

Comprehensive guidance for human embryology, andrology, and endocrinology laboratories: management and operations: a committee opinion

Practice Committees of the American Society for Reproductive Medicine (ASRM) and the Society for Reproductive Biologists and Technologists (SRBT)

American Society for Reproductive Medicine, Birmingham, Alabama

This document is a comprehensive guidance for human embryology, andrology, and endocrinology laboratories. Universal guidance applicable to all laboratories includes requirements and recommendations for accreditation and staffing in the United States, and specific guidance is included for each laboratory specialty. (Fertil Steril® 2022;117:1183-202. ©2022 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: Andrology, assisted reproductive technology, embryology, endocrinology, laboratory

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The American Society for Reproductive Medicine (ASRM) has previously published guidance and minimum standards for embryology and andrology (1) and embryology (2, 3) laboratories to serve as templates for assisted reproductive technology (ART) clinics to meet or exceed requirements suggested by the Centers for Disease Control and Prevention (CDC). This updated guidance was created in acknowledgment of the advances and changes in reproductive medicine and to be comprehensive in scope by providing general guidance to embryology, andrology, and endocrinology laboratories. Across the country, ART laboratories vary in the services provided, and laboratories may provide embryology, andrology, endocrinology, or some combination of 3 laboratories. Because of the significant overlap in standards between the 3 types of laboratories, universal guidance is provided in this document that can be applicable to all sections of the ART laboratories with specific guidance detailed where necessary. Other non-US-based guidance has been published elsewhere (4).

This document is organized into 5 laboratory sections and was written by laboratory directors and embryologists ranging in setting (private, academic, and hybrid) and experience. Sections were edited and reviewed by the executive council of the Society for Reproductive Biologists and Technologists and the ASRM Practice Committee.

Table of Abbreviations

AAB: American Association of Bioanalysts
ABB: American Board of Bioanalysis
ABOR: AAB Board of Registry
AH: Assisted Hatching
AI: Artificial intelligence
ART: Assisted Reproductive Technologies
ASRM: American Society for Reproductive Medicine
CAP: College of American Pathologists
CASA: Computer Assisted/Aided Sperm Analysis
CC: Clinical Consultant
CDC: Centers for Disease Control
CLIA: Clinical Laboratory Improvements Amendments
CME: Continuing Medical Education
CMS: Centers for Medicare and Medicaid Services
CRB: College of Reproductive Biologists
DFI: DNA Fragmentation Index
DO: Doctor of Osteopathy
DOB: Date of Birth
DPM: Doctor of Podiatric Medicine
EHR/EMR: Electronic Health/Medical Records
ELD: Embryology Laboratory Director
eSET: Elective Single Embryo Transfer
ET: Embryo Transfer
FDA: Food and Drug Administration
FET: Frozen-Thawed Embryo Transfer
HCLD: High-Complexity Clinical Laboratory Director
HHS: Health and Human Services
HIPAA: Health Insurance Portability and Accountability Act
HSA: Human Serum Albumin
ICM: Inner Cell Mass
ICSI: Intracytoplasmic Sperm Injection
MD: Medical Doctor
MEA: mouse embryo assay
MESA/PESA: Microsurgical/Percutaneous Epididymal Sperm Aspiration
NASS: National ART Surveillance System
niPGT: non-invasive PGT
OSHA: Occupational Safety and Health Administration
PGT: Preimplantation Genetic Testing
PhD: Doctor of Philosophy
PN: Pronuclei
PT: Proficiency Testing
PVP: Polyvinylpyrrolidone
QMS: Quality Management System
SA: Semen Analysis
SART: Society for Assisted Reproductive Technologies
SRBT: Society for Reproductive Biologists and Technologists
SSA: human sperm survival assay
TE: Trophectoderm
TESA/TESE: Testicular Sperm Aspiration/Extraction
TJC: The Joint Commission
TLI/TLM: Time-Lapse Imaging/Microscopy
ZP: Zona pellucida

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UNIVERSAL GUIDANCE FOR ALL ART LABORATORIES

Laboratory Certification and Accreditation

The Centers for Medicare and Medicaid Services (CMS) regulates all clinical laboratory testings performed on humans in the United States through the Clinical Laboratory

TABLE 1**Embryology laboratory staff minimum requirements for education, training, continuing education, and experience.**

Title	Education	Training	Continuing education	Experience
Laboratory supervisor^a	Have an earned bachelor's or master's degree in a chemical, physical, or biologic science or in medical technology from an accredited institution	Have documented completion of training in and performance of a minimum of 60 ART procedures under supervision with attestation from the training laboratory	Obtain a minimum of 24 hours of documented CEUs every 2 years	Minimum 4 (BS/BA) 2 (MS), and 1 (Doctoral) year of experience. Perform 20 procedures or satisfactory number annually to maintain technical proficiency.
Senior embryologist	Have an earned bachelor's or master's degree in a chemical, physical, or biologic science or in medical technology from an accredited institution	Have documented completion of training in and performance of a minimum of 30 ART procedures under supervision with attestation from the training laboratory	Obtain a minimum of 24 hours of documented CEUs every 2 years	Minimum 3 years of experience. Perform 20 procedures or satisfactory number annually to maintain technical proficiency.
Embryologist	Have an earned bachelor's or master's degree in a chemical, physical, or biologic science or in medical technology from an accredited institution	Have documented completion of training in and performance of a minimum of 30 ART procedures under supervision with attestation from the training laboratory	Obtain a minimum of 24 hours of documented CEUs every 2 years	Minimum 2 years of experience. Perform 20 procedures or satisfactory number annually to maintain technical proficiency.
Junior embryologist	Have an earned bachelor's or master's degree in a chemical, physical, or biologic science or in medical technology from an accredited institution	Have documented completion of training in and performance of a minimum of 30 ART procedures under supervision with attestation from the training laboratory	Obtain a minimum of 24 hours of documented CEUs every 2 years	Minimum 1 year of experience. Perform 20 procedures or satisfactory number annually to maintain technical proficiency.
Embryology trainee	Have an earned bachelor's or master's degree in a chemical, physical, or biologic science or in medical technology from an accredited institution	Have documented completion of training in and performance of a minimum of 30 ART procedures under supervision with attestation from the training laboratory	Obtain a minimum of 24 hours of documented CEUs every 2 years	Less than 1 year of experience. Perform 20 procedures or satisfactory number annually to maintain technical proficiency.

Note: ART = assisted reproductive technology; CEU = continuing education credits/unit.

^a **Laboratory supervisor:** have the education and experience required of a technical supervisor accredited by the American Board of Bioanalysis regardless of whether the laboratory director is on-site or off-site. Accreditation by the American Board of Bioanalysis as a technical supervisor in embryology is recommended but not required for the laboratory supervisor and/or the laboratory director.

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TABLE 2**Recommended laboratory staffing based on embryology cycle volume.**

Number of total cycles	Minimum number of embryologists
1–150	2–3
151–300	3–4
301–600	4–5
>600	1 additional embryologist per additional 150 cycles

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Improvement Amendments (CLIA). The full CLIA regulations and interpretive guidelines are available (5). The CLIA regulations and guidelines apply to clinical laboratories that perform diagnostic tests on humans and generate reports of test results. Before a clinical laboratory begins operations, they are required by the CMS to apply for a CLIA Certificate of Registration. At present, andrology and endocrine laboratories are considered the reproductive clinical laboratories that fall under the CLIA and state (varies by state) regulations and guidelines. The CLIA regulations do not extend to the embryology laboratory, but fertility clinics that are members of the Society for Assisted Reproductive Technology (SART) must have an embryology laboratory that is accredited by either the College of American Pathologists (CAP) or The Joint Commission (TJC).

If the andrology laboratory provides quantitative semen analysis (SA) or any procedure that includes diagnostic quantitative analysis of sperm concentration (sperm count), the laboratory must satisfy the requirements of and be registered as a high-complexity clinical laboratory as specified in the CLIA regulations (5). Laboratories or medical practices that limit reporting to the presence or absence of sperm and detection of motility fall beneath the threshold requirement of a high-complexity clinical laboratory. It is important to note that even if only 1 test performed in the laboratory is high complexity, the entire laboratory must be registered and treated as a high-complexity laboratory. Endocrine laboratories typically use automated immunoanalyzers to report serum fertility hormone levels for patients. Due to the automated nature of the analyzer, these laboratories are considered of moderate complexity. Both andrology and endocrine testings are considered nonwaived by the CLIA. Waived testing in CLIA laboratories includes urine pregnancy testing and urinalysis.

Andrology and endocrine laboratories must submit to inspection by individual states' departments of health, which ensure compliance with the CLIA regulations (5). If laboratories successfully pass inspection, the laboratory will be granted a CLIA Certificate of Compliance. In lieu of inspection by the CLIA, the laboratory may be accredited by an authorized accrediting organization, such as the CAP or TJC. The requirements for accreditation by these organizations is as stringent, if not more so, as those enforced by the CLIA. If the laboratory is accredited by a CLIA-authorized accrediting organization (CAP or TJC), it will have a CLIA Certificate of Accreditation

(as opposed to a Certificate of Compliance) as well as the CAP or TJC Certificate of Accreditation. After initial accreditation, clinical testing laboratories must submit to regular biennial inspections by the state's department of health or the laboratory's accrediting organization. These inspections may be announced or unannounced. They include review of the laboratory's quality management and quality assurance programs, as well as all other aspects of preanalytic, analytic, and postanalytic testings. The CMS and CLIA still have ultimate authority over the operations of the laboratory.

Laboratories that are part of a hospital or health system where the parent entity is accredited by TJC are also subject to TJC standards even if the laboratory is already accredited by another accrediting organization, such as the CAP. It is important for the laboratory to work closely with the parent institution to ensure that the laboratory is compliant with the standards of all relevant accrediting organizations.

This document provides overview for setting up and organizing laboratories rather than an exhaustive checklist. Because the CLIA, CAP, and TJC have detailed standards and requirements with which ART laboratories in the United States must comply, laboratories should refer to specific checklists and requirements provided by their accrediting body to achieve and remain in compliance.

Food and Drug Administration

The US Food and Drug Administration (FDA) is the federal agency with regulatory authority over human cells, tissues, and cellular and tissue-based products (HCTPs). Sperm, oocytes, and embryos used in ART are classified as HCTPs by the FDA, and their use is, thus, regulated by Title 21 of the Code of Federal Regulations (CFR), part 1271 (6).

The FDA issues specific guidance on subjects such as donor eligibility (7). Laboratory staff are encouraged to review the guidance and work in coordination with the designated clinical individual overseeing eligibility determination to ensure all donor materials are appropriately handled and distributed. The ASRM also provides guidance based on best practices, ideally evidence-based, on third-party reproduction within various Practice Committee documents (8, 9).

Those entities using HCTPs must, within 5 days of beginning operations, register their establishment with the FDA and submit to periodic unannounced inspections of the fertility clinic including the laboratory for which the main focus of the FDA is cryostorage and labeling. The frequency of these inspections is at the discretion of the FDA, but generally, they occur biennially. During inspection, the FDA will review compliance with donor eligibility requirements and ensure that the fertility clinic is following FDA guidance to prevent the spread of infectious disease in the context of third-party reproduction. The FDA has the authority to order immediate cessation of patient care should they deem the quality of care to be sufficiently low that there is an imminent risk to patient safety.

In addition to the FDA, some states may also require fertility clinics to have a tissue bank registration or license. The state tissue bank may oversee activities and services provided, such as donor solicitation, artificial insemination, and all tissues in

cryostorage. Regulations include requirements for facilities that recover, process, store, and/or distribute cells and tissues. Each fertility clinic should confirm with their State Department of Health the existence and scope of a tissue bank license.

Finally, the FDA issues specific guidance periodically on emergent issues, such as testing for Zika virus, West Nile virus, and coronavirus disease 2019 (10, 11).

Society for Assisted Reproductive Technology

Membership in the SART is voluntary but is encouraged for fertility clinics. The mission of the SART is to “set up and help maintain the standards for ART in an effort to better serve members and patients” (11). The SART works with the CDC to analyze ART practice patterns and outcomes to ensure that all clinics operate under the current standard of care. The SART member clinics upload ART outcome data on an annual basis to the SART. The SART then reports those data to the CDC National ART Surveillance System. Clinics who choose not to be SART members must report their outcomes directly to the CDC National ART Surveillance System.

Importantly, fertility clinics that elect to be members of the SART must have an embryology laboratory that is accredited by either the CAP or TJC.

Quality Management System

A quality management system (QMS) is the framework established to manage and monitor activities related to quality standards to achieve an organizational goal. Quality control, assessment, and improvement are essential parts of the QMS. The QMS must cover all areas of the laboratory and must be reviewed at least annually by the laboratory director for effectiveness. Major organizations providing infrastructure for creating a QMS are the Clinical and Laboratory Standards Institute and the International Standards Organization. Different accrediting agencies will have their own specific elements required in a QMS. The important elements of a QMS system include:

- Meeting applicable regulatory, licensing, and accreditation requirements (CLIA, Occupational Safety and Health Administration, Health Insurance Portability and Accountability Act, and Fire and Building codes).
- Customer service and satisfaction surveys.
- Processes to identify and evaluate errors, incidents, or other problems that may interfere with patient care, frequently achieved through documentation and review in an incident report format.
- At least biennial review of laboratory documents including (but not limited to) policies, procedures, and forms.
- Quality control of all equipment and procedures. This should include daily quality control methods for each test performed and by each technologist performing the test.
- Calibration maintenance of equipment, which includes microscopes, hoods, centrifuges, pipettes, thermometers, and environmental conditions—performed at defined intervals.
- Assurance of personnel satisfying education and training requirements for the: laboratory director, clinical/technical

consultant(s), technical supervisor(s), general supervisor(s), and testing personnel.

- Measurement of key performance indicators. Establishment, maintenance, and documentation of parameters in the *preanalytic*, *analytic*, and *postanalytic* phases.
- Audits to assure the accuracy and completeness of laboratory reports.

Each fertility clinic should have a policy regarding disclosure of medical errors involving gametes and embryos as soon as they are discovered, such as loss, misdirection, or damage. Disclosure of errors causing no harm or near misses is recommended (12).

Proficiency Testing

The CLIA regulations require laboratories to participate in some form of proficiency testing (PT) for every test that they perform on patient specimens at an interval of not less than twice per year. Accrediting agencies may have their own PT requirements for nondiagnostic tests or services such as those provided by the embryology laboratory. Some testing requires participation in an external PT program that compares ones results with those of colleagues, whereas for others, an in-house developed alternative assessment or other method of proficiency may be conducted biannually. For testing in which external PT is required, results are usually reported directly to regulatory accreditation bodies (13). Materials used for PT can be provided by accrediting bodies such as the CAP or by other groups or industries such as the American Association of Bioanalysts (AAB).

The examples of testing that require participation in an external PT program, such as from the CAP or AAB, include sperm count, sperm viability, and endocrine (hormone) assays. The examples of testing that requires a minimum of an alternative assessment (not external PT) include sperm morphology, sperm motility, and all embryology procedures/tests.

Laboratory Director Requirements and Duties for On-Site and Off-Site

Laboratory directors are responsible for the overall quality and function of the laboratory. The duties of the laboratory director will be similar for all laboratories, but the requirements may vary depending on the complexity of the laboratory (high vs. moderate). Details are described in the CLIA regulations in 42 CFR 493 and interpretive guidelines as follows: <https://www.ecfr.gov/cgi-bin/textid?SID=1248e3189da5e5f936e55315402bc38b&node=pt42.5.493&trgn=div5> (14) and https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Interpretive_Guidelines_for_Laboratories.html (15).

Duties

The laboratory director duties include the following:

- Ensuring the testing systems provide quality services in all phases of testing (preanalytic, analytic, and postanalytic) and are appropriate for the patient population.

- Establishing and maintaining policies and procedures.
- Approving and reviewing test methodologies.
- Ensuring continued standards through quality control, assurance, and improvement.
- Overseeing training and continued competency of personnel.
- Ensuring that the laboratory has the appropriate number of trained staff and each employee's duties are specific in writing.
- Ensuring that a general supervisor (high-complexity testing) is available to provide day-to-day supervision of all testing personnel and reporting of test results as well as provide on-site supervision for specific minimally quality testing personnel when they are performing high-complexity testing.
- Ensuring that adequate space, equipment, and facilities and resources are available and that the environment for employees is safe from physical, chemical, and biologic hazards and safety and biohazard requirements are followed.
- Ensuring the quality of laboratory reports and turnaround time of testing.

The duties of an on-site or off-site laboratory director are the same, and each must be available for consultations (in-person, telephone, or electronic) as needed by the laboratory and referring clinicians. Off-site directors must visit the laboratory frequently to monitor the function and quality of the laboratory at minimum 4 times a year (the CAP). For any regulatory surveys for accreditation, certification, or licensure, the laboratory director must be present and on-site to ensure immediate access by the surveyor(s). Laboratory directors may direct no more than 5 laboratories performing non-waived testing (5 CLIA certificates) and no more than 5 embryology laboratories (non-CLIA). Because the off-site laboratory director is responsible for the operation and performance of the laboratory and staff, meaningful visits to enable observation and evaluation of services and patient care at an appropriate frequency are required.

Requirements

The requirements for education and experience for a laboratory director will vary whether the laboratory is high complexity or moderate complexity and whether the laboratory includes embryology. Additionally, some states, such as New York, New Jersey, Florida, and California, have specific requirements for the laboratory director, and ART laboratories are encouraged to check for any state-specific requirements. These requirements may also vary by accrediting agency.

Moderate-Complexity Laboratory Director

A moderate-complexity laboratory director must possess a current license as a laboratory director issued by the state in which the laboratory is located, if such licensing is required
AND

The laboratory director must be a Medical Doctor (MD) or Doctor of Osteopathy (DO) with a current medical license in the state of the laboratory location and be board certified in anatomic and/or clinical pathology

OR

An MD, DO, Doctor of Podiatric Medicine (DPM) with a current medical license in the state of the laboratory location and laboratory training/experience consisting of the following:

- One-year experience as a director or supervising non-waived tests *OR*
- Twenty Continuing Medical Education credit hours in laboratory practice commensurate with director responsibilities *OR*
- Equivalent laboratory training (20 Continuing Medical Education credit hours) during medical residency *OR*
- A doctoral degree (Doctor of Philosophy [PhD]) in chemical, physical, biologic, or clinical laboratory sciences from an accredited institution with board certification *OR* 1 year's experience directing or supervising nonwaived testing.

* While the CLIA permits non-physician or non-doctoral degree candidates to serve as the director of a moderate-complexity laboratory, the CAP does not.

**If the laboratory has an annual test volume of >500,000, the director must be qualified as a high-complexity clinical laboratory director (HCLD), even if only moderate-complexity testing is performed.

High-Complexity Clinical Laboratory Director (for ART Laboratories)

An HCLD must have a doctoral degree (PhD) in a chemical, physical, or biologic science or a medical degree (MD or DO) from an accredited educational institution *OR* have qualified as a laboratory director before July 20, 1999.

The laboratory director must have the following: specific training and expertise in biochemistry, cell biology, and the physiology of reproduction and experience in experimental design, data management, and statistical analysis and knowledge of and experience with the full array of assisted reproductive techniques, including but not limited to, culture medium design, gamete and embryo culture, cryopreservation, vitrification, experience in micromanipulation including assisted hatching (AH), intracytoplasmic sperm injection (ICSI), embryo and blastocyst biopsy, and biopsy preparation for genetic testing.

As of January 1, 2006, a laboratory director must have earned certification as an HCLD or embryology laboratory director from the American Board of Bioanalysis (ABB).

Two years of documented relevant experience in a clinic performing in vitro fertilization (IVF) and ART is required, including the following:

- Cell and tissue culture and aseptic techniques.
- Clinical andrology including diagnostic SA and semen processing and preparation of sperm for treatment.
- Completion of a minimum of 60 ART procedures under supervision, defined as a combination of egg retrievals from follicular aspirates, insemination, assessment of fertilization, assessment of embryo stage of development

and morphology, and preparation of embryos for and performance of embryo transfer (ET), with attestation of satisfactory performance by the director of the laboratory in which training was obtained.

- Demonstration of technical competence in the performance of specific ART procedures as measured by the accepted metrics of the clinic in which training was obtained.

It is recommended but not required that MD and PhD embryology laboratory directors hold the embryology subspecialty certification (technical supervisor, ABB) or equivalent to direct a CAP- or TJC-accredited, SART-reporting embryology laboratory.

Clinical/Technical Consultant

Laboratories that are high complexity require a clinical consultant (CC). The CC must be an MD, DO, DPM with a current medical license in the state of the laboratory location or a doctoral scientist certified by a Health and Human Services-approved board. The CC should be available to provide clinical consultation to the laboratory's clients and ensure appropriate tests are ordered to meet clinical expectations.

Moderate-complexity laboratories only require a technical consultant if the laboratory director is not qualified as an HCLD. The technical consultant must be an MD, DO, DPM with a current medical license in the state of the laboratory location that is certified in clinical or anatomic pathology or has at least 1 year of experience or training in nonwaived testing. Alternatively, the technical consultant can have a doctoral or master's degree in chemical biologic, physical, or clinical laboratory science with at least 1 year of experience or training in nonwaived testing or a bachelor's degree in chemical biologic, physical, or clinical laboratory science or medical technology with at least 2 years of experience or training in nonwaived testing.

Document Control System

Document control refers to a system to ensure only current policies, procedures, and forms are in use and that there are records of approval and review by the laboratory director and records of discontinuance of retired documents are in place. This is frequently accomplished through a control log of all policies, procedures, and forms with the location of each. There should be a defined process and records indicating all personnel are knowledgeable about policies and procedures.

Employee Competency and Employee Development

Employees must be evaluated for competency after 6 months of employment in the first year and then annually thereafter. Additionally, competency must be assessed before patient testing and reporting results when new methods or instruments are put into place. The competency evaluation should encompass all aspects of the job description and evaluate the individual in all phases of the testing procedure, preanalytic, analytic, and postanalytic phases, and should be determined via observation of sample handling. Several elements of competency assessment are performed throughout the

year and can be recorded. The elements of competency include the following:

- Direct observation of routine test performance, including patient identification and preparation, and specimen collection, handling, processing, and testing
- Monitoring the recording and reporting of test results including, as applicable, reporting critical results
- Review of intermediate test results or worksheets, quality control records, PT results, and preventative maintenance records
- Direct observation of performance of instrument maintenance and function checks
- Assessment of test performance through testing previously analyzed specimens, internal blind testing samples, or external PT samples
- Evaluation of problem-solving skills

Those individuals who hold a specific license or qualification, such as HCLD (ABB), technical supervisor (ABB), embryology laboratory scientist (AAB), and/or andrology laboratory scientist (AAB), must complete the required number of hours of accredited continuing education to maintain their qualification.

Universal and Standard Precautions and Laboratory Sanitation

Universal precautions are an approach to infection control that treats all human blood and certain body fluids as if they may be infectious. Universal precautions should be used at all times when handling all samples. Details are described in the Bloodborne Pathogen Standard 29 CFR 1910.1030(d) (1) (16).

The samples encountered in ART laboratories that carry the risk of disease transmission include semen, blood, and follicular fluid. Serum from patients with semen, oocytes, or embryos destined to be cryopreserved should be tested for infectious diseases before cryopreservation. Sanitation of the work area and equipment using an approved disinfectant should occur any time that there is a spill and at the end of every shift.

Laboratories may handle gametes from virus-positive patients. Patients who are positive for blood-borne viruses, such as human immunodeficiency virus or hepatitis B or hepatitis C virus, may seek fertility care, and laboratories should have policies and procedures for safe handling of oocytes and semen and sanitation of the laboratory. Guidance for establishing policies and procedures has been published (17). Aerosolized viruses, such as severe acute respiratory syndrome coronavirus 2, may be transmitted between patients, staff, and samples. Augmented sanitation protocols and risk mitigation strategies should be established as part of each clinic's safety program (18).

Laboratory Safety

In addition to the Bloodborne Pathogen plan described earlier, laboratories must maintain a chemical hygiene plan to protect laboratory workers from hazardous chemicals. Details are

described in the Occupational Safety and Health Administration 29 CFR1910.1450 (19, 20).

Notable details include maintaining policies and procedures for safety and ensuring that all personnel are trained and reviewing safety procedures annually, written policies and procedures for reporting laboratory accidents, a mechanism for the safe handling and disposal of biohazardous waste material in the laboratory, properly maintaining equipment to avoid possible injury, appropriate personal protective equipment, and correct storage and disposal of chemicals and reagents in accordance to the manufacturer's recommendations and/or local regulations.

Disaster Preparedness Plan

Every ART laboratory needs to maintain an up-to-date disaster preparedness or emergency plan (21). The scope of the plan may vary based on the laboratory's activities. Laboratory priorities should be considered ahead of time to reduce the decision-making burden during an emergency. Consideration should be given to coordinating the plan with others in the same hospital system (where applicable), or other tenants within the same building, and local first responders. Andrology and embryology laboratories need to have an exit strategy that includes a logical way to rescue storage tanks containing cryopreserved specimens, as well as backup and contingency plans for specimens in culture and cryopreserved specimens in the case of extended power outages or shortage of supplies. Resources are available at www.Redcross.org, www.disasterassistance.gov, and state agencies. Disaster preparedness plans should routinely be evaluated to identify gaps.

Patient Reports

The laboratory should have a written record of each diagnostic test or IVF cycle that details the testing/procedures that were ordered and completed. These records can be either paper based or based in an electronic record. In each case, there should be adequate backup procedures, and the records themselves should be easily retrievable. Each clinic/laboratory should have a policy specifying the amount of time they intend to retain these patient reports and records.

As a part of the American Recovery and Reinvestment Act, all public and private healthcare providers and other eligible professionals were required to adopt and demonstrate the "meaningful use" of electronic health records/electronic medical records (EHRs/EMRs) by January 1, 2014, to maintain their existing Medicaid and Medicare reimbursement levels. The EHRs/EMRs have been shown to improve quality, safety, and efficiency and reduce health disparities as well as maintain privacy and security of patient health information.

EMBRYOLOGY LABORATORY GUIDANCE

Definition of Service

Embryology laboratories provide safe and effective IVF procedures to requesting physicians with trained staff (embryologists). Basic procedures provided by embryology laboratories are the identification of surgically retrieved oocytes, fertilization of oocytes, culture, transfer, and cryopreservation of embryos. Several laboratories also provide additional services

such as oocyte cryopreservation, embryo biopsy for preimplantation genetic testing (PGT), and the ability to use fresh or frozen donor gametes or embryos.

Laboratory Space and Design

Embryology laboratories are highly specialized and sensitive areas that require thoughtful design and layout (22). The size of the laboratory will vary by IVF volume. General considerations for all embryology laboratories are the following:

- Use of low volatile organic compound paint and construction materials.
- Floors, counters, and walls that can be easily cleaned and disinfected and the use of solid ceilings (no drop-down tiles).
- Sufficient electrical outlets and outlets that are tied to a backup power source (generator).
- Dedicated clean air into the laboratory, with consideration given to high-efficiency particulate absorbing filters, carbon, and permanganate filters to limit particles, volatile organic compounds, and inorganic air pollutants.
- Positive air pressure inside the laboratory, relative to the procedure room and any other adjacent rooms.
- Use of incandescent lights with the ability to dim and no fluorescent or bright lights.
- An adjacent procedure room for oocyte retrieval and ET, preferably with a pass-through window for materials.
- An adjacent or nearby room for gas tanks and liquid nitrogen tanks. The tanks should not be stored inside the laboratory.
- Sufficient gas line hookups inside the laboratory for incubators and for antivibration tables as needed, with a backup system in place.
- The ability to limit access through badge readers or similar method.

Instrumentation

Embryology laboratories require a wide array of specialized equipment. At a minimum, these would include the following:

- Incubators: either "benchtop" style (humidified or nonhumidified) or traditional "big-box" water or air jacketed incubators. In addition to supplying CO₂ to enable an appropriate pH for embryo culture, incubators should provide low O₂ concentration through the use of a premixed gas or nitrogen gas input. A sufficient number of incubators should be available to limit door openings and provide enough space in the event of downtime or maintenance of an incubator.
- Warming ovens: nongassed warming ovens are typically needed to warm media or materials that do not require equilibration with CO₂.
- Heated stages and warm blocks: heated stages should be available for any surface that would hold embryo culture dishes and/or micromanipulation dishes. This may include microscope stages, stages inside workstations, or stand-alone warming stages. Warm blocks should be available to hold media or tubes containing fluid and oocytes from oocyte retrieval procedures.

- **Microscopes:** stereo or dissecting microscopes for moving oocytes and embryos between dishes, retrieval of oocytes, and vitrification and warming procedures should be available. Some may require heated surfaces, and some may be used at room temperature depending on the vitrification and warming protocol. It is useful to have the ability to provide both. Light microscopes with phase contrast and bright-field optics should be available if sperm preparation or morphology is performed within the embryology laboratory. Inverted microscopes should be equipped with Hoffman modulation contrast, differential interference contrast, or similar for micromanipulation procedures such as ICSI, AH, and embryo biopsy and for embryo grading at high resolution. Inverted microscopes should also be equipped with a micromanipulation system for ICSI, AH, and embryo biopsy, as well as a laser objective for AH, blastocoel collapse, and embryo biopsy. It is recommended that inverted microscopes used for micromanipulation procedures be placed on antivibration tables.
- **Refrigerators and freezers:** both a refrigerator and freezer should be available in the embryology laboratory to hold media and other temperature-dependent supplies with an independent monitoring system. Typically, a $-20\text{ }^{\circ}\text{C}$ freezer is sufficient, and a $-80\text{ }^{\circ}\text{C}$ freezer may only be needed for laboratories performing a significant amount of research.
- **Workstations and/or laminar flow hoods** for media preparation and during certain procedures such as ET.
- Some laboratories may use “isolette” style workstations that provide a gassed and heated environment for short-term embryo manipulation outside the incubator.
- **Liquid nitrogen supply and tanks:** a supply line of liquid nitrogen should be available within the laboratory, along with adequate number of dewars and liquid nitrogen storage tanks and an O_2 monitoring system.
- **Real-time monitoring and alarm system** connected to equipment and cryotanks: to monitor equipment in normal operational range and alarm laboratory personnel when out-of-range or deviation has been detected.

Supplies and Reagents

Embryo culture media are available commercially from a variety of vendors. Similarly, disposable materials manufactured specifically for ART laboratories are typically available and are preferred. These generally come with data from a relevant bioassay, such as a mouse embryo assay, that demonstrate efficacy or sperm survival assay. Any materials or media that do not come with appropriate bioassay must be tested with an appropriate bioassay in-house before using the materials. It is also recommended to verify that the pH of any new lot of culture media falls within the laboratory’s defined limits before use. If the media or protein supplements are modified or prepared in-house, records should indicate they were tested.

Environmental Daily Quality Control

Quality control can be determined by comparing a set of inherent characteristics against a set of requirements or

acceptable limits. Daily quality control performed in the embryology laboratory should include the following:

- Incubator gas concentrations
- Gas supply, including line pressure and gas tank consumption
- Incubator temperature
- Refrigerator and freezer temperatures
- Temperatures of all heated surfaces
- Room temperature and humidity
- Laser alignment
- Liquid nitrogen tanks

In addition to the standard daily quality control (QC) checks, the following should be performed in an embryology laboratory as part of the overall QC program:

- All new protocols should be validated by parallel testing (when possible, before clinical implementation). Protocol documentation should include a description of the assay, standards, controls, calibration, accuracy, precision, and tolerance limits where applicable.
- Equipment should be maintained and calibrated on a regular basis (daily, weekly, monthly, and yearly). This includes a record of instrument calibration; functional checks of equipment, when possible; evidence of an active review of records; and documentation of corrective action taken when instruments malfunction.
- All reagents, media, and chemicals should have expiration dates recorded, and lot number if applicable, as suggested by the manufacturers. All outdated materials should be discarded in an appropriate manner.

Embryology Laboratory Staffing

Table 1 summarizes the minimum embryology laboratory staff requirements for education, training, continuing education, and experience.

Embryology Laboratory Supervisor: Definition and Duties

The laboratory supervisor provides oversight of the daily operations of the laboratory. Working closely with the laboratory director and with responsibilities authorized in writing by the laboratory director, the supervisor may oversee staff training and efforts for continual technical improvement and delegate operational tasks such as instrument maintenance, inventory management, correspondence with patients about their cryopreserved samples, and maintenance of laboratory records and documents. The supervisor is an on-site resource for the laboratory personnel for technical questions and assistance, as well as to the clinical and administrative staff in the center. The laboratory director may also fulfill the role of laboratory supervisor. In fertility centers where the laboratory director is also the medical director or where the laboratory director is off-site, there must be a designated full-time on-site laboratory supervisor. An embryology laboratory supervisor should have no less than 4 years of experience as an embryologist.

Senior Embryologist and Embryologist: Definition and Duties

The senior embryologist performs all, and the embryologist performs some or all, of the array of ART procedures for which training has been provided under the supervision of the laboratory director or supervisor, as well as any other tasks assigned to maintain and operate the embryology laboratory. An educational background or technical experience in cell and tissue culture and the reproductive biology of mammalian systems are desirable. Acquisition of skill in clinical embryology will be obtained through a documented training program administered by the embryology laboratory. A senior embryologist has no less than 3 years of experience, and an embryologist has no less than 2 years of experience, as an embryologist.

Junior Embryologist and Embryology Trainee

Junior embryologists and embryology trainees perform some of the array of ART procedures for which training has been provided under the supervision of the laboratory director or supervisor, as well as any other tasks assigned to maintain and operate the embryology laboratory. An educational background or technical experience in cell and tissue culture and the reproductive biology of mammalian systems is desirable. Acquisition of skill in clinical embryology will be obtained through a documented training program administered by the embryology laboratory. A junior embryologist has no less than 1 year of experience as an embryologist. An embryology trainee has <1 year of experience as an embryologist.

Embryology Training

All embryologists, in their uniquely sensitive management of patients' gametes, embryos, and reproductive tissues, play a central role in patient care. Technical training and acquisition of competency must be achieved through a well-organized, structured plan with appropriate metrics by which to set measurable goals and timelines. As a first step of the training process, the trainee must review the procedure and quality assurance (QA) manual and have all questions answered to his/her satisfaction by the laboratory director or supervisor. New employees must sign manuals after reviewing them. Throughout the training process, the trainee must observe all procedures numerous times before actually performing the task independently. Following observation sessions, trainees will perform certain tasks while being observed by a supervisor (e.g., preparation of culture medium) and participate in ART cases performed by the trainer (e.g., scan a few dishes during oocyte retrieval and strip 1–2 eggs for fertilization check and ICSI).

For procedures that require analytic steps (sperm count, morphology assessment, motility assessment, and embryo and oocyte grading), parallel readings will be performed until consistent readings within the tolerance range are achieved. Training checklists outline the average number of required training sessions. However, these numbers

may be individually altered (increased or decreased) at the discretion of the trainer depending on the new employee skills, performance, and prior ART experience. Generally, the new employee will be cleared to perform most tasks independently after approximately 3–9 months of the training period. Some procedures (e.g., ICSI) may require a significantly longer training period. If the practice attempts are not successful, repeated steps may be necessary. After the initial 6 months of training, the laboratory director will review all training records as well as directly observe the trainee and at this point will decide if the trainee has acceptable skills to continue with training in embryology.

Recommended Laboratory Staffing Based on Cycle Volume

The complexity and time requirements for contemporary ART laboratory activities has increased compared with traditional IVF cycle requirements. A traditional IVF cycle typically required roughly 9 personnel hours, but a contemporary cycle can require up to 20 hours for completion (23). The increased use of PGT and embryo/oocyte vitrification and warming has driven this added complexity and time, and the number of embryologists, not including the laboratory director, required for safe and efficient operation of the ART laboratory has, therefore, increased. Proper scheduling of cycles is required to ensure appropriate staffing levels. The main reasons for ensuring adequate laboratory staffing include avoidance of staff burnout, avoidance of mental errors or shortcuts due to overwork, coverage during emergencies and disasters, and appropriate responses to alarms, which can occur at any time, day or night. Assisted reproductive technology laboratories are encouraged to consider laboratory assistants to support their embryologists in completing tasks that are important and time-consuming but do not require specific training. These tasks include paperwork completion and filing, documentation and scanning into the patient chart, and embryo shipments to and from other laboratories. Embryologists may prepare sperm samples for therapeutic use in an IVF cycle, but embryologists do not routinely perform diagnostic andrology or endocrine laboratory services. Laboratory director, assistants, andrologists, and endocrine technologists are not included in the embryology staffing levels recommended in Table 2.

Table 2 is an update of the recommended staffing according to total cycle volume (1). According to the SART, an oocyte retrieval cycle and a frozen-thawed ET are considered 2 different cycles.

Patient Identification and Traceability

Each laboratory should have in place a protocol to ensure the positive identification of specimens at each manipulation step in the laboratory's established procedure protocols. Positive identification of the patient and/or specimen should be verified by at least 2 qualified witnesses. Only staff members who

have been thoroughly trained in aspects of specimen hand-off and in the basic laboratory protocols for specimen handling are qualified to serve as witnesses for such tasks. Depending on the staffing level in the laboratory and the established workflow, an electronic witnessing system may be appropriate for serving the purpose of witnessing key manipulation events. The laboratory director is responsible for assessing staffing needs and determining the best system for specimen tracking.

All planned embryology procedures for a specific patient should be clearly ordered in writing by a physician and provided to the laboratory in advance of the IVF cycle. If the laboratory staff believe the plan should be amended, changes to the orders should be approved and clearly documented by the physician to ensure clear communication and responsibility.

Detailed protocols for oocyte retrieval, sperm preparation, conventional insemination and ICSI, fertilization check, embryo culture and development, incubation, embryo grading, ET, AH, embryo biopsy, embryo cryopreservation and warming, embryo/oocyte cryostorage, and shipping of cryopreserved tissues are described elsewhere and are customized and validated by each embryology laboratory. General principles and overviews are presented here.

Oocyte Retrieval

During all embryology procedures, sterile technique should be used, and an appropriate pH should be accomplished using either a gassed chamber or media buffered to maintain appropriate pH in room air or performing the procedure in a timely manner in media overlaid with oil. Before beginning the oocyte retrieval, a time-out is called, and the following are recorded: patient's 2 identifiers (typically name and date of birth) and planned procedure. Searching of follicular aspirates for oocytes should be performed in an area that has appropriate communication and proximity to the oocyte retrieval area.

Sperm Preparation

Preparation of sperm for oocyte insemination should be performed using sterile technique and universal precautions. If donor sperm is to be used for insemination, the FDA guidelines described in 21CFR part 1271 and described elsewhere in this guidance should be followed. Acceptable criteria for sperm samples to be used for conventional IVF or ICSI should be defined and may include, but are not limited to, concentration, motility, morphology, forward progression, and/or frozen-thawed sperm.

Conventional IVF and ICSI

Defined criteria should be established for which patients may use conventional insemination/IVF or which patients require ICSI. Intracytoplasmic sperm injection should only be performed by trained embryologists. Written protocols defining training requirements before performing ICSI, including acceptable levels of performance for the laboratory and for individual embryologists, should be in place. Records of

corrective action are maintained when the acceptable levels of performance are not achieved.

Fertilization Check

Written procedures for performing fertilization check should include a defined period of time that fertilization check is to occur and the time and technician performing the fertilization check, the status of each oocyte should be recorded (number of pronuclei and if not fertilized the maturity and number of polar bodies as applicable), and there should be a written procedure that for the immediate disposition of oocytes with an abnormal number of pronuclei. This may include disposal, continued culture, freezing, training, or institutional review board-approved research.

Embryo Culture and Development

Media. Today's media products are predominately manufactured by large commercial entities capable of sustaining a high level of quality care, with minimal lot to lot variation not previously attained by traditional in-laboratory media preparations. The types of media used have been reduced to 2 schools-of-thought: sequential or one-step media. Detailed reviews discussing the pros and cons of these opposing media formulation strategies and the differential energy needs of the developing embryos have been published (24–26). There are also 2 types of protein supplementation: either purified or recombinant human serum albumin or a synthetic protein supplement. Synthetic protein supplements contain human serum albumin (80%–85%) and a residual fraction of α - and β -globulins mixed with other macromolecules (e.g., growth factors, hyaluronic acid, and cofactors) that have been shown to be beneficial supplements to media formulations.

Variation also exists in terms of whether a laboratory prefers culturing in microdroplet (10–50 μ L) and microwell (200 μ L) culture dish setups, in conjunction with either single embryo or group culture strategies. Although single embryo microdroplet culturing is required after embryo biopsy, group culturing of embryos to the blastocyst stage is commonly performed to gain possible beneficial paracrine effects. In addition to diverse culture medium choices, IVF laboratories must decide on a mineral oil brand and type (e.g., light mineral oil and paraffin oil) to use in their incubation system. Most commercial oil sources are prewashed and chemically stable at 37 °C in culture. Conversely, light (ultraviolet) exposure to the oil product in storage/use should be minimized to prevent chemical changes caused by reactive oxygen species (ROS) generation.

Incubation. It is well adopted that a tri-gas mix of CO₂ (5%–7%), O₂ (5%), and N₂ (88%–90%) best mimics physiological conditions for growing preimplantation embryos. CO₂ adjustment is the key variable to adjust pH, typically between 7.25–7.35, but no single optimal pH has been defined. Conventional, high-capacity box incubators have been commonly replaced by miniaturized versions to provide improved gas recovery times, which help maintain ideal

equilibration conditions and sustained reliability in both humidified and nonhumidified chambers. Some incubators are being further specialized to include time-lapse imaging/microscopy capabilities, which may combine with algorithm or artificial intelligence software. Note that time-lapse imaging/microscopy has proven to be an important technology to understanding early embryo development (i.e., time intervals of cell divisions and documented anomalies) and serving as an embryo selection/deselection tool but is still not standard practice in ART laboratories because it has not been shown to improve pregnancy rates over standard embryo grading techniques (27).

Embryo grading and selection. Embryo quality assessment and grading are key procedures in the embryology laboratory and major determining factors for clinical outcome success. Transferring top-quality fresh or frozen-warmed embryos combined with selection criteria and applicable elective single-embryo transfer has been associated with higher implantation rates and better clinical outcomes (28).

Each laboratory should choose the most feasible methodology in grading and selecting embryos. Several grading/scoring systems have been developed by examining cell number (cleavage stage), symmetry, fragmentation, overall blastocyst formation (blastocyst stage), inner cell mass, and trophectoderm (TE) (29). Additional comments on unique characteristics of each embryo, for example, uneven cleavage, multinucleation, cytoplasmic granularity, thickness/color of the zona pellucida, and contamination, should be noted in the laboratory records. Factors to consider when implementing and revising the laboratory's embryo grading system include scientific basis, comprehensiveness, consistency, ease of use, efficiency, reliability, and interlaboratory communication.

Embryo Transfer

The ET process is a key procedural step that has been the sole topic of prior Practice Committee guidelines (30), as have limits pertaining to embryo number per age groups (31). Elective single-embryo transfer is recommended to increase the possibility of singleton, healthy, term live births while avoiding multiple pregnancies (32), especially in conjunction with PGT for aneuploidy (33).

The laboratory must manage and organize a daily schedule to optimize workflow and workload and ensure that a doctor's orders and signed consents are received. In the laboratory, embryologists are responsible for proper ET dish setup/labeling and equilibration of media products. Each laboratory may have unique variations in standard operating procedures pertaining to culture/ET medium, culture ware, ET catheter selection, embryo loading, and how the embryologist actually assists the physician (34). Similar to fertilization events, the time of ET represents an acutely sensitive time where correct embryo selection and patient identification verification are of paramount importance. Embryologists typically perform a "time-out" procedure to verify patient identification, and they may

directly confirm the plan for the number of embryos to transfer with the patient.

Assisted Hatching

Assisted hatching is a laboratory procedure involving the breaching of the zona pellucida to facilitate herniation of TE cells to facilitate embryo biopsy procedures, previtrification blastocoel collapse, and/or post-ET implantation. The process, history potential advantages, and concerns of AH for fresh and frozen-thawed ET cycles and its necessity for cell removing-embryo biopsy procedures have been previously reviewed by the ASRM (35). The value of AH on clinical outcomes remains debatable at this time. Computer-mediated safe infrared diode lasers have become a laboratory standard as laser energy is delivered directly through an inverted microscope objective to ablate a specific defined target (i.e., zona pellucida and cellular junctions). The infrared diode laser (1,480 nm) pulses are nontoxic but generate damaging thermal energy in the form of localized heat, whose target range is controlled by presetting the energy levels and pulse duration, and the total number of pulses delivered. Key components to effectively breaching the zona pellucida for AH procedures have been described elsewhere (36).

Embryo Biopsy and PGT

Embryo biopsy is a procedure required for PGT for aneuploidy screening, specific genetic defects involving monogenic disorders (33), chromosomal structural rearrangement, or polygenic disorders. Today, blastocyst biopsy has essentially replaced pronuclear or cleavage-stage embryo biopsy procedures based on numerous advantages, including the following: increased accuracy and reliability of PGT; removal of a smaller proportion of total cells from embryo; removal of nonfetal TE cells only; and no apparent negative impact on cryopreservation or implantation potential (37, 38). Blastocyst biopsy, like all micromanipulation techniques, should only be performed by skilled personnel with proven competency using metrics such as low no-result rates.

Embryo Cryopreservation

It is imperative that informed consent be obtained before cryopreservation of oocytes or embryos. The consent form must include options for disposition of the cryopreserved samples and instructions for the fertility clinic and the laboratory to follow. It is common for the patients to be billed for cryostorage. When a patient no longer wishes to continue storage, a discard consent needs to be filled out properly and completely before the oocytes or embryos being discarded. Further guidance on disposition of cryopreserved tissues and unclaimed cryopreserved tissues can be found in the ASRM Ethics Committee Opinion (39).

Embryo cryopreservation should be a requirement for a modern embryology laboratory. Oocyte cryopreservation may be considered optional. Written protocols for cryopreservation should be developed specific for each laboratory. Further guidance can be found in the ASRM Practice Committee Opinion on rapid-cooling vitrification best practices (40).

Embryo/Oocyte Cryostorage

Each laboratory must have specific protocols for storing cryopreserved tissues. Protocols should be written and records kept regarding procedures for maintaining these liquid nitrogen storage tanks. Appropriate alarm systems should be installed on liquid nitrogen tanks. Ideally, the system should be able to remotely alert the laboratory staff in the case of a mechanical problem. Care should be taken to ensure that alarms will alert users when power, phone, or Internet access is down. Alarm systems should be tested at periodic intervals to ensure that they are functioning correctly and will properly alert staff if there is a problem. Regular alarm testing should be documented. Proper placement of temperature or level probes in liquid nitrogen is critical for providing adequate time for staff to respond to an alarm of tank warming.

Hazards during any kind of work with liquid nitrogen are considerable. Accordingly, safety standards have been established by the CAP and TJC, including the use of special cryogloves, safety goggles, closed-toed shoes, protective clothing, and face masks. The introduction and widespread use of vitrification has increased the hazards because it requires manual work using open containers filled with liquid nitrogen. The vitrification process also requires delicate manual handling and frequent shifts between the microscopic and macroscopic examination of the sample, which cannot be performed by following all possible cryo-safety measures. However, complete elimination of safety measures exposes inexperienced people to serious hazard. Further guidance can be found in the ASRM Practice Committee Opinion on cryostorage management (44).

Shipping of Cryopreserved Tissues

Cryopreserved specimens, including embryos, oocytes, and semen, must be shipped in dry liquid nitrogen (LN₂) shippers. This is to ensure temperatures below -150°C . Most commercial shipping companies will not insure these specimens. It may be a better option to use a shipping company that specializes in handling cryopreserved gametes or embryos. These companies will share this risk. Each laboratory should have specific written protocols for shipping and the handling of these specimens. The HCTPs must be shipped with a completed donor eligibility form and/or summary of records. A receiving laboratory must check for and keep on file all documentation regarding the donor specimen (summary of records).

ANDROLOGY LABORATORY GUIDANCE

Definition of Service

The andrology laboratories encompass a variety of diagnostic and clinical laboratory procedures. The primary testing performed in an andrology laboratory is SA. The ASRM defines SA as the microscopic examination of semen (the male ejaculate) to determine its volume, the number of sperm (sperm count), their shapes (morphology), and their ability to move (motility) in addition to other parameters. Some portions of this test (concentration and motility) may be performed with computer-aided/assisted semen analysis (CASA) equip-

ment. Further testing of semen and sperm, for example, tests of seminal plasma for constituents such as fructose or pH and tests of spermatozoa such as deoxyribonucleic acid (DNA) fragmentation or viability, may be performed. In addition, sperm preparation for insemination by simple or complex methods may be performed as may sperm cryopreservation. Furthermore, the analysis of specimens of epididymal fluid (obtained by microsurgical/percutaneous epididymal sperm aspiration) or from testicular biopsy (obtained by testicular sperm aspiration/extraction) may be performed in the andrology laboratory.

Laboratory Space and Design

The andrology laboratory should have adequate space and a design that is appropriate for the volume and type of procedures performed and that ensures safe and comfortable working conditions. The andrology laboratory may share space physically with other laboratory activity. However, any activity requiring sterile technique (i.e., sperm preparation for intrauterine insemination [IUI]) should be physically separated from other activities. Adequate space should be provided for record keeping, data entry, and related administrative functions. Materials for laboratory construction, ventilation of the area, and cleanliness should be appropriate to the laboratory work. The use of carpet in tissue culture or work areas is prohibited. The andrology laboratory does not necessarily need the same level of air quality and design features as the IVF laboratory.

Instrumentation

Laboratories are required to maintain or have access to equipment necessary to perform andrology services. It is the responsibility of the laboratory director to ensure that the proper equipment is in place to perform the necessary assays. Certain laboratory equipment (i.e., laminar flow hoods, biohazard laboratory hoods, and balances) must be certified by a qualified agency on an annual basis. Certifications must be maintained on file for review. The laboratory should have a program for checking and calibrating laboratory equipment, such as pipettors, thermometers, pH meters, centrifuges, and refrigerators, on a regular basis. Manufacturer-supplied manuals or maintenance manuals for all laboratory equipment must be maintained in the laboratory.

Supplies and Reagents

All material that comes in contact with sperm that is being prepared for cryopreservation or IUI must be tested for toxicity. This testing requires the use of an appropriate bioassay if one is not provided by the manufacturer. Quality control testing is optional when commercial media is purchased and used within its labeled expiration period and recommended period after opening the container. Documentation of quality control testing using an appropriate bioassay system, for example, Certificate of Analysis, must be supplied by the manufacturer for each lot of the product. All laboratory chemicals and reagents must be labeled with the date received and date opened and should be stored as recommended by the

supplier/manufacture. Similar to standards for other media, each lot of cryopreservation medium should have undergone quality control testing using an appropriate bioassay.

Daily Quality Control

Daily quality control must be completed before any testing begins in the andrology laboratory. For nonwaived testing, the CLIA directs laboratories to follow all manufacturer instructions and mandates 2 levels of quality control for some testing including manual and automated counting of sperm. Other accrediting agencies and state regulations may dictate frequent quality control for other aspects of SA including morphology and motility. In addition to quality control of specific tests, daily quality control of the testing environment should occur and meet the laboratory's accreditation requirements (CLIA, CAP, and TJC). This can include, but is not limited to, recording room temperature and humidity, temperature control of storage areas including refrigerators and freezers, and water quality control.

Laboratory Supervisor: Definition and Duties

The general supervisor who oversees the day-to-day laboratory operation ensures that the testing system is operating properly and supervises the accuracy of results generated by the laboratory. They are responsible for supervising testing personnel and orienting and training new personnel. The general supervisor must meet the CLIA '88 qualifications, at minimum hold a bachelor's degree in science, and have at least 1 year of experience in high-complexity testing. The general supervisor must be on-site when testing is being performed.

The technical supervisor is responsible for the technical and scientific oversight of the laboratory; appropriate test methodology selection; verification of procedure and performance and enrollment into appropriate PT programs; and establishing QC, resolving technical issues, and training personnel including ongoing competency assessments. The technical supervisor must meet the CLIA '88 qualifications, at minimum hold a bachelor's degree in science, and have at least 2 years of experience in high-complexity testing.

Testing Personnel/Andrologist: Definition and Duties

Andrologists perform diagnostic and clinical analysis and processing of fresh or frozen human sperm and testicular tissue. The minimum requirements include the following:

- Doctor of Medicine or DO with current medical license in the state of laboratory's location *OR*
- Doctorate in clinical laboratory science, chemical, physical, or biologic science *OR*
- Master's in medical technology, clinical laboratory, chemical, physical, or biologic science *OR*
- Bachelor's in medical technology, clinical laboratory, chemical, physical, or biologic science *OR*

- Associate degree in chemical, physical, or biologic science or medical laboratory technology *OR*
- High school graduate or equivalent and successfully completed military training of 50 or more weeks and served as a medical laboratory specialist *OR*
- High school diploma or equivalent and appropriate training/experience as specified in CLIA '88 493.1423.

Testing personnel are responsible for adhering to all laboratory procedures and policies, ensuring that daily quality control is completed before reporting any patient results and record keeping for results generated and reported. Testing personnel must be capable of identifying when a test system is not performing correctly and report this to the general or technical supervisor, CC, or laboratory director.

Andrology Training

Laboratories should implement a training protocol and schedule for new laboratory employees. This must be documented, and proficiency demonstrated before unsupervised testing on patient samples can be performed.

Patient Accessioning and Semen Collection

There must be documented procedures for assuring that semen specimens used in diagnostic and clinical procedures were produced by the intended sperm source (patient and donor). Once the specimen is collected, the laboratory must uniquely identify and label the specimen in such a way that it is unquestionably a specimen from the intended sperm source. For diagnostic testing, the specimen should receive a unique identifier for use throughout the testing and reporting process. Specimens intended for therapeutic use must be identified with a higher level of scrutiny. For these specimens, a system of double checks should be employed to assure that the identity of the specimen is maintained throughout processing, every change of vessels, and insemination (cervical, intrauterine, or in vitro insemination). Reliance on only 1 method of identification has proven to be insufficient to avoid errors; therefore, further checks should be employed (identification by 2 independent personnel or by 1 person and a secondary independent, identification system).

SA, Manual, and CASA

First developed and described 1929, a complete SA is the conventional method and first step in assessing male fertility potential (41). Current protocols for SA and sperm function testing can be found in the 5th edition of the World Health Organization Manual (42). Analysis of results of 2 or more SAs over a reasonable period of time (e.g., several weeks) makes the most accurate evaluation of the male patient's semen (42). It is important to emphasize that a complete SA is needed; during collection, the entire ejaculate must be produced into the specimen cup under specified conditions.

A semen specimen is collected by masturbation into a sterile specimen container or approved condom (no spermicide or lubricant other than a laboratory-approved lubricant). The patient should remain abstinent for 2–7 days before

collection for a complete SA (42). Time of collection and days of sexual abstinence are recorded. The ejaculate liquefies for 30–60 minutes at room temperature. Delayed liquefaction should not be confused with increased viscosity. After liquefaction, the sample volume is measured by a serologic pipet. The sample needs to be mixed by gentle pipetting or swirling; accurate results can only be generated with a uniform sample. Semen pH is measured during an SA. Count, motility, forward progression, agglutination and morphology need to be observed and recorded. A portion of the sample is analyzed manually by a counting chamber or using an automated system, such as CASA. The CASA systems measure sperm motility and kinematics, and some can estimate sperm concentration.

Sperm Function Testing

Besides the routine conventional SA, sperm function testing methods have been proposed and used by various laboratories. Sperm vitality testing, or viability testing, assesses whether sperm are dead or alive: this test can be performed using a supravital dye, such as eosin B or by hypo-osmotic swelling. The DNA fragmentation tests aim to detect DNA damage during spermatogenesis. The DNA fragmentation index can be assessed by sperm chromatin structure assay, terminal deoxyribonucleotidyl transferase-mediated 2-Deoxyuridine, 5-Triphosphate nick end-labeling, sperm chromatin dispersion, or the comet assay (43). Other sperm function testing less often used but included here for completeness are the following: antisperm antibody testing when there is an increased amount of agglutination observed, to detect whether there is a presence of sperm antibodies on spermatozoa; qualitative fructose testing to guide diagnosis of azoospermia; measurement of ROS, which may be correlated with potential pathological effects. The significant level of ROS production can be detected using various chemical luminescence methods or oxidative indicators.

Sperm Preparation for IUI and IVF Procedures

Semen samples need to be properly processed before an IUI. Proper preparation will concentrate the motile sperm, remove nonmotile sperm, and remove seminal plasma. Raw semen should not be placed into the uterine cavity. Similar to preparing semen for IUIs, semen is prepared for IVF procedures. Depending on the quantity of motile sperm in the semen sample, the ejaculate can be layered over a gradient, or a simple wash can be performed. The resulting pellet is washed and used for insemination via conventional insemination or ICSI.

Semen Cryopreservation and Thawing

There are several clinical indications for sperm cryopreservation, including fertility preservation, infertility treatment, and travel to locations where infectious disease transmission is possible. Before any sperm cryopreservation, a consent should be signed by the patient confirming they are aware of risks and benefits to the procedure and designation of disposition of the semen vials in the event of death. The goal of cryopreservation protocols is to cryopreserve the

specimen with minimal intracellular ice crystal formation. To prevent cellular damage to sperm, proper cryoprotectants need to be present in media used to cryopreserve the specimen. In addition, the rate of cooling needs to minimize the amount of intracellular ice formation. Slow cooling before submerging in liquid nitrogen can be accomplished by exposing the sample to liquid nitrogen vapor for a defined period of time, as part of the cryopreservation protocol. Another reason to cryopreserve sperm is to provide donor specimens to those seeking fertility treatment. Healthy sperm can be cryopreserved and donated to patients and/or couples who do not have autologous sperm available for insemination. Sperm can be donated anonymously, or as directed, and appropriate testing and screening must be performed before clinical use. Thawing sperm, whether partner sperm or donor sperm, is performed by warming the sample by following a protocol provided by the laboratory that performed the sperm cryopreservation and then washing out cryoprotectant before use for insemination. Before any sperm thaw, a consent should be signed by the patient or owner confirming that they give permission for their sample to be thawed and used in a procedure that will potentially create a pregnancy. There are several protocols that are not necessarily interchangeable. Before thawing any sperm specimen, it is important to have the correct protocol. The manner in which the sample was cryopreserved determines how the sample should be thawed and processed. For example, a sample can be cryopreserved washed (IUI ready) or unwashed (intracervical insemination ready), which requires postthaw wash for IUI use. Some samples are for IVF specifically and will not have enough motile sperm to use for an IUI after thaw.

Management of Cryopreserved Semen

Cryopreserved semen can be stored directly in liquid nitrogen or in liquid nitrogen vapor. Special attention to labeling and documentation is needed for proper patient identification; this includes a system for labeling all samples, and the actual label and text on the specimen container need to be tested for durability at extremely cold temperatures. The tanks used to store the specimen should be alarmed for critical temperature and/or liquid nitrogen levels, as well as measured manually. The alarm should be tested routinely, and all tests should be recorded. Similarly, manual measurements taken should be recorded and followed for changes in tank functionality. Tanks will need to be filled with liquid nitrogen on a regular basis, defined by standard operating procedures of the laboratory. It is common for the specimen owners to be billed for specimen storage. When a patient no longer wishes to continue storage, a discard consent needs to be filled out properly and completely before the specimen being discarded. Further guidance can be found in the ASRM Practice Committee Opinion on cryostorage management (44).

Cryopreserved semen may be received from an external facility; these samples should be logged in and logged out appropriately. Any sperm cryopreserved and thawed on-site should also be logged in and logged out in the same appropriate manner. Should the andrology laboratory use

EHRs/EMRs or a database system, all information written on worksheets or reports should match all electronic data entries. All procedures, including receipt of samples, use of samples, movement of sample locations, and labeling of samples, should be documented with date and initials.

Patient Reports

Semen analysis reporting should be performed in a timely manner. A preliminary report including sperm count and motility can be performed the same day of collection, with morphology slide staining occurring the same day or intermittently during the work week depending on staffing and sample volume. The turnaround time for a complete SA should be defined by the laboratory standard operating procedures and monitored regularly for compliance.

ENDOCRINOLOGY LABORATORY GUIDANCE

Definition of Service

The ART hormone assay laboratory, or reproductive endocrinology laboratory, entails the use of an automated hormone analyzer to process patient serum samples, usually for the determination of levels of relevant hormones for treatment or ART cycle management. As most ART hormone laboratories now use automated analyzers, these facilities are usually performing moderate-complexity testing. As such, personnel should meet this moderate-complexity minimal qualified standard.

Laboratory Space and Design

The laboratory should have adequate space and a design that is appropriate for the volume and type of procedures performed and ensures safe and comfortable working conditions. Special attention to ventilation requirements need to be met for health and safety codes. In addition, energy and water requirements need to be identified when designing the laboratory space. Traditionally, a compartmentalized design is suitable for manual bench testing, whereas the newer trend leans toward open-plan design, which provides more flexibility for automated analyzers if space is allowed. Adequate space should be provided for record keeping, data entry, and related administrative functions. Material for laboratory construction, ventilation of the area, and cleanliness should be appropriate to the laboratory work.

Instrumentation

Laboratories are required to maintain or have access to equipment necessary to perform ART hormone assay services. It is the responsibility of the laboratory director to ensure that the proper equipment is in place to perform the necessary assays. Evaluation of automated analyzers should be made based on the logical protocol that fits individual laboratory needs, with capacity to perform the workload. All the testing should be performed according to manufacturer's instructions. Preventative maintenance should be performed regularly following the manufacturer's instructions with certified technicians. Certain laboratory equipment (i.e., laminar flow hoods,

biohazard laboratory hoods, and balances) must be certified by a qualified agency on an annual basis. Certifications must be maintained on file for review. The laboratory should have a program for checking and calibrating laboratory equipment, such as pipettes, thermometers, centrifuges, and refrigerators, on a regular basis. Manufacturer-supplied manuals or maintenance manuals for all laboratory equipment must be maintained in the laboratory.

Supplies and Reagents

There must be an established inventory system to maintain sufficient amounts of supplies and reagents. A laboratory must establish protocols that clearly indicate the process of placing and tracking orders. The protocol should also implement alternate solutions in the circumstance of supplies lapse or backorder. The laboratory protocol must also define acceptable temperature range and condition for proper storage of supplies and reagents. The criteria must be consistent with manufacturer's instructions. There must be a mechanism for the safe handling and disposal of biohazardous waste material in the laboratory. All laboratory chemicals and reagents must be labeled with the date received and opened and should be stored as recommended by the supplier/manufacturer. Reagents and supplies must not be used when they have exceeded their expiration date or the quality has compromised. The components of reagents kits of different lot numbers should not be interchanged unless permitted by the manufacturer.

Endocrine Laboratory Testing Personnel: Definition and Duties

Testing personnel in endocrine laboratories access and perform analysis of endocrine levels in blood samples, typically using an automated hormone analyzer. The minimum requirements for testing personnel include the following:

- Doctor of Medicine or DO with current medical license in the state of laboratory's location *OR*
- Doctorate in clinical laboratory science, chemical, physical, or biologic science *OR*
- Master's in medical technology, clinical laboratory, chemical, physical, or biologic science *OR*
- Bachelor's in medical technology, clinical laboratory, chemical, physical, or biologic science *OR*
- Associate degree in chemical, physical, or biologic science or medical laboratory technology *OR*
- High school graduate or equivalent and successfully completed military training of 50 or more weeks and served as a medical laboratory specialist *OR*
- High school diploma or equivalent and appropriate training/experience as specified in 493.1423
- Testing personnel are responsible for all laboratory procedures and policies, ensuring that daily quality control is completed before reporting any patient results and record keeping for results generated and reported.
- Testing personnel must be capable of identifying when a test system is not performing correctly and report this to

the general or technical supervisor, CC, or laboratory director.

Endocrine Training

Most companies who supply reproductive hormone analyzers provide training at a central facility as well as on-site training during equipment install. Training is required before clinical implementation and often entails a review of analyzer operations and required maintenance. Background on the type of assays used and how they function is often recommended. Additionally, training on handling of samples, entering of patient information, and obtaining accurate results is required. Information on these items is kept in a formal operation manual, which is usually accompanied by a practical bench manual for day-to-day functions and troubleshooting. Training records should be filled out and kept in the employee file.

Training also involves comprehension and interpretation of daily control values to understand when it is permissible to release patient results as well as how to troubleshoot if daily quality control values are out of range.

Daily Quality Control

A startup procedure and checklist should be completed each day before running patient samples and reporting results. This includes verifying appropriate environmental conditions (room temperature and humidity), equipment function, and reagent suitability. Daily hormone controls must be run each day before reporting patient results to confirm analyzer function and accuracy. At least 2 levels of controls should be used for each hormone assay, although 3 levels may be more appropriate. Controls must fall within prior established means and standard deviations before patient results can be reported. The laboratory should establish what their acceptable ranges are and use appropriate tools including Levy-Jennings plots, single control rule, and/or apply multirules (e.g., Westgard) in determining when a control run is valid/accepted or if a run is rejected. Laboratory daily quality control values should be compared against a peer group, when possible, to confirm accuracy on a regular basis, often monthly.

Test Requisitions

Test requisitions must come from an authorized medical professional and must include the following elements: name and address or other identifiers of the authorized medical professional; patient's name and unique identifier; sex and birth date of the patient; tests to be performed; source of the specimen if necessary; and date and time of specimen collection.

Serum Collection, Accessioning, and Processing

The patient should state their full name and confirm that the tube labeling is correct. The time and date of blood draw should also be recorded. The type of collection tube used for blood collection is test dependent and should be drawn in a specific order to prevent cross-contamination of additives. The time and date of the blood sample received in the

laboratory should be recorded. After collection of the whole blood, the blood should be allowed to clot by leaving it undisturbed at room temperature. This usually takes 15–30 minutes. The clot should then be removed by centrifugation with or without refrigeration as per test manufacturer at $1,000\text{--}2,000 \times g$ for 10–15 minutes. The resulting supernatant is designated serum if no anticoagulant treatment is in the tube or plasma if anticoagulant treatment is in the tubes (e.g., EDTA or citrated-treated tubes).

Test Reports

Laboratories must have an adequate manual or electronic system to ensure test results are accurately and reliably sent from the point of data entry to the final report destination in a timely manner. All test reports should include the following items: results; patient name and unique identifier; name and address of the testing laboratory; test report date; date of performance; units of measurements; and reference intervals or normal values. If an error is detected in a patient laboratory report, the authorized person ordering the test or the individual using the test results of the error should be immediately notified. Corrected reports should be issued promptly. Moreover, the original as well as the corrected report should be maintained. All patient test reports should be easily accessible for surveys or audits.

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Guía integral para el manejo y operación de los laboratorios de embriología humana, andrología y endocrinología: una opinión de comité.

Este documento es una guía integral para laboratorios de embriología humana, andrología y endocrinología. Es una guía universal aplicable a todos los laboratorios que incluye los requerimientos y las recomendaciones para la acreditación y la dotación de personal en los Estados Unidos y a la vez se incluye una guía para cada laboratorio especializado.