Chapter 1

Establishing and Equipping a New IVF Laboratory

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Introduction

Attention to detail and robust quality control systems are essential components for a successful in vitro fertilization (IVF) laboratory, necessary to maintain high success rates. This not only pertains to daily laboratory operations, such as adequate staff training, monitoring of equipment function and weekly/monthly success rates, but also entails proper laboratory design and construction. A highly successful IVF laboratory requires careful consideration of layout and workflow and use of appropriate materials to avoid introducing potentially embryotoxic factors into the laboratory environment.

1.1 Background

The design and equipping of a new IVF laboratory can be a daunting and tedious endeavour. Numerous factors must be considered, including space requirements to accommodate staff and equipment, as well as layout for optimal workflow. Proximity to other rooms, such as medical gas storage, operating/procedure rooms and transfer rooms, as well as IVF storage, is also relevant. The potential for future laboratory expansion is also often desirable. Thus, initial planning of space requirements should consider these items. Each facility will have its own unique demands that will affect the ultimate size and layout of the laboratory space. However, commonalities exist between highly successful laboratories in terms of how the laboratory is built and equipped. Furthermore, key steps are often taken prior to clinical use to ensure proper functioning of the built space.

The following are abbreviated procedures addressing key components to ensure proper establishment and equipment of a modern IVF laboratory. Many key components focus on use of appropriate materials and systems to ensure proper air quality and growth conditions. Of paramount importance is constant oversight during the construction process to ensure that key details are met. Once these requirements have been met, diligence and a thorough quality management programme are required to ensure that optimal laboratory conditions remain intact.

1.2 Supplies and Equipment

- A professional team of architects and a general contracting firm experienced in medical facility build-out
- A large suite or stand-alone building, allowing for proper laboratory layout
- Elevator access along with a loading dock for various deliveries, including equipment and medical gas delivery

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- A functional laboratory/clinic design plan that is approved by the medical and laboratory directors as well as architectural and construction teams
  - Careful attention to required workflow, equipment, electrical and information technology (IT) needs

    Appropriately chosen construction materials
  - Low or no volatile organic compounds (VOCs)
    - Flooring /adhesives – sheet vinyl with welded seams, low-VOC adhesive
    - Insulation – avoid around perimeter of laboratory; formaldehyde-free product or mineral wool if required
    - Paint – no-VOC latex paint product for all laboratory spaces
    - Cabinetry – powder-coated/painted-metal cabinetry, no particle board or laminate
    - Countertops – Corian, Trespa or some other low-VOC hard material without adhesives
    - Furniture – medical- or laboratory-grade furniture with vinyl covering and low-VOC materials
    - Avoid use of printers, corkboards, xylene markers inside the laboratory space
    - Copper piping for gas lines with brazed connection; stainless steel piping also appropriate
    - Tyvek wrap around lab perimeter behind drywall to help maintain positive pressure
  - Minimum 36-inch doors for equipment installation – with gaskets and sweeps
  - Security system on entry doors (lockable)
  - Gas manifold system – gas regulators, Tygon tubing
    - Automatic tank switchers may be used but are not required
    - Regulators to measure tank pressures are needed at the gas source
    - Low-pressure regulators at the gas outlet are recommended to meet varying pressure requirements of different incubator models
  - Required laboratory equipment/vendor list
    - Microscopes, micromanipulators, centrifuges, laminar flow hoods, incubators, refrigerators, alarm system, computers, consumables, etc.
  - Back-up generator allowing for all equipment to be supplied with uninterrupted power
    - Natural gas or diesel – may be dictated by code or building requirements. A minimum of 8 hours to a preferred 96 hours of back-up is recommended. The fuel tank size should be sized accordingly.
    - Battery back-ups may be used for some equipment, but must be adequate to supply several hours of power
    - Ensure appropriate number and placement of generator plugs throughout the laboratory space allowing for room for extra equipment based on planned site growth

  - Appropriate, dedicated heating, ventilation and air-conditioning (HVAC) system
    - VOC filtration (various systems exist that use combinations of UV light, carbon filters and potassium permanganate)
    - High-efficiency particulate air (HEPA) filtration
    - Properly sized and designed unit to maintain positive pressure inside the laboratory
    - Proper placement of air vents to avoid being directly over critical equipment
  - Cleaning products
    - Hydrogen peroxide solution (3%) or commercially available low-VOC, embryo-safe cleaning solutions
  - Required laboratory manuals
    - Quality management programme, protocols and policies, equipment maintenance, safety (Material Safety Data Sheets), etc.

1.3 Quality Control

- Keep a record of meeting minutes and plan revisions with construction company and contractors to track discussions.
- Continue to monitor the construction process on a daily/weekly basis to ensure that design and specifications are followed.
  - Ensure the use of low-VOC products in the full range of materials used to construct the laboratory (and procedure room if in proximity to the laboratory).
- Air quality testing prior to and after construction is recommended to achieve appropriate laboratory air quality (measurement of VOCs in parts per billion (ppb) levels is recommended).
- Perform a mouse embryo assay (MEA) or approved bioassay prior to clinical cases.

1.4 Procedure

1.4.1 Initial Project Planning

1. Identify a location that suits the needs of the clinic/laboratory.
   a. Proximity to an existing clinic is recommended.
   b. Must be adjacent to procedure room/operating room (OR) and embryo transfer room.
   c. Adequate laboratory space for offices, storage, equipment, specimen collection, medical gases, etc.
2. Locate and interview several construction and architectural companies based on previous experience in medical facility design and build-out in order to ensure that quality standards are clearly understood and met.
3. Prepare a laboratory floor plan considering workflow, including all laboratory equipment, maintaining close proximity between intracytoplasmic sperm injection (ICSI) stations and other IVF workstations to all incubators.

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a. Compile equipment list and plan locations.
b. Plan placement of lights, air vents and electrical and IT outlets appropriately.
c. Design a separate dedicated medical gas/liquid nitrogen storage room. It is recommended to be a sound proof, well-ventilated room located in close proximity to a freight elevator or delivery area, if possible. If feasible, locating this room near the IVF liquid nitrogen or vapour tank storage area with vacuum jacketed lines for filling is recommended. Material for the floor should be taken into consideration as minor spills of liquid nitrogen (LN_2) over time will deteriorate most commonly used materials.
   i. Ensure that building regulations allow for use and transport of high-pressure medical gases and liquid nitrogen.
d. Design a separate room for consumables storage and off-gassing.

4. Once plans are approved and construction is initiated, ensure that HVAC is designed based on the required square footage and filtering capacity and meets requested standards (discussed further in Section 1.4.3).
5. Ensure that a natural gas or diesel back-up power generator is included in the laboratory design and is sufficient to support more than eight hours of back-up power supply. Set up a generator service schedule to include an initial two-hour load bank test, as well as monthly or semi-annual maintenance/inspections and yearly load tests. Additionally, consider an automatic transfer switch unit (ATS) that will provide seamless power changeover in the event of an outage.
   a. If a generator is not feasible, uninterruptible power supply (UPS) units are required on all crucial equipment with supply long enough to permit corrective action in case of power failure.
6. Fill out and submit required laboratory applications and paperwork to the relevant governing agencies.

1.4.2 Build-Out Process

1. Verify that all materials used are low or no VOCs (verify during onsite inspections).
   a. Insulation: insulation is often used in construction. However, chemicals such as formaldehyde are often present. The presence of insulation on the direct periphery of the IVF laboratory should be avoided if possible. If unable to avoid due to the presence of an outside wall, use of a formaldehyde-free product is recommended. Alternatives for sound dampening include mineral wool.
   b. Flooring: welded instead of glued seams of sheet vinyl flooring are recommended for sanitary reasons as well as minimal VOC release. Prior to clinical use, floors need to be cleaned with appropriate cleaners, such as hydrogen peroxide, along with simple regular sweeping, vacuuming or steam mopping. Avoid the use of any potentially harmful cleaners or waxes inside the laboratory.
   c. Paints: latex-based no-VOC paints should be used on all painted surfaces.
   d. Cabinetry: powder-coated metal cabinetry or stainless steel is suggested to avoid concerns with laminate and particle board, which would likely contain adhesives with high levels of VOCs.

   e. Furniture: purchase all medical- or laboratory-grade chairs with vinyl-coated seating surfaces that are easily cleaned of any contamination. Tables and countertop should be made of either Trespa, Corian, stainless steel or some other hard material devoid of adhesives (laminate).
   f. Cleaners: alcohol is discouraged due to VOCs. Hydrogen peroxide-based cleaning solutions (3%) are recommended.

2. Ensure that HVAC ductwork uses cleaned steel instead of plastic or other materials.
   a. Ductwork should be cleaned onsite by the installation crew using alcohol. Swabs can be taken to verify cleanliness and absence of oil and dust, etc.
   b. Verify that ductwork is sealed during the construction process to avoid dust and contaminants.

3. Ensure that sufficient gas supply is provided for all planned equipment inside the IVF laboratory.
   a. Verify that gas piping is in the correct location.
   b. Verify that proper manifold system and regulators are present and functional.

4. Ensure proper placement and functioning of various items.
   a. Confirm placement of light switches and outlets and all necessary equipment for performing daily operations. Quantify and pay particular attention to placement of emergency power outlets (if using a generator).
   b. Confirm the placement and swing of doors, proper locks, seals, sweeps, etc.

5. Verify the function of the generator. If a power outage creates a lag prior to generator power surge, ensure that all equipment is plugged into the UPS.
6. If windows are present, ensure that blackout blinds are available to help regulate light/heat within the laboratory. Incubators and ICSI workstations should be protected from direct sunlight to avoid potential issues with light and/or temperature regulation.
7. Confirm the absence of cork boards, printers/toners or unapproved markers containing xylene within the confines of the laboratory during move-in. These items may be kept in a separate laboratory office area away from embryo culture and handling locations.

1.4.3 HVAC

1. Select an HVAC company.
   a. Decide on a commercially available 'plug-and-play' filtration system or have the HVAC company built from scratch based on required IVF laboratory air quality demands. The system should be dedicated to the IVF laboratory.
      i. Filtration should include pre-filters (MERV) and HEPA filtration to remove particulates. Importantly, filtration should also reduce VOC content and can include use of ultraviolet (UV) light for photo-catalytic oxidation or use of chemical filter beds with carbon and potassium permanganate mixtures.
      ii. The placement of the filtration system is important; it should be as close to the outlet air ducts in the laboratory as possible to avoid risk for introduction of contaminants in-line after the filters.

iii. Ensure that air supply duct placement is not directly above/near ICSI stations or incubators, as this will affect temperature regulation of the stage warming units.

b. Ensure that only metal ductwork is used. This should be pre-cleaned and sealed during construction to avoid introduction of contamination.
c. Achieve positive pressure in the laboratory.

 i. Request Tyvek wrapping of the laboratory, hard deck ceiling, gasketted lights and doors and door sweeps.

d. Use proper air exchange rates and ratio of outside-to-inside air to achieve desired air quality.

 i. Recommendations vary and depend on the HVAC system/beginning air quality.

e. Ensure a proper water supply drawn to the HVAC unit to allow for constant humidity control. Monitor humidifier drainage as the frequency of air exchanges puts this unit in high demand. Blockage is common.
f. Ensure that a pressure display panel is installed inside the laboratory to monitor and record positive pressure for proper system functionality as per daily laboratory quality control.
g. Set up a regular maintenance contract with an appropriate company for servicing the belts and other items of the HVAC unit as well as all necessary filter changes to allow for initially targeted air quality standards.

1.4.4 Equipment

1. Determine volume estimates for the laboratory, and obtain quotes for selected equipment.

 a. Quotes and equipment specifications (size, electrical requirements, heat output) should be obtained early on in the design process.

  i. Back-up units of critical equipment should be considered (ICSI microscopes, incubators, fridges, freezers, etc.).

 b. Low-oxygen incubators are mandatory.

  i. A mix of bench-top units and box-type incubators is recommended.
  ii. Low oxygen may be supplied via pre-mixed tanks or through the use of separate nitrogen and carbon dioxide sources depending on type of incubator.
   (1) Nitrogen may be supplied through gas cylinders, high-pressure liquid nitrogen tanks or via a nitrogen generator. Cost, ease of delivery and usage are all factors to consider.
  iii. Use in-line VOC gas filters between gas supply and incubators – change out every four to six months.

2. Attempt to purchase equipment from vendors that are able to service the items within a short amount of time if equipment failures arise.

3. Set up a regular laboratory equipment maintenance system with local service providers (hoods, centrifuges, pipette calibration/validation).
4. Ensure that all incubators and cryostorage vessels are monitored by an alarm with the ability to email and/or call in case of an emergency.
    a. Wireless systems are now available to help with equipment movement and location and are recommended.

1.4.5 Burn-In

1. After construction, the laboratory should be wiped down with an approved disinfectant/cleaner.
    a. Walls, floors, cabinets and other surfaces should be wiped several times over the course of the burn-in period.
2. Equipment should be moved into the laboratory and cleaned/tested prior to clinical use.
    a. Of critical importance is burn-in of laboratory incubators. Incubators should be cleaned according to manufacturer's instructions and temperature raised to greater than 45 °C for several days or up to two weeks to promote off-gassing, cleaned and tested.[1]
    b. Laboratory temperature can be raised to help with off-gassing of other laboratory items.
    c. Verify correct temperature, gas and functioning of all equipment for several days after burn-in on quality control sheets to verify proper environmental conditions and functioning.
3. Perform pH testing of culture media used for embryos and gametes with the aim of achieving the desired pH based on incubator carbon dioxide concentration.[1–3]
4. Perform air quality testing measuring VOCs and particle counts before and after burn-in, and record the differences in the readings for quality control records.
    a. This can be performed by a professional company or by laboratory personnel if hand-held particle counters and VOC meters have been purchased by the laboratory or can be obtained from vendors. Sensitivity of these units should be considered (ppb recommended for VOC assessment).
5. Perform an MEA to ensure proper incubator conditions.
    a. All culture supplies should also be pre-tested with an appropriate bioassay prior to clinical use.

1.5 Notes

A. The rationale behind using low-VOC materials and a dedicated HVAC system is based on various publications suggesting the cytotoxicity of VOCs.[4–7] VOCs include various types of alkanes, aldehydes, ketones and alcohols commonly concentrated at high levels in paints, glues and flooring.

B. After laboratory commissioning, ongoing maintenance and quality control are required to ensure optimal function and culture conditions.

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i. Schedule for HVAC filter changes, routine cleaning and disinfecting of the laboratory, daily monitoring of incubator gas and temperature, testing of generator and alarm systems, etc.
ii. Monitoring of key performance indicators (KPIs) to identify possible issues.

(1) Fertilization rates, embryo development rates, clinical pregnancy, etc.

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