or delete questions. What is important is to receive feedback about areas we can do something about. For example, nowadays, we are facing a problem with our parking area. We have been looking for a new area with no luck, so we erased this question from our questionnaire. We know patients are not satisfied with this specific issue, but solving this is impossible for the time being. We are aware of the problem and are working on a solution. We do not need to read the same complaint over and over again.

Laboratory Performance Measures

As for our laboratory performance, we determined the indicators that were going to be monitored, such as fertilization rates and embryo development. We also determined how often they were going to be analyzed. This "quality control" was already in place before the establishment of the ISO system. We just had to improve it, setting meetings to analyze data in a more systematic way, recording all actions decided during these meetings, and adjusting parameters to better comply with worldwide performances and also to continuously improve our own. Currently, these meetings occur regularly and involve the laboratory staff, laboratory director, and quality manager. Besides being a way of monitoring and guaranteeing our laboratory performance, they also serve to detect the need of training, purchasing new equipment, hiring or changing staff, and so on. Everything that involves and affects the laboratory is analyzed and discussed during these meetings. Despite that, one of the main difficulties we face now is to have these meetings on a regular basis. That means that as we all have other responsibilities besides the quality system, other activities keep getting in the way of our scheduled meetings. It demands a great deal of discipline to hold meetings regularly and not prioritize other daily activities that may interfere with our schedule. Of course, the time scheduled and sometimes the date has to be changed due to unplanned situations; however, we have to reschedule the meeting for the nearest date and time so as not to compromise our quality system.

Communication

Regular meetings are also important in all other areas. They are very time-demanding, but very important to maintain the staff united and also to keep everybody on the "right track" and committed with the quality system. The periodicity of these meetings may be determined according to the need of each team, but they have to be held and they have to be regular, so that the staff knows they have their say.

Another thing that was very critical to us was our internal communication. We started using a computer system for internal communication so as to avoid communication problems, such as forgetting to tell something or forgetting you got some information that was told. Everything is written and therefore registered. This system also facilitated information that had to be passed on to the teams urgently and that could not wait for the regular meetings. Besides facilitating daily communication that was before done over the phone, it was very important to schedule meetings, to pass on important information, and in other words, "keep the channel open" and keep communication immediate and straightforward, without bureaucracy. It does not substitute face-to-face communication and team meetings, but it does work very well for daily communication.

Establishing this quality management system was very demanding and took a lot of time and work from all our team. It took hours of training, hours of work, and countless meetings to come up with the complete system we have now in place. However, now we see that creating it was much easier than maintaining it. People tend to put a lot of effort on obtaining a certification, but upon getting it, they tend to change focus to a different challenge. That is why we still need regular training, even to the people who were involved since the beginning, and we need to make an effort to keep information updated and hold regular meetings to analyze our data. Discussing what we do is now much more important than simply doing it as established. Our staff must keep a critical eye on every step of their work to be able to improve. And this is our challenge. When we describe all processes, things tend to be mechanical, so we cannot let these "instructions" of how to do things, even if successful, forbid us to make changes or worse blind ourselves to these possible improvements.

Conclusion

From our experience, we concluded that having a quality manager, in other words, having someone solely in charge of the quality system, with no other responsibility, is very important. This way the system can really work effectively, with someone working only on that. If the quality manager performs other activities, then insufficient time will be dedicated to the quality system, especially if the quality manager is also the general manager as in our case. Because of this observation, we are now under many structural changes to better distribute tasks and responsibilities and enable our manager to focus on quality exclusively. We are sure that after this changes are in place, the whole system will benefit, for there will be someone with an eye on it all the time.

In our view, an ART center should have a manager responsible for the quality system and another manager responsible for the administration of the center. In our case, however, we are following a different direction. We decided to focus on our laboratorial services, both diagnostic and therapeutic, and let doctors work as associates. In other words, we are now focused on providing the doctors and patients a

high-quality environment for assisted reproduction techniques. Therefore, we are not managing medical appointments, clinical evaluations, and ultrasounds, for example, inside our ART center any longer. Doctors perform those activities in their own clinics and are responsible for their patients. Patients only come to our center for procedures, such as sperm collection (including sperm retrieval techniques), intrauterine insemination, oocyte pickup, and embryo transfer. We also provide services from our andrology laboratory and sperm bank. This strategy has allowed us to have more time to focus on our laboratories' performance and on our quality system. Our main goal now is to offer high-quality services to both associate doctors and their patients, which include having good results in our laboratories and offering a good hospitalization service (nurses and anesthesiologists).

Regardless of the certification we obtained, the process of establishing a quality management system was very enriching. Everybody learned a lot in the process and at a certain point obtaining a certification was not "that important" anymore. We wanted so much to have a good and complete quality system that the focus was more on making it work than on getting a certification. Getting a certification was rewarding of course, but it was not as important as it was when we first started. One of the things that we have learned and that we believe is that if one decides to establish a quality system, regardless of a certification, it is better to do it yourself and take more time, as we did, than to hire a consulting company as many places do to develop the system for you. Only the people involved can really see what is needed and what is important. It sure is difficult, it sure is time-demanding, but it is certainly worthy. Seeing now the difficulties to maintain the system we created ourselves and know exactly how it works, we can imagine greater difficulties if someone else had created it for us and we had not been fully involved. It is certainly more time consuming, but it is certainly more time effective.

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Chapter 19
Belgium: ISO 9001:2000 Certification as a Base for Total Quality Management in ART

Kelly Tilleman, Etienne Van den Abbeel, Ilse De Croo, Anneleen Van de Velde, Bjorn Heindryckx, Sandra Deltombe, Isabelle Stuyver, Annick Geril, and Petra De Sutter

In February 2011, the Department for Reproductive Medicine at the Ghent University Hospital celebrated its 25th birthday. These 25 years have been characterized by huge technical achievements like the successful implementation of IVF and ICSI in the beginning years, later extended by affiliated techniques such as preimplantation genetic diagnosis (PGD) or assisted oocyte activation (AOA) and by growth (from about 50 cycles a year in 1987 until close to 2,500 cycles in 2010).

The first goal of every ART clinic in those days and even today was and is to provide a successful treatment for subfertile or infertile couples, resulting in an ongoing pregnancy. Although scientific progress in the ART field had supplied our ART laboratory with technical advantages like IVF, ICSI, the mouse oocyte activation test [1] and more recently assisted oocyte activation to overcome failed ICSI [2, 3], there were/are still patients that we were unable to help.

Therefore, our definition, mission and vision of a successful ART treatment changed 5 years ago. We wanted to make sure that our patients received the best qualitative care, even when treatment did not result in the desired pregnancy. Therefore, the concept of 'quality management' was introduced in our centre. Additionally, the World Wide Web made it possible for patients to get detailed information on available laboratory techniques. They had a chance to come in contact with each other through Websites where they could discuss and compare their experiences in different IVF centres. In short, the demands of our patients evolved and changed from a rather passive, undergoing position towards playing an active role in their treatment, where demands for information, communication and discussion were set out.

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In order to comply with these needs of our growing patient group, setting up and implementing a quality management system became mandatory. Given the global reputation of the ISO 9000 family of international quality management standards, the ISO 9001:2000 standard was chosen. This standard specifies the requirements for a quality management system for any organization that needs to demonstrate its ability to consistently provide a product (pregnancy, care) that meets the customer (patient) and applicable regulatory requirements (EU directives, national laws) and aims to enhance customer satisfaction [4].

Obtaining the ISO 9001:2000 Certificate: Where Did We Start?

When the idea to obtain ISO accreditation first emerged into the minds of our management team, the concept of quality systems or accreditation was unfamiliar to our staff. It took motivational meetings, explanation and training to install the conviction in every one's mind that quality management could be an asset to our ART clinic. In the mid-2006, together with the help of an external consultancy agency, a team was appointed to plan and help to execute this project, which would have to result in the certification of our ART centre. This team consisted of one member of each disciplinary group (physicians, nurses, lab technicians, administration) and the head of service as team leader. Several meetings were held, and a project plan was designed. One senior embryologist was appointed as part-time quality manager. The first priority was to review, update and document all our procedures ranging from different treatment programs in the ART clinic, counseling and instructions for patients, the procedure of cryopreservation of embryos in the ART laboratory and the necessary administration that needs to be performed. Additionally, many forms were standardized, numbered and sometimes even translated in different languages. The entire organization was put to work in order to obtain a uniform set of clearly written, manageable documents. Staff meetings were organized on a regular basis to inform, create awareness and involve the entire organization.

Although many procedures were written down (the first issue of our quality manual consisted of 48 procedures, 41 detailed instructions, 81 forms divided into checklist forms, documentation forms and fill-in forms), the ISO 9001:2000 standard actually requires to have documented procedures for only six processes (1) control of documents, (2) control of records, (3) internal audit, (4) control of nonconforming products, (5) corrective action and (6) preventive action.

During this period of creating and editing a written quality management system, the organization automatically started to develop and implement a process-driven management approach where our processes were clearly identified, the interactions between them described and, based on the feedback from staff and patients, adjustments were made. The use of this management approach was put to the test when one of the ISO-required documented procedures was implemented, namely, the process for corrective action. In this procedure, it is important to register complaints of patients but also to record irregularities or deviations in procedures and abnormalities during

certain processes. The staff particularly was rather unwilling to report the latter as it was perceived as finger pointing solely to find out who was responsible for one or another mistake. The management took its responsibility to create a culture of open communication and showed that these reports served as input for the analysis of causes of these errors and complaints leading to process optimization. After putting this into practice, the staff soon realized that this was an instrument that they could even put to their advantage (to motivate the management to invest in personnel, equipment…); hence, a culture for honest detailed registration of irregularities was born.

During this preparatory phase, two internal audits were performed, one by an audit team of another ISO-certified department from the university hospital and another by our consultancy agency. Processes were adjusted and optimized, key performance indicators were set and follow-up was guaranteed. Approximately 1 year after this project started, formal certification was sought in October 2007 where a 3-day audit resulted in the ISO 9001:2000 certification of our ART centre.

Having the ISO 9001:2000 Certificate: What Have We Learned

Although it is a hard work to obtain a certificate, the greatest effort is actually putting the quality management system into everyday practice. The management process used in our ART centre was and is still based on the PDCA cycle also known as the Deming cycle [5, 6] (Fig. 19.1). The Deming cycle shows the interaction between design, production, sales and redesign through research, and the four steps rotate constantly with the quality of the product or service as the aim [5].

The design of the product correlates with the planning phase of the management. To plan (P) is to set out the objectives, the goals. In our ART centre, some of these goals are shorter waiting times, customer satisfaction, higher pregnancy rates, clear and uniform communication to patients and external physicians.

The production corresponds to doing-making. To do (D) is to find out what is needed to achieve the goals and to actually perform these actions. When a certain goal or objective is a multistep process where collaboration with several groups or even departments of the hospital is needed, it is preferred to make a detailed project plan that is supported and coordinated by a team leader. This person is responsible for monitoring the project, keeping in touch with several people/groups/departments working on the project. He/she has to observe that the deadlines are kept; if not, those changes can be made, all in order to make the project a success. It is of utmost importance that the staff is informed on a regular basis of the upcoming changes. In this phase, adjustment to documents is made and procedures adapted where necessary.

The sale is actually the phase where you check (C) whether the customer is satisfied by the product. If the goal to obtain shorter waiting times is achieved, this should absolutely be noticed by the patient and can be measured in a patient survey where answers should be quantifiable. Comparing the data to the predictions, making statistical analyses and summarizing them take us to the next step in the Deming

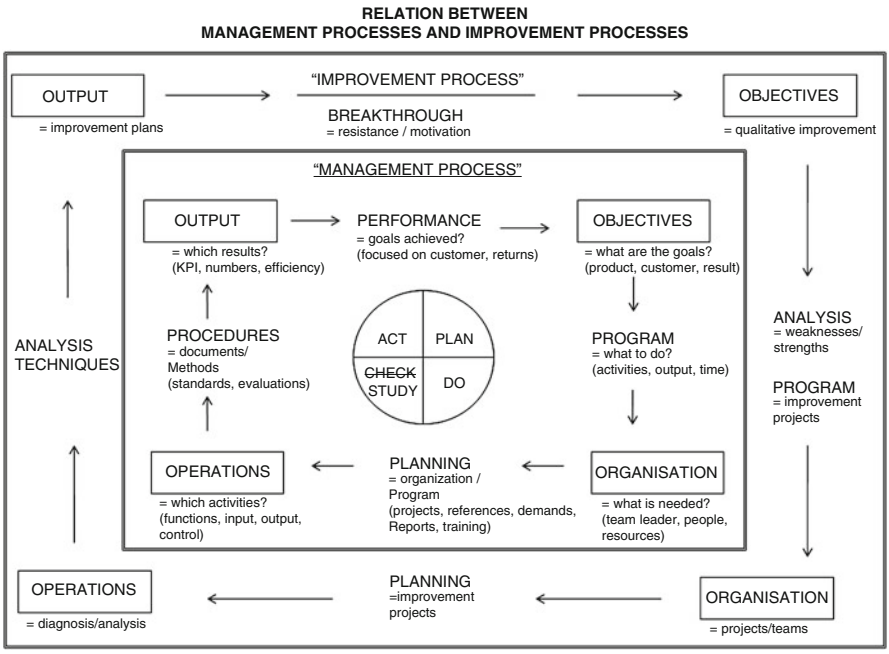

Fig. 19.1 Total quality management: the relation between management processes and improvement processes (translated from Amelior vzw: Total quality management, Kortrijk, Belgium, with permission)

cycle: redesign through research, also called the action phase (A). Based on the results obtained and the analyses performed, changes have to be made. Even if the goals that were set out are obtained, a quality management system has to continuously improve.

Because 'to check' actually means 'to hold back', Deming stated to call it the PD*S*A cycle where you do not only check the results, you actually study (S) the data in order to learn and to build new knowledge [7].

Looking back on our first 2 years (2007–2009) of using our management process, we would have to conclude that the Deming cycle is easy to learn and use. However, our experience is that the time spending at each phase should be more evenly divided. It is critical to take sufficient time to plan and set out the goals. This makes it easier to compare results to the predictions made in the first phase. Extended time spending in the doing phase is inefficient. It is better to move forward to the analysis of a small set of data and be able to adjust and make small changes, consequently having to go through several PDSA cycles as your organization undergoes the quality management process.

It is also important to keep the quality manual together with its procedures up to date. Sometimes, the enthusiasm to start or implementing new and more efficient procedures is put first, while the administration falls behind. It has happened that we have changed protocols, while the written standard operating procedure was updated

only a few weeks later. Actually, this should be an exception rather than a rule. It is impossible to correctly inform your staff of a new way of working if the procedure is not yet available. Moreover, this will result in an inconsistent way of working and will have a direct negative effect on the patient as the patient will receive different kinds of information or will be treated differently upon contact with various staff members. A well-written, up-to-date, self-explanatory and easily accessible procedure is the basis to achieve a uniform way of working. It is a guide for the staff in times where a lot of changes are made to the organization.

And many changes have been made, and we are still in the process of improving our way of working. In the last 2 years (2009–2010), we have not only moved our laboratory to a newly built clean room facility but also our clinic was renovated and relocated. These two huge projects were brought to success without temporary closure of our ART centre by a team effort and good communication (regular staff meetings, a detailed brochure stating day to day what was going to happen, detailed process flow charts of reproductive material) and also patients had to adapt to the new setting. However, now, 3 months after the final movement phase, still a lot of administration is not up to date. Although the essence of the procedures has not changed, they need to be adapted to the new location. Also, much new equipment was bought, and calibration reports and manuals have to be categorized, ordered and put in new logbooks. Although we are aware of the need and importance of detailed written procedures and clear registered logs of equipment, it is easier to put the paperwork on hold when patient care is put first. To have an updated quality manual and standard operating procedures is one of the important aims for the year to come.

Keeping the ISO 9001:2008 Certificate: A Basis for Total Quality Management

We have moved our management process based on the PDSA cycle to a higher level, where we aim at a continuous improvement of our system (Fig. 19.1). Going through the cycle of an improvement process, you will encounter the same steps as during a management process. However, the most crucial step is when the improvement process leads to a breakthrough. This breakthrough is the result of a very delicate balance between resistance and motivation. ‘Change’ is not always perceived ‘as better’ in an organization.

Defining goals and objectives is mostly directed towards the costumers: the patients, the external physicians and the suppliers. However, it should be emphasized that the objectives concerning the internal organization and the needs of the staff should also be implemented in the management process.

Quality management systems are based on customer satisfaction, on setting out, monitoring and analyzing many kinds of key performance indicators. In our opinion, this is not the core of what makes a quality management system in ART stand out. As quality management is a climate that has to grow in an organization and that cannot be imposed, it is crucial to not only ask the opinion of your customers and

suppliers but equally important to ask feedback from your staff. We are convinced that open communication between co-workers and making sure that feedback can be given in constructive way will motivate the staff and form the basis for a total quality management (TQM) in an ART centre.

Total quality management (TQM) is defined by the American Society for Quality Control as (1) policy, planning and administration; (2) product design and design change control; (3) control of purchased material; (4) production quality control; (5) user contact and field performance; (6) corrective action; and (7) employee selection, training and motivation [8].

We believe that after years of focusing on the customer, control of materials, techniques and products, the motivation of the employees has been left behind. Therefore, in our definition of TQM, we aim at moving 'employee selection, training and motivation' upstream in the definition. A motivated well-informed staff will make a huge contribution to the improvement process, and this takes time and effort of the management.

The challenge in quality management in many ART centres today is how do you keep improving the quality of the ART treatment when well-informed, empowered patients with varying and very personal demands have the possibility and the freedom to take their reproductive material and care to their centre of choice?

In our ART centre, we want to make sure that our patients receive the best qualitative care, even when treatment does not result in the desired pregnancy. This care should be based on the fact that every patient, each couple is unique and should take into account the psychological and emotional aspects of a fertility treatment. In this way, it is our intention that we offer individual guidance of patients and couples where the human and holistic aspects are put first.

We are convinced that well-trained and enthusiastic staff is the key to make your ART centre the centre of the patients' choice. Therefore, our scope has been extended:

Our employees must be individuals who set the tone and are present where the debate is conducted and the policy is made. Our ART centre must be a department where employees feel comfortable and where a good collegial atmosphere with continuous growth opportunities exists. Team activities, further education, training and retraining are tools that contribute to this.

Conclusion

The high demands and expectations of our patients are placed upon our standards of work—and quite rightly too, because we would have to account for the consequences of any mistakes we might make. Although countless couples become pregnant and give birth to healthy children, the number of unsuccessful treatments still outweighs the successful ones. The ART clinics are therefore under constant pressure to improve the quality of their services and increase the percentage of successful treatment cycles.

A quality control system is the tool with which this expectation is met. It is a concept adapted from the industry sector. The aim of this is to establish procedures (standard work methods), which ensure that these established levels of quality are reached and maintained. Furthermore, the result must be visible in order to prove that standards are being adhered to and met. The principles of the quality system are straightforward enough: say, what you do, do what you say and do it better.

After a year of preparing, we obtained the ISO 9001:2000 certificate. Almost 4 years later, we are still an ISO 9001:2008-certified ART centre, and we have obtained recognition as a tissue bank for reproductive human tissue and cells. We have implemented a quality management system based on the PDSA cycle and have extended it to a total quality management adjusted to the specific needs of an ART treatment. We are still in the process of learning and shaping our TQM, as stated by Vasconcelos et al. [9]: Quality is truly a matter of mind, and it requires motivated and skilled staff for its implementation.

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Chapter 20
The Netherlands

Peter M.M. Kastrop and Sjerp M. Weima

In spring 1995, it became obvious that mixed-race twins had been born in the Netherlands as the result of an IVF treatment in early 1994. Subsequently, the incident became worldwide front-page news and shocked the world of assisted conception [1]. A mistake with irremediable and disastrous consequences had taken place in one of the licensed Dutch ART laboratories which raised questions about their professional practice. A thorough internal inquiry was instigated by the hospital board of directors of the ART laboratory involved. An internal inquiry commission in conjunction with an external ART expert reviewed all laboratory procedures and working methods in an attempt effort to clarify what exactly went wrong. Several possibilities were investigated but the cause could no longer be ascertained. The commission concluded that the IVF procedures practised complied with generally accepted standards in ART laboratories and stated that protocols were in place and adhered to. Nevertheless, the commission also expressed their anxiety and recommended that procedures should be improved and tightened as ART by its very nature requires meticulous attention to detail. They took the stand that embryos which are generated in an ART laboratory can be considered as unique living 'products', and therefore, IVF and ICSI procedures should follow the strict guidelines of good manufacturing practice (GMP), as used by the pharmaceutical industry. The board of directors of the hospital agreed with the conclusions of the inquiry commission and enacted the ART laboratory to start implementing GMP regulations into daily practice. Although the applicability of GMP rules in an ART laboratory was debatable, it provided a framework for establishing a quality management system.

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Art and GMP Guidelines

As a first step to optimise the standardisation of the laboratory procedures and improve quality assurance, safety and transparency, the applicability of GMP regulation in daily practice had to be investigated, since not all GMP rules can be simply introduced into an ART programme. For instance, regulations about maintaining of reserve samples, random sampling of the end products and automatic labelling and packaging of products seem far from applicable. On the other hand, several important and basic GMP rules do fit perfectly in ART procedures. Amongst them:

- Availability of detailed written standard procedures of every step in the process
- Validation of critical steps in the procedures (risk assessment)
- Adequate labelling of containers to assure unambiguous identification
- Performance and recording of every transfer of components by one person and the verification by a second one

Furthermore, GMP contains rather some general guidelines concerning qualification and responsibilities of personnel, availability and proper functioning of equipment, documentation and record-keeping, and location, construction and facilities.

As a consequence, all laboratory operations had to be further detailed and supplemented. Especially, procedures in which critical steps were identified, e.g. all actions in which samples are transferred from one dish or tube to another, all moments where samples of different origin come close to each other, as well as regulating the transfer of samples to or from patients, were carefully described. Accompanying laboratory forms were adapted in order to record that a particular procedure had been performed correctly by one person and checked by a second person. Consequently, all physicians, nurses and embryologists involved in the fertility treatment of a certain couple, i.e. from ovum pick-up to embryo transfer, are registered on these laboratory forms to guarantee that procedures have been performed accurately and that each gamete and/or embryo was handled properly and identified unambiguously. Besides, it should be validated that all persons involved have read the written procedures. All these measures have to prove the standardised and proper execution of a certain procedure and to assure traceability. Only then it is possible, even after years, to investigate how a certain procedure has been performed and who was involved.

In addition, also procedures concerning the logistics within the laboratory and the use, calibration and maintenance of equipment were introduced. All the operating procedures were drawn up in a standard format and managed according to fixed rules. But as mentioned before, GMP guidelines did not completely cover all aspects within an ART programme and therefore was not adequate for setting up a complete and integral quality system. Therefore, based on the applicable GMP guidelines implemented, additional quality measures were taken to extend the quality system towards accreditation.

Quality Evolvements Within the Professional Society

The Dutch Society of Clinical Embryologists (KLEM) was officially founded in 1991. Only fully trained clinical embryologists, employed in 1 of the 13 licensed IVF units in the Netherlands, can become a registered member. One of the main aims of the society is to enhance the knowledge of its members and to ensure high standards of quality in their laboratories. As a result of the publicity about the twin incident, everyone working in the field of ART became even more aware of the responsibility and risks of their work. Therefore, the society, already working on quality measures for ART laboratories, speeded up and extended their activities. In 1995, the society embarked on a process in which all members were challenged to start implementing a quality management system in their laboratory. The society also join the coordinating committee for the promotion of quality control of laboratory research and testing pertaining to health care sector (CCKL), an authoritative body for the development of quality management systems in medical laboratories and their accreditation. In cooperation with CCKL, the society developed a Model Quality Handbook of Clinical Embryology which was based on the second edition of the CCKL Code of Practice for implementation of a quality system in laboratories in the health-care sector. This Code of Practice includes all CCKL standards and describes the conditions which quality systems in clinical laboratories must meet if quality is to be assured. The Model Quality Handbook of Clinical Embryology, released in December 1996, interprets CCKL guidelines for the field of ART laboratory practice, as the CCKL Code of Practice was originally issued for diagnostic laboratories in the health care sector. The handbook describes the conditions required to fulfil a quality system in general terms. It does not contain protocols, but instead guidelines for setting up protocols in a standardised manner. Every ART laboratory has to write its own local quality handbook or quality manual according to these guidelines. In this way, the Model Quality Handbook forms the basis for setting up an integral quality system in an ART laboratory and, unlike GMP guidelines, suffice for accreditation. During the last decade, the Model Quality Handbook has been revised several times in order to comply with the requirements of revised editions of the CCKL Code of Practice. The latest version of this CCKL Code of Practice, released in 2005, completely complies with the international standard ISO 15189 (2003), entitled Medical laboratories—particular requirements for quality and competence. As a consequence, CCKL accreditation according to the CCKL Code of Practice can be compared with accreditation according to ISO 15189.

Beside the Model Quality Handbook, several ART-related standards and guidelines have been developed and issued. In 2001, the Society of Clinical Embryologists released specific quality standards for in vitro fertilisation (IVF) laboratories. This standard was dedicated to specific requirement for ART laboratories as their daily work transcends the usual diagnostic role which most medical laboratory disciplines exhibit. Also in collaboration with other professional societies or related associations,

additional standards and guidelines were developed and issued during the last decade. Amongst them:

- National protocol for sperm banks: This standard, first published in 2004, contains additional requirement for sperm banks, based on national legislation and drafted according the CCKL Code of Practice. Whenever a Dutch sperm bank seeks accreditation, these specific requirements have to be met as well. This accounts both for homologous (i.e. partner donation) and heterologous (i.e. sperm donation other than by partner) cryopreservation of sperm.
- National protocol for the laboratory phase of intrauterine insemination: As most of the IUI programmes are run in mostly local hospitals outside the 13 licensed IVF laboratories and not supervised by a clinical embryologist, specific and detailed requirements for these so-called IUI laboratories were issued for the first time in 2005. Together with the Netherlands Society for Clinical Chemistry and Laboratory Medicine, this standard was developed in order to ensure the same high level of patient care with regard to sperm preparation for IUI. Accreditation of such an IUI laboratory can only be achieved when all sperm preparation activities are in compliance with the requirements of this standard.
- Position paper with regard to infection screening in ART: The Working Group for Clinical Virology, together with the Dutch-Belgium Society for Artificial Insemination, the Dutch Society for Obstetrics and Gynaecology and representatives of the society, a guideline for the screening of fertility patient with regard to the treatment and the cryopreservation of sperm and embryos was released in 2004. In 2010 a revised version of this position paper was issued in order to comply with adapted national and European legislation.
- Position paper with regard to air quality in ART laboratories: Due to European legislation, (Directive 2004/23EC) incorporating requirements with regard to air quality in ART laboratories, a working group of the society drafted this position paper in 2008.
- NTA 8070—Devices for assisted reproductive technology (ART): This Dutch technical specification (NTA) was drafted in collaboration with the Netherlands Standardization Institute (NEN) and together with interested parties form the industry that join the NTA working group. The NTA incorporates criteria focused on gamete and embryo safety in an attempt to fill the gap between legislation and CE marking and final testing and approval of devices used for assisted reproduction. Since the Ministry of Health, Welfare and Sports supported the need for a NTA, a grant was provided to cover a substantial part of the costs [2].

Local Quality Evolvements

Wherever GMP guidelines were not adequate for setting up a complete quality system, the Model Quality Handbook of our professional society did suffice for accreditation. The more so as the CCKL Code of Practice demands more than ‘production

and process control' protocols. ART laboratories are also expected to meet requirements concerning the supply of goods and services, management and use of means of research, facilities, management of documentation, complaints and deviations and internal and external assessments of the quality system. Furthermore, the organisation of the laboratory should be described at both the management and execution levels, i.e. regulations pertaining to professional expertise, and responsibilities of clinical embryologists and technicians have to be laid down in the quality manual.

In order to meet all CCKL requirements and conditions laid down in the Model Quality Handbook, all Dutch ART laboratories began to work towards extending their quality system. In 1999, the first ART laboratory in the Netherlands became accredited, according to the CCKL Code of Practice. This accreditation currently involves the complete ART programme of our laboratory, i.e. all aspects of the treatment of infertile patients with IUI, IVF or ICSI, and cryopreservation of human embryos and sperm including the organisation and management of the sperm bank, the PGD programme as well as semen diagnostics. Ever since, all licensed IVF centres in the Netherlands have implemented an integral quality management system and almost all have become accredited according to the CCKL Code of Practice. Accreditation by CCKL is not mandatory, and although all Dutch clinical embryologists agreed to endeavour accreditation by CCKL, some ART centres have decided to start with ISO 9001 certification or otherwise postponed the leap to formal acknowledgement. Nevertheless, the implementation of a quality system in the Dutch ART laboratories has improved the assurance of proper identification of all samples, the standardisation and transparency of all procedures and the traceability of all actions. It is now our responsibility to maintain the high standards of quality control and assurance of all services and to continue improving and optimising the treatment for all of our patients.

National and International Legislation

At the end of last century, the Dutch government had the growing need to regulate and to enforce legally a number of issues related to assisted reproduction. In 1998, the Planning Decree In Vitro Fertilisation was the first to review. In this decree of 1989, the permit for a limited number of IVF centres was already established. Shortly after the millennium turn, various laws entered into force: amongst them the Artificial Insemination (Donor Information) Act (2002), the Embryo Act (2002), the Safety and Quality of Body Materials Act (2003) and appended the Requirements for Body Materials Decree (2004). All acts contain rules governing many of the features and consequences of ART in order to ensure that gametes and embryos are handled properly and with respect, to give them special protection as the beginning of life and to safeguard the interests of the child such an embryo may become. A major part of the Embryo Act is concerned with conditions governing the use of embryos in research and contains a number of specific permanent prohibitions like cloning, creating chimeras, and applying sex-determining techniques. The acts

were also intended to place control over all institutions performing activities with gametes and embryos. Besides the 13 already licensed IVF laboratories, also IUI laboratories and sperm banks had to be designated by the Minister of Health.

In 2004, EU Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells entered into force [3]. The standards of quality and safety, laid down in this Cells and Tissue Directive, were further specified into additional directives, Commission Directive 2006/17/EC [4] and Commission Directive 2006/86/EC [5]. Due to this European legislation, rules concerning ART activities were further tightened and national laws had to be adapted necessary to comply with EU Directive 2004/23/EC. Additional provisions had to be adopted, and consequently, the Safety and Quality of Body Materials Act and the corresponding Requirements for Body Materials Decree were revised and entered into force in 2006 and 2007.

One of basic provisions on quality and safety of human tissues and cells in the Cells and Tissue Directive is that every tissue establishment, i.e. IVF laboratory, IUI laboratory and sperm bank, has to put in place and update a quality system. Since most of these laboratories had already implemented a quality management system and had been accredited by CCKL, only minor additional adaptations had to be made. Accreditation according to the CCKL Code of Practice or ISO 15189 turned out to allow for at least 80% compliance with statutory requirements.

Summary

In general, one of the major reasons to start implementing a quality system within an ART programme is governmental mandatory regulation. Another decisive reason is the occurrence of an incident with more or less disastrous consequences within the own clinic or even elsewhere, which triggers an awareness of the impact of our work, as was our experience. Handling human gametes as well as producing human embryos in order to achieve much-sought pregnancies form the key tasks of an ART laboratory. Considering the impact of the activities and the possible risks strongly emphasises the necessity to assure the safety and reproducibility of all methods. To achieve and maintain the highest level of patients' care and safety, a quality management system was implemented into our daily practice.

In the beginning, written procedures and working instructions concerning the critical steps in our daily practice were in place. But these brief protocols did not exceed the level of general rules and could not be considered as in any way a comprehensive quality system. In our attempt to establish a quality management system, we defined our scope of practice and what we ultimately hoped to achieve. Objectives were drawn up in order to clarify why, who, when and for whom the quality system should be implemented. We realised that certification or accreditation of itself could never be the driving force to start this enormous and time-consuming task, as formal acknowledgement by an authoritative body is not the end point. Once implemented, the quality system has to be adjusted and improved continuously and reviewed periodically in order to ensure that the various elements within the quality system are

effective and suitable for achieving the stated quality objectives. Establishing and maintaining a quality system and achieving the stated objectives require substantial changes at all levels, both within and outside the ART laboratory. The end result depends on everyone's will to change, i.e. participation and cooperation, as well as the commitment of the management, which is a prerequisite to provide the means for bringing about the change. Undoubtedly, individuals involved in an ART programme are well aware of the duties and responsibilities as well as the importance and consequences of their work. Therefore, the impact of vital aspects such as communication and motivation should not be underestimated in the attempt to get everyone involved when implementing a quality system and its attendant changes.

The implementation of an integral quality management system in our laboratory has improved the assurance of proper identification of all samples, the standardisation and transparency of procedures and the traceability of all our actions. It is now our responsibility as an accredited ART laboratory to maintain the high standards of quality control and quality assurance of all services and to continue improving and optimising patients' care. The whole 'operation' has proved to be a huge amount of work and has changed our day-to-day practice substantially. Nevertheless, we have come to the conclusion that, although sometimes frustrating, it was worthwhile and rewarding.

Everyone should realise that bringing about the change of such magnitude requires a lot of investments in all kind of means. Appointing a quality manager as well as extending the laboratory personnel are absolutely prerequisites in order to create possibilities to work on establishing and maintaining a quality management system. Quality management is not a task that can be performed besides regular work, since it results in a huge amount of additional work without an increase of the number of analyses and treatment cycles. But there is no doubt that the quality of work increases substantially and that the positive consequences far outweigh the negative ones. But be aware that how good protocols and practice in place may be, it can never compensate for negligence or human error, and in our work, any error will have far-reaching effects.

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Chapter 21
Australia: QMS in IVF Centres

James Catt

The Reproductive Technology Accreditation Committee (RTAC) controls IVF in Australia, and an IVF unit must be accredited by RTAC guidelines before it can operate. I have been lucky enough to have worked in 4 Australian IVF centres over the past 22 years, two of those as scientific director. During this time, we have implemented quality management systems in these centres that comply with the RTAC guidelines and have proven to be of huge benefit for the efficacious delivery of patient care. Optimal IVF, our current company, is a consultation IVF business dedicated to the implementation of QMS systems to optimise outcomes for the IVF industry. I would like to take the opportunity of this chapter to illustrate how QMS can be implemented in both new and established programmes.

Reproductive Technology Accreditation Committee

The first set of RTAC guidelines was introduced in 1986, and there have been five revisions since then. The most recent revision (2008) has been the most important with a paradigm change away from being proscriptive to allowing IVF units to develop their own procedures and policies that adhere to quality management principles. In other words, risk analysis should be used to define when and what procedures should be used to ensure the best outcomes for the patients.

The RTAC guidelines specify certain principles that must be adhered to. These include adherence to federal laws regarding tissue donation and embryo research, having qualified competent personnel, having a defined QMS, ensuring patient and

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sample traceability, ensuring correct drug administration and to minimise multiple pregnancy (twins are regarded as a multiple pregnancy). RTAC accredits IVF centres with professional third-party certifying bodies that employ suitably qualified auditors.

The defined QMS is probably the most important of the guidelines and is expressed as 'The organisation must have a management system allowing planned, implemented, coordinated and appropriate service delivery which meets the needs of all stakeholders'. *Stakeholders* is the key word here because they would include owners, staff and associated service providers, in addition to patients, thereby encompassing all the activities of the IVF centre.

Implementation of a QMS System

In our view, there are two ways of implementing a QMS system depending on whether a new unit is being commissioned or whether an established unit wants to introduce one. The methodologies are quite different as in the new unit processes can be designed to incorporate QMS principles whereas the established unit has to be moved slowly to a QMS system without disrupting the current processes.

New Units

These are best designed by a 'top down' approach. The quality assurance (QA) programme can be designed and written as an overarching scheme to include, within the quality manual, how the business is run from a managerial perspective, down through patient management and treatment, to how the laboratories are set up and run. This is often referred to total quality management (TQM), and centres utilising a quality approach depend on the participation of all members to give long-term consistent success, creating benefits for all participants. All manuals can be written before treatments start and all equipment and procedures validated before exposure to clinical material. Generally, this approach allows the new unit to 'hit the ground running' and obtain good results from the outset. Obviously, to implement a QMS before clinical treatment requires intimate knowledge of how an IVF centre works along with expectations (benchmarks) of what the outcomes should be.

Established Units

Most established units would have at least a rudimentary QMS, although this is not always the case. Given that IVF centres are by nature very conservative, then an introduction of a TQM can be very difficult due to staff resistance to change.

The phrase 'if it is not broken, don't fix it!' is often used and indeed has some merit. To introduce wholesale change into any organisation is difficult, and the key to doing this is to get the staff involved so they 'buy into' the change and end up with some 'ownership'. Laboratory staff are scientists and as such are more used to the application of scientific methodology and, therefore, are more accepting of structured change providing the benefits are tangible (i.e. better results). Therefore, the introduction of a QMS is easier to implement in the laboratories and, once the benefits are realised, can then be applied to the rest of the organisation. We have used this methodology on several occasions, and it has always worked taking about 3 months for the laboratory and a further 6–9 months for the rest of the organisation.

Important Features of a QMS System

Quality Manual

This does not have to be a large document, but one that includes a quality statement outlining the purpose of the QMS and the elements used to achieve that purpose. The details of the quality process are usually an inherent part of the procedure manuals, to integrate them as much as possible into the everyday events in the IVF centre.

Procedure Manuals

Procedural manuals should include all aspects of the business of IVF centre, laboratories, clinical, nursing and administration. The manuals should reflect the patients' journey through their treatment cycle to ensure consistency of treatment and outcome. Space prohibits detailing all the quality activities within the manuals, and so we shall just examine the QMS within a laboratory manual.

Laboratory Manual

As well as detailing the procedures within the laboratory manual, the QMS should ensure that the procedures have been optimised by setting them up correctly and monitoring the outcomes from any one procedure. The general laboratory setup should be so to reduce any factors that can impinge on embryo development. Although gametes and embryos spend most of their time in an incubator, they must be handled outside of the incubators, and so temperature, pH and atmosphere become paramount. The use of controlled environment chambers can reduce all of

these effects by controlling them to 37°C, 6% CO_2, and eliminating VOC with appropriate filtration. If these controlled environment chambers are not used (and most laboratories do not have them), then great attention should be paid to ambient conditions. Many scientists are not aware of several critical factors. These include laminar flow cabinets that give little protection to samples and the airflow rapidly cools samples. The use of warm stages and 'hot' areas should be thoroughly modelled, as these do not effectively heat dishes for the first 5 min, due the air trapped between the dish and stage being a very effective insulator that must be heated before heat transfer to occur.

Everybody uses a pipetting device to move gametes and embryos, and unless these devices are at 37 °C, they will cause the temperature to drop (often as much as 5 °C). This is further exacerbated if glass pipettes are used, particularly in under airflow conditions. Keeping the pipettes in a warm box does NOT help whatsoever, as they revert to ambient temperature within seconds after removal from the warm box. Every laboratory should model their conditions using data logging temperature probes to see what happens under their own ambient conditions. We cannot emphasise the importance of this modelling, as it is the most neglected part of embryology.

The above detailed example illustrates how a QMS can be used to reduce variation, but how do we know that reducing these variations work? The answer to this is in the next part of the QMS system, that is to monitor outputs (quality control).

Quality Control

Each procedure should have quantitative outputs that are recorded and compared with previous data along with a realistic expectation (internal benchmarking). Ideally, the results should be compared with other IVF centres (external benchmarking), but schemes to manage this are virtually non-existent.

Commonly used outcomes such as pregnancy rates are not useful, as they are often not well defined, often do not take account of the number of embryos transferred and take no account of the rest of the embryos produced but not transferred. Detailed outcomes that document the quality of the oocytes, efficacious sperm preparation, ICSI results, embryonic development and utilisation and effectiveness of the cryopreservation programme should be derived. There are many parameters (often referred to as laboratory performance measures or key performance indicators) that can be used, and each unit must decide which ones are most informative for their own programmes.

One such indicator, which can define the success of a programme, could be the cumulative pregnancy rate (for a defined population) where the cumulative rate is defined as the total pregnancies arising from any one stimulated cycle when the frozen embryos from that cycle are taken into account. Embryo utilisation rates (defined as the percentage of zygotes produced that are either transferred or frozen) are useful indicators for the overall programme focussing mainly on the laboratory but also including elements of stimulation.

Early entry into syngamy (<25 h post insemination) can be used as a measure of oocyte quality, as the timing of the first division is largely under the control of the oocyte cytoplasm and not culture conditions. Early division (within limits) is also a predictor for implantation potential. For those IVF centres practising blastocyst culture, early blastocele formation (late day 4 or early day 5) has also been extensively used as an indicator of appropriate culture conditions and implantation potential.

Conclusions

Some of the elements of a QMS for IVF centres have been discussed in this chapter, but space precludes a more detailed discussion. Suffice to say that a QMS should be an integral part of an IVF centre, being used to drive the organisation, with willing staff involvement, to achieve optimal outcomes for all stakeholders.

Australia has effective guidelines that aid IVF centres to implement their own QMS programmes whilst maintaining quality standards that ensure patients receive efficacious and safe treatment.

Detailed modelling of IVF procedures (as part of a QMS) can lead to changes in our thinking and methodologies that, in turn, can have benefits for our programmes. Although IVF is not a new technology, we still have much to learn to get the best possible outcomes for our stakeholders.

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